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A Novel Strategy for the Synthesis of Benzofuran Skeleton Neolignans: Application to Ailanthoidol, XH-14, and Obovaten

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A convenient and general approach to the synthesis of the benzofuran skeleton compounds ailanthoidol, XH-14, and obovaten was developed. Starting from vanillin, a series of reactions afforded **7** in 71% yield. Treatment of **7** with *n*-BuLi followed by addition of substituted benzaldehydes resulted in the formation of carbinols **11** and **31**. The substituted benzophenones obtained from oxidation of **11** and **31** were treated with trimethylsilyldiazomethane lithium salt to give diphenylacetylenes **15** and **33**, respectively. **15** and **33** were then cyclized in the presence of either mercury acetate in acetic acid or bromine in chloroform to give 3-chloromercurio- or 3-bromobenzofuran, respectively. The 3-chloromercurio intermediates could be reduced to proton or derivatized to ester or bromide, leading to the synthesis of ailanthoidol, XH-14, and obovaten, respectively. In addition, necleophilic substitution was used to introduce a formyl or methyl group into the 3-bromobenzofuran derivatives, providing an alternative pathway to XH-14 and obovaten. The final elongation and deprotection reaction furnished the desired ailanthoidol, XH-14, and obovaten in yields of 30, 15, and 11%, respectively.

Introduction

Ailanthoidol (**1**),[1] XH-14 (**2**),[2] and obovaten (**3**)[3] are natural products and characteristic members of the neolignan family. The lignanoids are dimers of propylbenzene units that connect at the side chain carbon. Those whose linkage of two phenylpropanoid units is other than the above type are known as neolignans.[4] Lignans and neolignans are widespread in nature. They have a wide variety of chemical structures and exhibit a broad range of biological activities such as anticancer,[5] antiproliferative,[6] antiviral,[7] immunosuppressive,[8] antiplatelet,[9] antioxidantive,[10] insecticidal,[11] anti-inflamanatory,[12] antifungal,[13] antifeedant,[14] and cancer preventative.[15] These compounds are also important sources of phytoestrogens.[16]

The structures of benzofuran lignans have one common characteristic: they all contain a 2-phenyl-7-methoxy-

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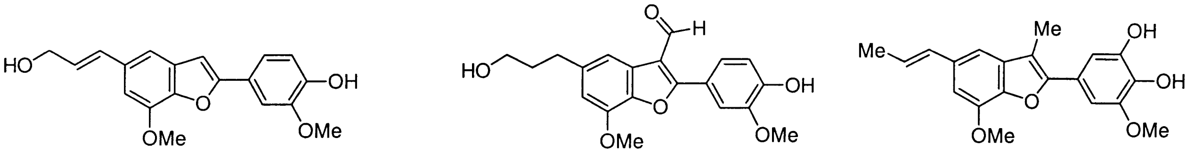
CHART 1



1, Ailanthoidol **2, XH-14** **3, obovaten**

benzofuran skeleton. The different lignans and neolignans are formed by different substitutions at the 3- and 5-positions and the 2-phenyl ring. XH-14 was the first reported nonnucleoside-type potent adenosine A_1 agonist[17] and obovaten is known as an active antitumor agent.[18] No biological activity has been reported for ailanthoidol. However, the limited supply of XH-14 and obovaten from natural sources has prevented the full characterization of their biological activities. As a result of our interest in developing an adenosine A_1 agonist,[19] and in view of the pharmacological interest of XH-14, we wished to develop a novel and general approach for the construction of the benzofuran skeleton. To achieve this goal, two fundamental criteria needed to be considered: (1) Since most benzofuran lignans contain a substituted phenyl ring at the 2-position and various functional groups at the 3-position, the synthetic approach must allow for the assemblage of the individual components of the molecules. (2) To investigate the relationship between lignan and macromolecule and develop potential candidate drugs, an efficient approach toward allowing the preparation of a variety of analogues from available building blocks is required. To meet these requirements, we set out to develop a general and convenient method for the synthesis of the benzofuran skeleton.Several approaches can be used to prepare ailanthoidol and XH-14; however, they do not all meet our proposed criteria. The prime method involves base-promoted cyclization of diphenylacetylene, which is obtained through cuprous coupling of *o*-halophenol derivatives with phenylacetylene derivatives.[20] However, this method is frequently limited in versatility by the availability of the requisite starting materials. A further drawback of this approach is that it generally uses an electrophilic reaction such as Gatterman−Adams formylation to install a functional group at the 3-position, but the reaction of benzofuran with electrophiles is complicated by competitive substitution at either C3 or C4. An alternative to the base-promoted reaction is to use palladium-catalyzed cyclization to construct the benzofuran skeleton.[21] Although organopalladium chemistry can induce the cyclization of diphenylacetylene and install an ester group onto the 3-position simultaneously[22] and overcome the problems of poor regioselectivity of electrophilic substitution encountered in base-promoted cyclization, this key reaction is not always efficient due to the low yields when this method is applied in reactions similar to the ones considered here.[23] The limited available starting material and inconvenient process also limit their application of both approaches as well. Moreover, both of the above methods require the presence of an *o*-hydroxy group to provide a nucleophilic center, necessitating additional synthetic steps to achieve this requirement. In addition, synthesis of ailanthoidol starting from a preparation of furan with subsequent benzo-annulation reaction to construct the benzene ring has also been reported.[24] This method gave ailanthoidol in 12% total yield. Nevertheless, application of this approach to the synthesis of 3-substituted benzofurans such as XH-14 and obovaten faces the problem of introducing a substituent at the 3-position. Another recently reported approach to constructing the benzofuran structure is the use of a biomimetic oxidative coupling reaction, which involves a homocoupling reaction of two cinnamic acid derivatives.[25] This approach has been found to give benzofurans in low to moderate yield. However, this strategy does not allow the heterocoupling reaction and is therefore not appropriate for our goal. Since the known strategies are of no advantage over analogous preparation, a novel diversity-oriented method is still needed.

Retrosynthetic Analysis

We began our work with the conjecture that 2-substituted phenyl-3-chloromercuriobenzofuran could be a key intermediate that, by reaction with various electrophiles and subsequent functionalization at the C-5 position, could lead to the three compounds of interest and a variety of their analogues. For the preparation of 2-substituted phenyl-3-chloromercuriobenzofuran, we selected substituted diphenylacetylenes as the appropriate precursor because of their ability to deliver a variety of 2-phenyl-ring substituents. The substituted diphenylacetylenes themselves can be prepared from substituted benzophenone, themselves obtained by a series of reactions starting from different benzaldehydes and using the

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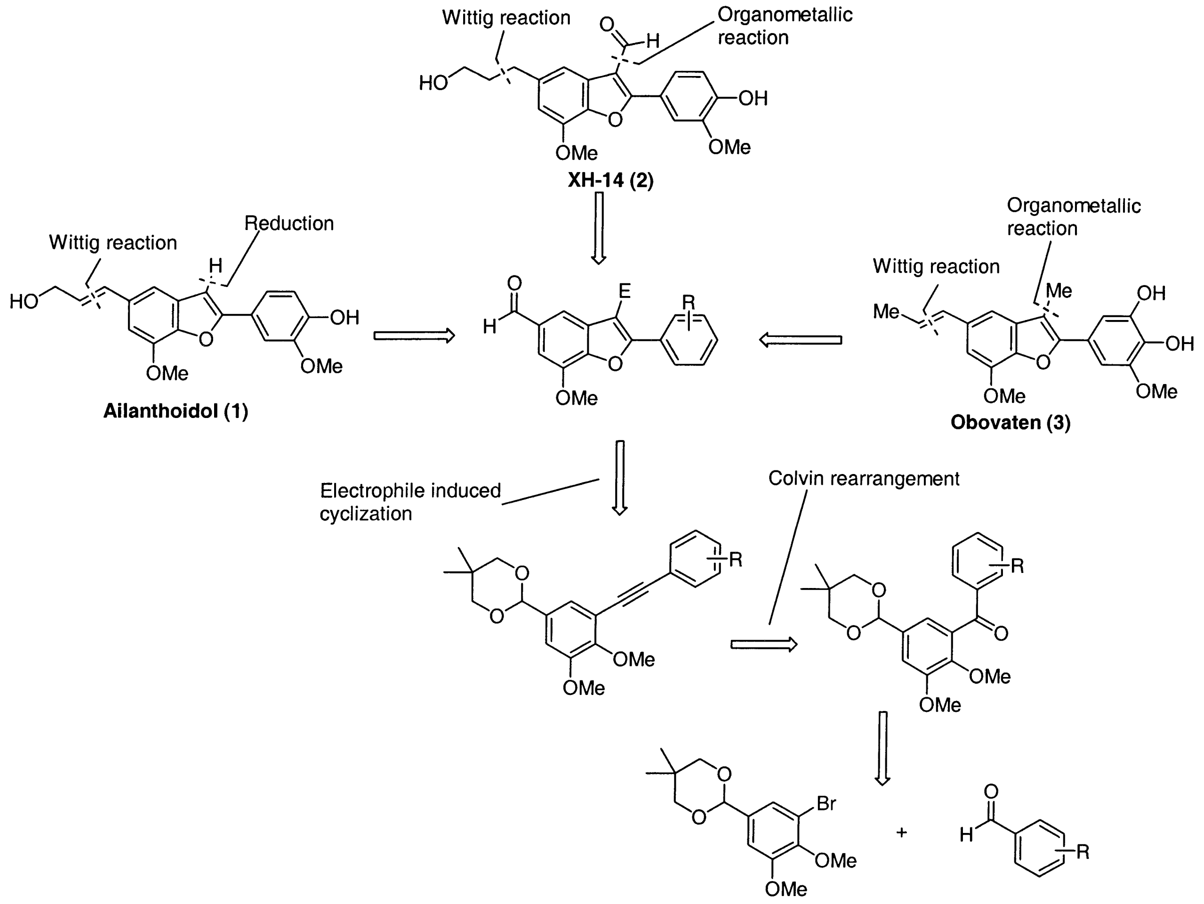

Ailanthoidol: R=4-hydroxy, 3-methoxy; G= H, A=OH
XH-14 : R=4-hydroxy, 3-methoxy; G= formyl, A=OH
obovaten : R=3,4-hydroxy, 5-methoxy; G=methyl, A=OH

FIGURE 1. Retrosynthetic analysis.

lithium salt of trimethylsilyldiazomethane in Colvin rearrangement.[26] Treatment of the resulting substituted diphenylacetylene with electrophiles will then induce cyclization with simultaneous removal of the *o*-methoxy group and afford the 2-substituted phenyl-3-chloromercuriobenzofuran derivatives.[27] Consequently, the choice of methyl group for protection of the *o*-hydroxy group allows the application of a wider range of reaction conditions in the subsequent steps because it provides greater stability than other ether-type protective groups. The chloromercurio group at the 3-position can be explored to introduce versatile substituents by adding a suitable electrophile to afford the desired functional group. In addition, the aldehyde group at the 5-position obtained after deprotection of the acetal group can be further derivativized.[28] Thus, the designed intermediate depicted in Figure 1 by a variation of functional group at the 3- and 5-position is able to enroll diverse reactions to give the desired target compounds. In a preliminary study,[29] we reported that mercury acetate could be utilized for the cyclization of the substituted diphenylacetylene and the resulting chloromercurio group could be further reduced to a proton. In addition, the aldehyde group could be transformed to a 3-hydroxypropenyl group through the Wittig reaction. This successful result prompted us to investigate the general application of this methodology for the preparation of other neolignans. Here we report an efficient and convenient general strategy for the synthesis of compounds of this type. To the best of our knowledge, this is the first report of the total synthesis of obovaten (**3**).

Results and Discussion

Synthesis of Key Intermediate 2-Substituted Phenyl-3-chloromercuriobenzofuran Derivatives. We began with the preparation of the benzophenone derivatives. 1-Bromo-2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)benzene (**7**) was prepared starting from vanillin (**4**) following the procedure in the literature.[30] A treatment of the dimethylpropandiol and methylated product **6**, which was obtained from the methylation of 3-bromo-4-hydroxy-5-methylbenzaldehyde (**5**) with meth-

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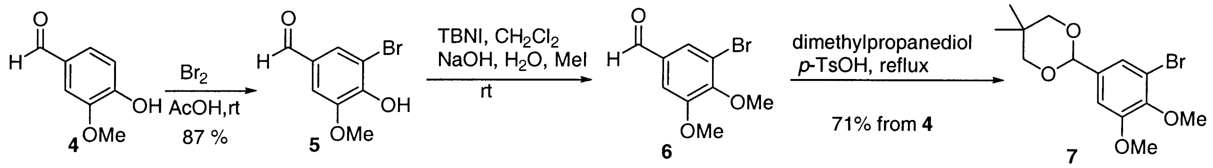
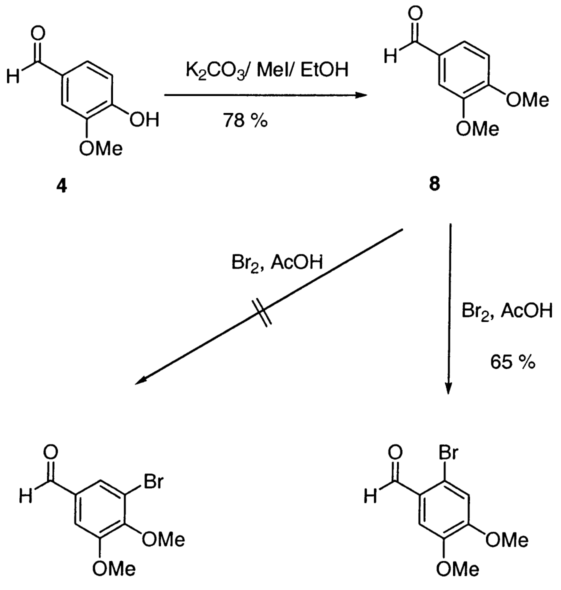
SCHEME 1



SCHEME 2



yl iodide in the presence of tetrabutylammonium iodide (TBNI)[31] as catalyst, with a catalytic amount of *p*-toluenesulfonic acid in benzene to afford compound **7** in 71% yield in one pot. However, an investigation on direct methylation of **5** with methyl iodide under other conditions was unsuccessful.[32] The failure of this approach may be due to the lower nucleophilicity of **5** in the polar solvent[33] (Scheme 1). It should be noted that when compound **8**, which was obtained from methylation of **4** with methyl iodide in the presence of potassium carbonate in ethanol, was treated with bromine in acetic acid, the result was a 65% yield of 2-bromo-4,5-dimethoxybenzaldehyde (**9**) instead of the expected **6** (Scheme 2).[34]

Compound **7** was treated with *n*-BuLi and then coupled with 4-benzyloxy-3-methoxybenzaldehyde (**10**) to give 1-(4-benzyloxy-3-methoxyphenyl)-1-(2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl)carbinol (**11**) in 77% yield. Two minor products have been isolated from this reaction and fully characterized as 1,2-dimethoxy-4-(5,5-dimethyl-1,3-dioxan-2-yl)benzene (**12**) and 1-*n*-butyl-2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)benzene (**13**). Compound **12** is the debrominated product of **7**, while compound **13** may be the result of the S_N2 reaction of **7** with *n*-BuLi via lithium−halogen exchange. The yield of these side products is related to the reactivity of the substituted benzaldehyde, the reaction temperature, and the concentration of the two starting materials. Preliminary investigation showed that the use of low concentrations of starting materials and slow addition rates reduce the amount of side products.

Oxidation of **11** with manganese oxide furnished 4-benzyloxy-3-methoxyphenyl 5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl ketone (**14**) in 96% yield. Compound **14** was then treated with trimethylsilyldiazomethane lithium salt at −78 °C to give the key intermediate, 1-(4-benzyloxy-3-methoxyphenyl)-1-(2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl)acetylene (**15**) in 98% yield via a Covlin rearrangement. Compound **15** was treated with mercury acetate in acetic acid and then quenched with saturated sodium chloride solution to afford a quantitive yield of 2-(4-benzyloxy-3-methoxyphenyl)-3-chloromercurio-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**16**).

Synthesis of Ailanthoidol. Since we had the key intermediate **16** in hand, we used it to synthesize ailanthoidol (**1**) as a model study. The chloromercurial intermediate **16** was isolated without further purification and then treated with $NaBH_4$ in THF to afford **17** in 85% yield. The catalytic hydrogenation of **17** afforded a debenzylated product in 88% yield, which was subsequently deacetylated in a mixture of acetone and 6 *N* hydrochloric acid to provide **18** in 72% yield. When these two reactions were carried out in the reverse order, the resulting product was 2-(4-hydroxy-3-methoxyphenyl)-5-hydroxymethyl-7-methoxybenzofuran, an unexpected over-reductive product accomplished with reduction of the aldehyde group, instead of the desired product **18**. Finally, elongation of the side chain at the 5-position of **18** via the Wittig reaction gave 2-(4-benzyloxy-3-methoxyphenyl)-7-methoxy-5-(carbethoxy-1-propen-1-yl)benzofuran (**19**), which was then treated with DIBAL-H to afford the target compound **1** in 97% yield (Scheme 4).

To facilitate the Pd-promoted cyclization in this strategy, it is necessary to replace the methoxy group at the ortho-position of **15** with a free hydroxyl group. Therefore, compound **4** was directly treated with dimethylpropandiol to give 2-bromo-6-methoxy-4-(5,5-dimethyl-1,3-dioxan-2-yl)phenol (**20**), which was then reacted with **10** in the presence of 2 equiv of *n*-BuLi to furnish (4-benzyloxy-3-methoxyphenyl)-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2-hydroxy-3-methoxyphenyl)carbinol (**21**) in 72% yield. However, the subsequent attempt to oxidize **21** with MnO_2 was unsuccessful. This reaction gave several inseparable products, of which the only identified product was 4-benzyloxy-3-methoxybenzaldehyde (**10**). Compound **10** is possibly formed through the reverse aldol reaction. Further unsuccessful attempts were made for oxidation of **21**, utilizing different kinds of deprotonative oxidative reagents including PCC, DDQ, Dess−Martin reagent, Mofft oxidation, and Swern oxidation, as well as a different reaction involving active palladium in air. All

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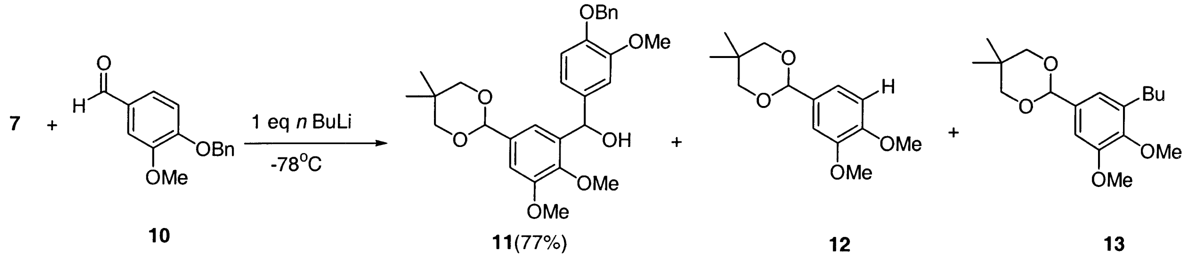
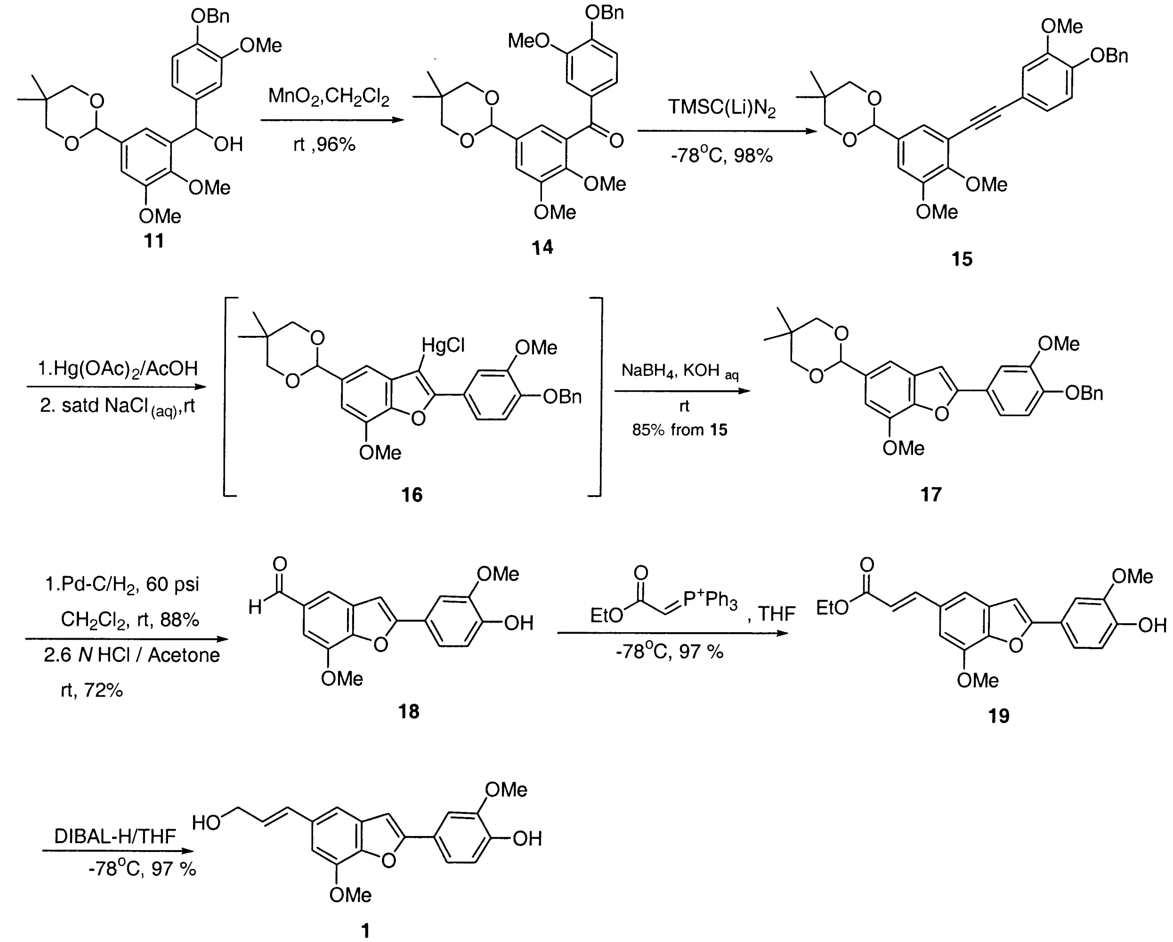
SCHEME 3



SCHEME 4

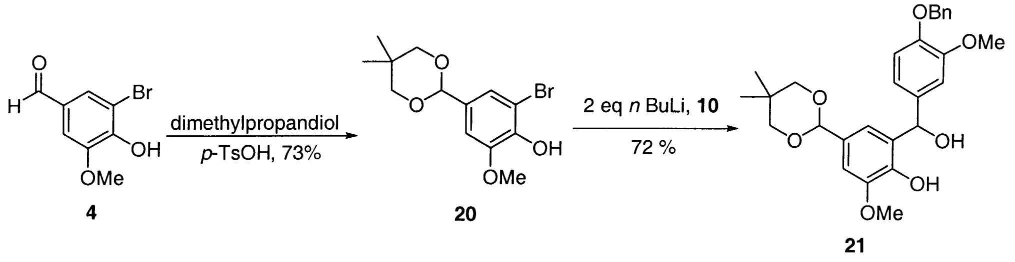


of these reactions gave **10** as the only identified product along with some other inseparable products. Given that the deprotonation process is the key step in oxidative reactions, the more acidic proton should be a better reactive center than the other one. This result ruled out the possibility of applying organopalladium chemistry in this strategy.

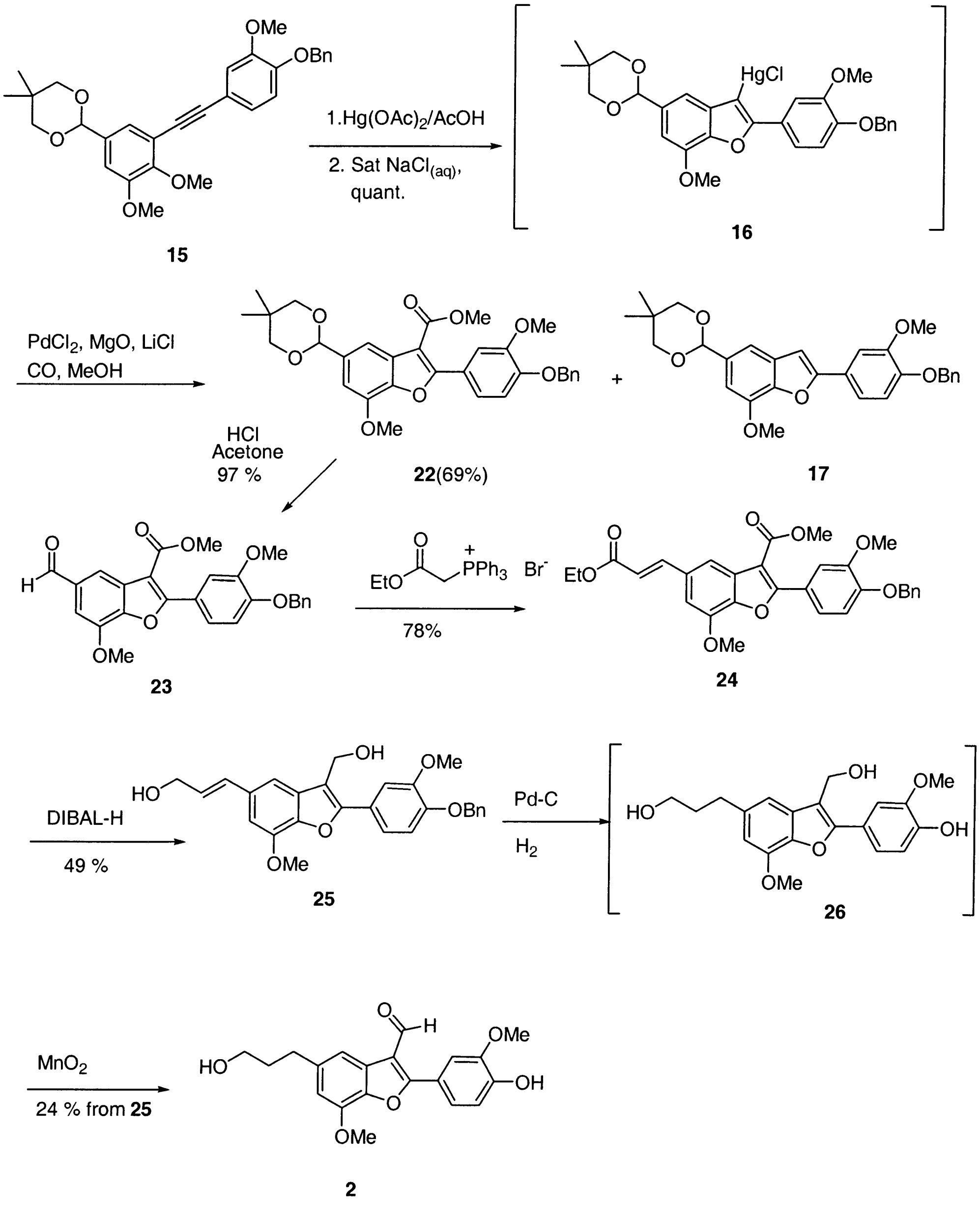
Synthesis of XH-14. We aimed to synthesize XH-14 (**2**) by conferring a formyl group at the 3-position of **16**. The strategy proposed for achieving this was the initial introduction of an ester group followed by reduction and then oxidation. To introduce the ester group at the 3-position, **16** was treated with a stoichiometric amount of $PdCl_2$, 2 equiv of MgO, and LiCl under a carbon monoxide balloon in methanol at room temperature to give 2-(4-benzyloxy-3-methoxyphenyl)-3-methoxycarbonyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**22**) in 69% yield for the two steps accompanied by a small amount of 2-(4-benzyloxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**17**) as side product. Acidic hydrolysis of **22** with hydrochloric acid furnished 2-(4-benzyloxy-3-methoxyphenyl)-7-methoxybenzofuran-5-carboxaldehyde (**23**) in 97% yield. Subsequent condensation of **23** with (carbethoxymethyl)-triphenylphosphonium bromide lithium salt afforded 2-(4-benzyloxy-3-methoxyphenyl)-3-methoxycarbonyl-7-methoxy-5-(carbethoxy-1-propen-1-yl)benzofuran (**24**) in 78% yield, which was then treated with DIBAL-H to give 2-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-5-(3-hydroxy-1-propen-1-yl)benzofuran (**25**) in 49% yield. The following catalytic hydrogenation and then selective oxidation with manganese oxide of the hydroxy group at the 3-position successfully furnished XH-14 (**2**) in 24% yield (Scheme 6).

Synthesis of Obovaten. The successful synthesis of ailanthoidol and XH-14 encouraged us to apply the same

SCHEME 5



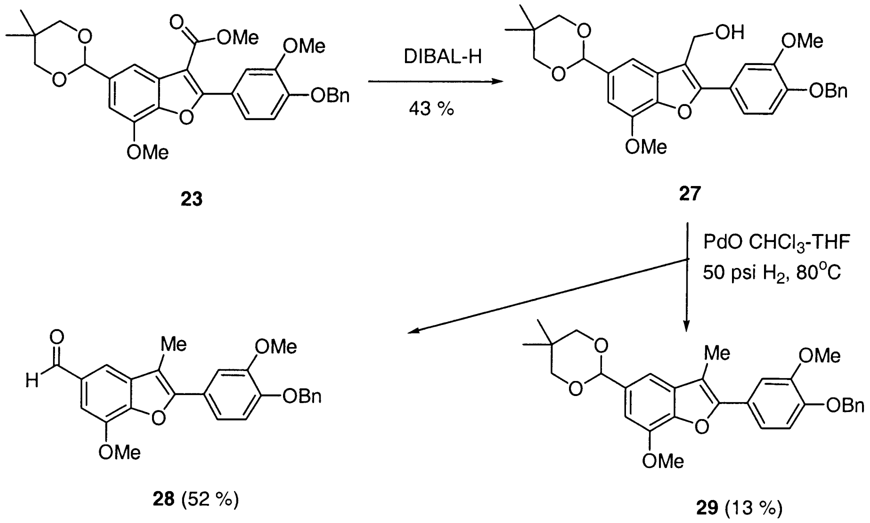
SCHEME 6



approach to the preparation of obovaten (**3**). To introduce a methyl group at the 3-position, 2-(4-benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**27**), obtained from the reduction of **23** in the presence of DIBAL-H, was treated with palladium oxide in $CHCl_3$ under 50 psi of hydrogen gas at 80 °C to afford 2-(4-benzyloxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxy-3-methylbenzofuran (**29**) in 13% yield and 2-(4-benzyloxy-3-methoxyphenyl)-3-methyl-7-methoxybenzofuran-5-carbaldehyde (**28**) as the major product (52%), which was formed from the further deprotection of **29** (Scheme 7).

The synthetic approach for the preparation of 2-(3,4-dibenzyloxy-5-methoxyphenyl)-1-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)acetylene (**33**) is similar to the procedure used to obtain **15**. 3,4-Dibenzyloxy-5-

SCHEME 7



methoxybenzaldehyde (**30**), which was obtained in 98% yield from benzylation of 3,4-dihydroxy-5-methoxybenzaldehyde with benzyl bromide and potassium carbonate in dimethylacetamide, were coupled with **7** in the presence of 1 equiv of *n*-BuLi to furnish 2-(3,4-dibenzyloxy-5-methoxyphenyl)-1-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)carbinol (**31**) in 77% yield. The key intermediate, 1-(3,4-dibenzyloxy-5-methoxyphenyl)-1-(2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl)-acetylene (**33**) was obtained in 99% yield via Colvin rearrangement of the corresponding ketone (**32**), which was prepared in 96% yield by oxidation of **31** in the presence of MnO_2. Remarkably, no side product was observed in the coupling reaction between **7** and **30**, in contrast to the coupling reaction between **7** and **10**, which formed the side products **12** and **13**. Exposure of **33** to mercury acetate in acetic acid provided 2-(3,4-dibenzyloxy-5-methoxyphenyl)-3-chloromercurio-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**34**), which was then subjected to Pd-catalyzed carboxylation. However, The carboxylation reaction in the mixture of $PdCl_2$, MgO, and LiCl was unsuccessful in this case. The demercurated product (**35**) was isolated as a single product in 89% yield and none of the desired product, 2-(3,4-dibenzyloxy-5-methoxyphenyl)-3-methylcarbmethyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**36**), was isolated (Scheme 8).

Alternatively, the chloromercurio **34** was treated with a stoichiometric amount of bromine in $CHCl_3$ to provide 2-(3,4-dibenzyloxy-5-methoxyphenyl)-3-bromo-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**37**) in 64% yield. We found that the reaction conditions were crucial to the successful preparation of **37**. For example, higher reaction temperature and longer reaction times dramatically decreased the yield of product and give complicated results. Methylation of **37** with methyl iodide was performed in the presence of *n*-BuLi to give 2-(3,4-dibenzyloxy-5-methoxyphenyl)-3-methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (**38**) in 90% yield. The acetal group in **38** was then deprotected by hydrochloric acid in acetone to afford 2-(3,4-dibenzyloxy-5-methoxyphenyl)-3-methyl-7-methoxybenzofuran-5-carbaldehyde (**39**). The olefination of **39** with ethyltriphenylphosphine iodide gave **40**, which was then treated with borontribromide to cleave the benzyloxy ether linkage at low temperature to give compound **3** in 31% yield from the last two steps (Scheme 9).

Preparation of 3-Bromobenzofuran by Bromocyclization of Diphenylacetylene. In this mercury acetate induced cyclization, we overcome the regioselectivity at the 3-position and improve the reproducibility of cyclization. The advantage of the organomercury compound is its stability, which makes the chloromercurio intermediate easy to handle and means that the disadvantages of this synthetic route should be considered. This approach requires a stoichiometric amount of palladium chloride, which is an expensive material in comparison to other reagents. In addition, the toxicity of organomercury reagents may restrict future applications of this method. For these reasons, it would be worthwhile to develop an alternative reagent that can be used instead of mercury acetate. In this cyclization process, intramolecular alkoxymercuration of acetylene is assumed to proceed through a two-electron, three-center mercurinium ion. Due to the stability of the mercury-stabilized cation,[35] the oxymercuration reaction gave an oxonium ion instead of any rearrangment and the following demethylation procedure afforded the desired benzofuran skeleton. On the basis of this proposed mechanism, we conjectured that other electrophilic reagents might undergo this kind of reaction. Despite the lower reactivity of bromonium ion in comparison to mercurinium ion,[36] we believed that the bromine would be an alternative reagent for the cyclization, and directly provided 3-bromobenzofuran derivatives. The bromide planted on the 3-position could be used for various reactions via facile transformation into a variety of products (Scheme 10).

To test the synthesis with bromine, compound **15** was treated with bromine in chloroform at −15 °C giving a mixture of **41** and **42**. However, when the mixture was treated with hydrochloric acid it afforded **42** in 95% yield from **15**. Elongation of compound **42** with ethoxycarb-

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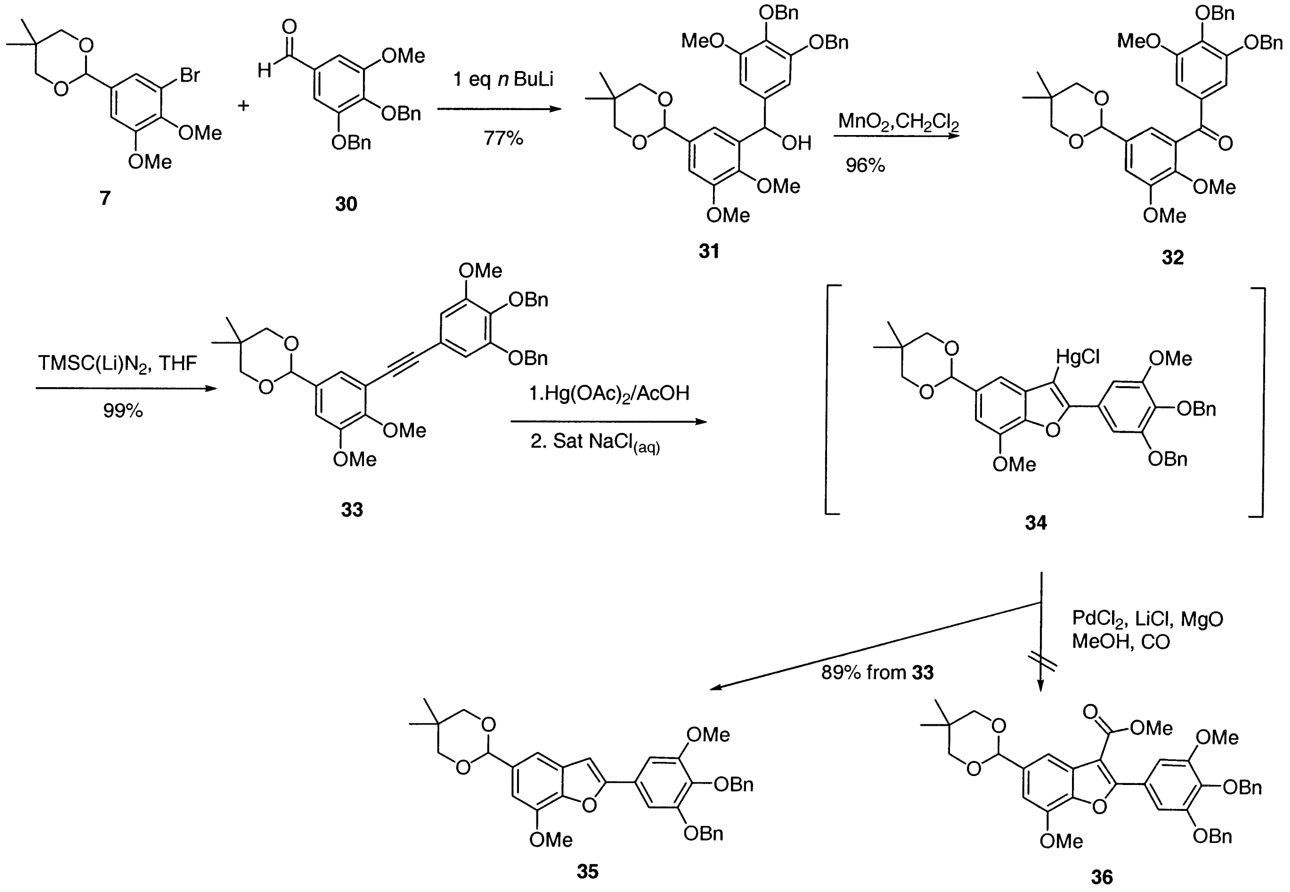
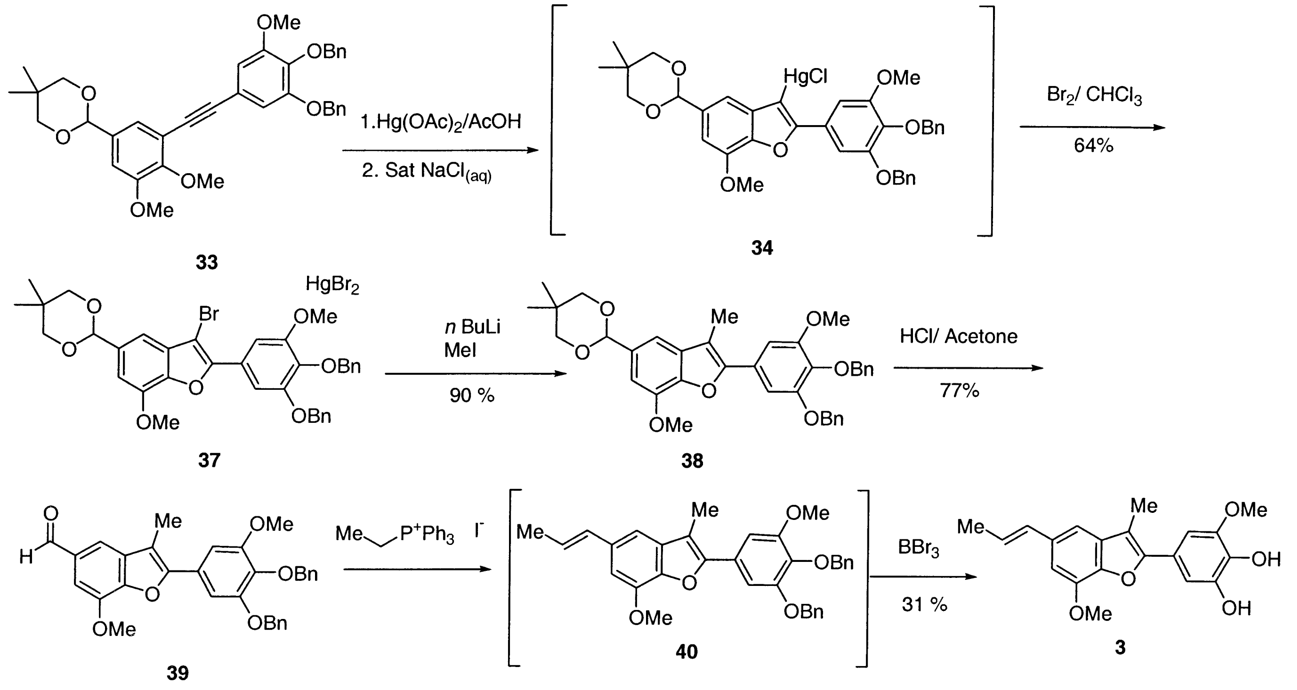
(36) Carey, F. A.; Sundberg, R. J. *Acvanced Organic Chemistry. Part A: Structure and mechanisms*, 3rd ed.; Plenum Press: New York, 1990; p 361.

SCHEME 8

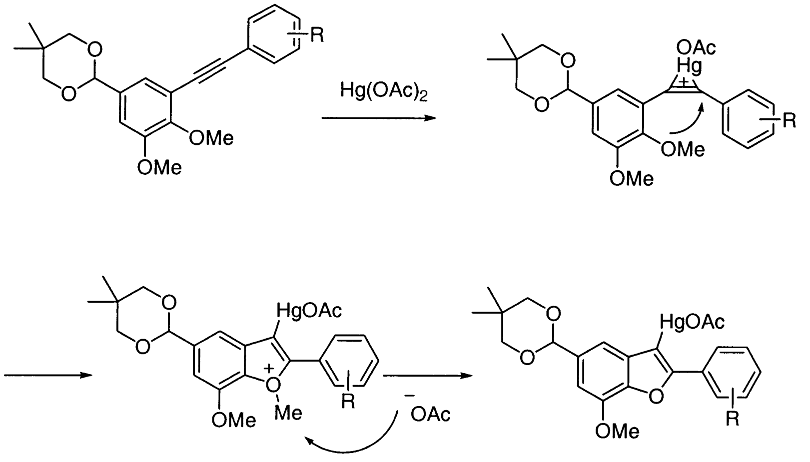


SCHEME 9

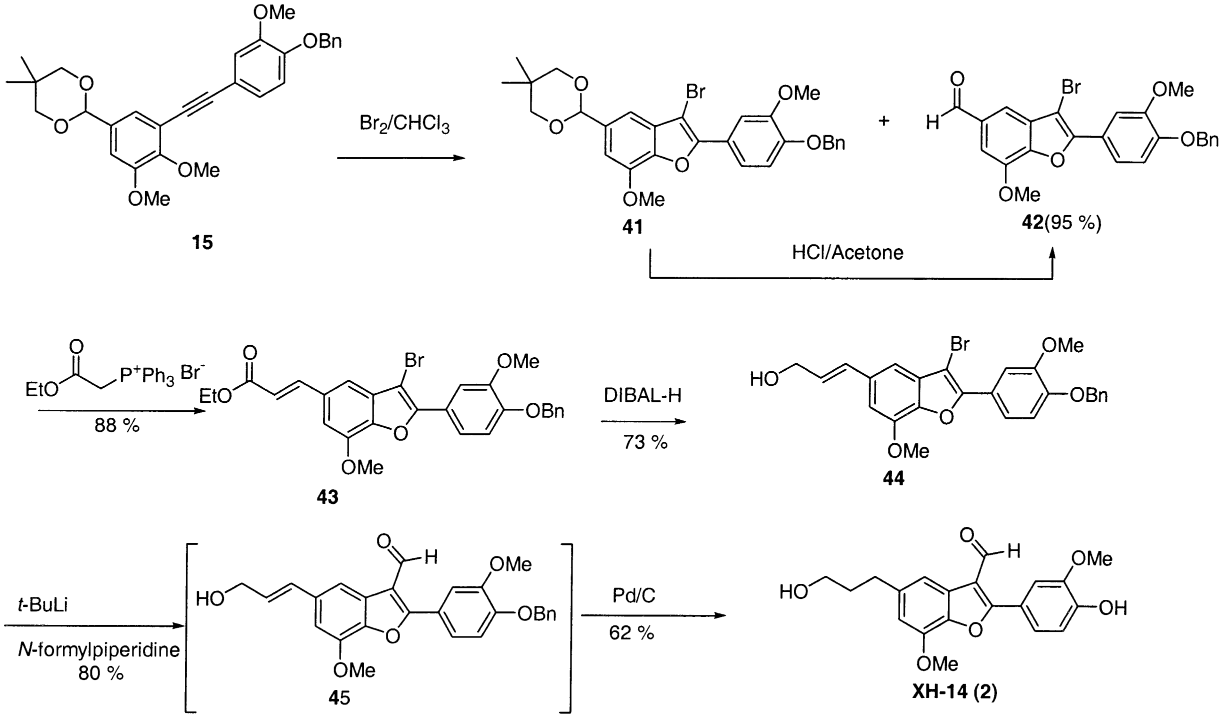


methyltriphenylphosphine bromide in THF afforded **43** in 88% yield. Reduction of **43** with DIBAL-H gave **44** in 73% yield, which was treated with 5 equiv of *t*-BuLi and then coupled with 5 equiv of *N*-formylpiperidine to furnish **45**. The formylated compound **45**, without purification, was reduced with activated palladium under hydrogen to afford the desired XH-14 (**2**) in 62% yield. It is noteworthy that the halogen−lithium exchange will only occur in the presence of five or more equivalents of *t*-BuLi. In addition, when *n*-BuLi was used instead of

SCHEME 10



SCHEME 11

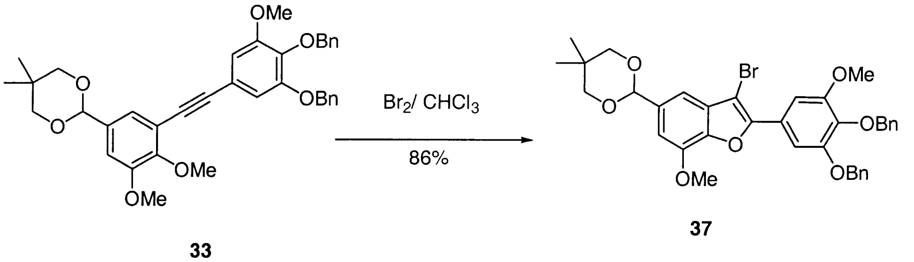


t-BuLi, the debrominated compound was isolated as major product and a trace amount of 3-butylbenzofuran was obtained as minor product. Besides, an attempt to apply *N*,*N*-dimethylformamide instead of *N*-formylpiperidine was unsuccessful.

After the successful synthesis of XH-14 (**2**) through the bromine-promoted cyclization of **15**, we applied this method to the preparation of the key intermediate **37** which led to the synthesis of obovaten. To develop an efficient process for the preparation of obovaten, compound **33** was subjected to the same conditions, which previously afforded compound **41**. As expected, **37** was obtained as the sole product without removing the acetal group at the 5-position. This result suggests that the 5-acetal group is stable in this skeleton and further implies that the substituted phenyl ring at the 2-position may have certain influence on the electronic properties of the 5-position (Scheme 12).

In conclusion, a novel strategy for constructing 2-phenylbenzofuran skeletons has been established. TMSC(Li)-N_2-induced Colvin rearrangement of benzofuran derivatives provided substituted diphenylacetylenes as key intermediates. Mercury acetate-induced or bromine-induced cyclization of these intermediates affords the corresponding 3-chloromercurio- or 3-bromobenzofurans, respectively. Reduction of 3-chloromercuriobenzofuran with sodium borohydride gave compound **17**, a precursor of ailanthoidol. Subsequently, the 3-chloromercurio group could be utilized to introduce a variety of functional groups at the 3-position of the benzofuran skeleton, for example the ester group or methyl group. Transformation of the functional group from 3-bromide to the formyl group or methyl group was achieved. However, the total yield of the reactions proceeding via bromine-induced cyclization was higher than that with mercury acetate. The syntheses of ailanthoidol (**1**), XH-14 (**2**), and obovaten

SCHEME 12



(**3**) starting from vanillin gave the excellent total yields of 30, 15, and 11%, respectively. As hoped, the strategy developed here can be generalized to other benzofuran systems. In addition to the development of new synthetic strategies, the successful synthesis of XH-14, obovaten, and ailanthoidol opens the way for the construction of designed 2-phenylbenzofurans for biological investigation of these natural products. By this approach, analogue preparation and screening should be accelerated to facilitate further detailed biological study of this family of compounds.

Experimental Section

General Methods. Analytical samples were homogeneous by thin-layer chromatography (TLC) and afforded spectroscopic data which were consistent with the assigned structures. The dried solvents were either heated to reflux in situ or stored in a freezer. The *n*-BuLi and *t*-BuLi were titrated by α,α-diphenylacetic acid prior to use. Moisture-sensitive reactions were performed in predried glassware (in an oven at 100 °C over 24 h) under an inert atmosphere of argon.

1-Bromo-2,3-dimethoxy-5-(5,5-dimethyl-1,3-dioxan-2-yl)benzene (7). To a solution of vanillin (26.71 g, 175.6 mmol) in glacial acetic acid (300 mL) was added a solution of Br_2 (20 mL, 388.8 mmol) in acetic acid (30 mL) dropwise over 1 h at 0 °C. After the addition, the resulting solution was stirred at 0 °C for 1 h and at room temperature for 25 h. After removal of acetic acid with the assistance of toluene, the resulting red mixture was washed with EtOH. A green solid was recrystallized from EtOH to give **5** (36.43 g). Mp 156−158 °C [lit.[37] mp 158 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 6.57 (br s, 1 H), 7.34 (d, $J = 2$ Hz, 1 H), 7.61 (d, $J = 2$ Hz, 1 H), 9.76 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.9, 108.0, 108.2, 130.0, 130.1, 147.7, 148.9, 189.6; MS (EI, 70 eV) *m/z* 230 (M^+, 100%), 232 ($M + 2^+$, 100%). Compound **5** (36.43 g, 24.0 mmol) was dissolved in CH_2Cl_2 (600 mL) and $NaOH_{(aq)}$ (12.84 g in 200 mL of water) was added. To the resulting solution was added tetrabutylammonium iodide (12.92 g) with stirring at room temperature until the solid disappear. To the reaction mixture was added methyl iodide (18 mL, 291.0 mmol) with stirring at room temperature for 30 h. The reaction mixture was neutralized by 6 N HCl solution and the resulting solution was extracted with CH_2Cl_2 (200 mL × 5). The combined organic layer was washed with brine (300 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was washed with 2-propanol and the solid was recrystallized from 2-propanol to give **6**. Mp 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 3.92 (s, 3 H), 3.76 (d, $J = 2$ Hz, 1 H), 7.62 (d, $J = 2$ Hz, 1 H), 9.81 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 61.3, 110.7, 118.4, 129.2, 133.5, 152.3, 157.7, 190.4; MS (EI, 70 eV) *m/z* 246 ($M^+ + 2$, 100%), 244 (M^+, 100%). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 43.98; H, 3.76. To the bottle containing **6** was added 2,2-dimethylpropan-1,3-diol (63.81 g, 613.6 mmol), *p*-toluenesulfonic acid (11.80 g, 62.1 mmol), and benzene (250 mL), respectively. The resulting solution was heated at reflux with Dean−Stark apparatus for 26 h and then partitioned between CH_2Cl_2 (500 mL) and water (300 mL). The aqueous layer was extracted with CH_2Cl_2 (200 mL × 3). The combined organic layer was washed with brine (500 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow liquid. The liquid was purified by column chromatography (silica gel: ϕ 5 × 13.5 cm; eluent: Hex/EA = 7/3). The desired fraction ($R_f = 0.53$, Hex/EA = 3/1) was collected and the solvent was evaporated. The solid was recrystallized from 2-propanol to yield **7** (40.93 g, 71%). Mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 1.26 (s, 3 H), 3.61 (d, $J = 11$ Hz, 2 H), 3.74 (d, $J = 11$ Hz, 2 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 5.29 (s, 1 H), 7.00 (d, $J = 2$ Hz, 1 H), 7.27 (d, $J = 2$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.5, 30.7, 56.5, 61.0, 78.1, 101.0, 110.0, 117.9, 123.1, 136.0, 147.2, 154.1; MS (EI, 70 eV) *m/z* 251 (100%), 330 (M^+, 39%), 332 ($M^+ + 2$, 39%). Anal. Calcd for $C_{14}H_{19}BrO_4$: C, 50.77; H, 5.78. Found: C, 50.63; H, 5.83.

3,4-Dimethoxybenzaldehyde (8). To a solution of vanillin (6.73 g, 44.2 mmol) in EtOH (150 mL) was added K_2CO_3 (13.24 g, 96.0 mmol) with stirring until the solid disappear. To the resulting solution was added the methyl iodide (3.5 mL) in several portions. After being stirred at room temperature for 10 h, the solution was concentrated in vacuo to remove EtOH. The resulting mixture was partitioned between CH_2Cl_2 (150 mL) and water (100 mL). The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). The combined organic layer was washed with brine (100 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 3.5 × 12 cm; eluent: Hex/EA = 3/1). The desired fraction ($R_f = 0.72$, Hex/EA = 3/1) was collected and the solvent was evaporated to give a solid that was recrystallized from EtOH to obtain **8** (5.71 g, 78%). Mp 53−55 °C [lit.[38] mp 54−56 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3 H), 3.90 (s, 3 H), 6.92 (d, $J = 8$ Hz, 1 H), 7.34 (d, $J = 2$ Hz, 1 H), 7.40 (dd, $J = 8$ Hz, 2 Hz, 1 H), 9.79 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 56.5, 109.4, 110.8, 127.2, 130.5, 150.0, 154.9, 191.2, 191.3; HRMS calcd for $C_9H_{10}O_3$ 166.0630, found 166.0630.

2-Bromo-4,5-dimethoxybenzaldehyde (9). To a solution of **8** (5.71 g, 34.2 mmol) in glacial acetic acid (50 mL) was added a solution of Br_2 (2.5 mL, 48.6 mmol) in acetic acid (50 mL) dropwise over 5 h at 0 °C. After the addition was finished, the resulting solution was stirred at 0 °C for 1 h and at room temperature for 16 h. After azeotropic removal of acetic acid with toluene, the resulting green mixture was purified by column chromatography (silica gel: ϕ 4.5 × 12.5 cm; eluent: Hex/EA = 7/3). The desired fraction ($R_f = 0.51$, Hex/EA = 3/1) was collected and the solvent was evaporated to give a yellowish solid that was recrystallized from EtOH to obtain **9** (5.41 g, 65%). Mp 148−150 °C [lit.[39] mp 148−150 °C]; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 3.94 (s, 3 H), 7.03 (s, 1 H), 7.40 (s, 1 H), 10.17(s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 56.4, 110.4, 115.4, 120.3, 126.5, 148.7, 154.5, 190.7; MS (ESI) *m/z* 244 ($M + H^+$, 100%), 246 ($M + 2 + H^+$, 98%). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found C, 43.98; H, 3.76.

(4-Benzyloxy-3-methoxyphenyl)-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)carbinol (11), 4-(5,5-Dimethyl-1,3-dioxan-2-yl)-1,2-dimethoxybenzene (12), and 1-Butyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxybenzene (13). To a solution of **7** (4.48 g, 13.6 mmol) in THF (250 mL) was added *n*-BuLi (1.5 M, 10 mL) at −78 °C under argon. After the mixture was stirred at the same conditions for 1 h, to the resulting solution was added a solution of **10** (3.69 g, 15.2 mmol) in THF (150 mL) via cannula at −78 °C under argon. Without removal of the ice trap, the resulting solution was stirred under argon for 6 h. After being quenched with saturated $NH_4Cl_{(aq)}$ (50 mL), the resulting solution was partitioned between ether (300 mL) and water (10 mL). The organic layer was washed with saturated $NaHCO_{3(aq)}$ (30 mL), water (30 mL), brine (50 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 5 × 11 cm;, eluent: Hex/EA = 7/3). The slow moving fraction ($R_f = 0.20$, Hex/EA = 3/1) was collected and the solvent was evaporated to give yellowish solid that was recrystallized from the mixture of hexane and ethyl acetate (3/1) to yield compound **11** (4.71 g, 77%). Mp 69−71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.26 (s, 3 H), 3.12 (s, 1 H, exchangeable proton), 3.53 (s, 3 H), 3.58 (d, J = 11.0 Hz, 2 H), 3.70 (d, J = 11.0 Hz, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 5.06 (s, 2 H), 5.29 (s, 1 H), 5.91 (s, 1 H), 6.74 (s, 2 H), 7.00 (s, 1 H), 7.05 (d, J = 2 Hz, 1 H), 7.12 (d, J = 2 Hz, 1 H, exchangeable proton), 7.23 (d, J = 8 Hz, 1 H), 7.30 (t, J = 8 Hz, 2 H), 7.38 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.1, 30.2, 55.6, 56.0, 60.4, 71.1, 71.6, 101.5, 109.4, 110.9, 114.1, 117.6, 119.0, 127.4, 127.7, 128.5, 134.4, 137.3, 137.4, 146.6, 147.3, 149.6, 152.5; MS (ESI) *m/z* 494 (M^+). HRMS calcd for $C_{29}H_{34}O_7$ 494.2305, found 494.2304. The fast moving fraction (R_f = 0.65, Hex/EA = 3/1) was collected and the solvent was evaporated to give **12** as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.26 (s, 3 H), 3.60 (d, J = 11 Hz, 2 H), 3.72 (d, J = 11 Hz, 2 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 5.30 (s, 1 H), 6.81 (d, J = 8 Hz, 1 H), 6.99−7.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 23.4, 30.5, 56.1, 56.2, 77.9, 102.0, 109.4, 111.1, 119.0, 131.7, 149.2, 149.7; MS (EI, 70 eV) *m/z* 252 (M^+, 100%), 221 (10%); HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1360. The fastest moving fraction (R_f = 0.65, Hex/EA = 3/1) was collected and the solvent was evaporated to give **13** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3 H), 0.90 (t, J = 7 Hz, 3 H), 1.28 (s, 3 H), 1.32−1.38 (m, 2 H), 1.51−1.57 (m, 2 H), 2.60 (t, J = 8 Hz, 2 H), 3.61 (d, J = 11 Hz, 2 H), 3.74 (d, J = 12 Hz, 2 H), 3.77 (s, 3 H), 3.86 (s, 3 H), 5.30 (s, 1 H), 6.89 (d, J = 2 Hz, 1 H), 6.92 (d, J = 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.8, 22.6, 23.1, 29.6, 30.1, 32.9, 55.6, 60.4, 77.6, 101.7, 107.6, 119.7, 133.9, 136.3, 147.4, 152.5; MS (EI, 30 eV) *m/z* 115 (28%), 308 (M^+, 67%), 309 (M + H, 100%); HRMS calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1982.

4-Benzyloxy-3-methoxyphenyl 5-(5,5-Dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl Ketone (14). To a solution of **10** (1.52 g, 3.1 mmol) in CH_2Cl_2 (70 mL) was added active MnO_2 (90%, 6.03 g). After the mixture was stirred at the same conditions for 15 h, the resulting solution was filtered through Celite 545 to give a yellowish liquid. The mixture was purified by column chromatography (silica gel: ϕ 4.5 × 10 cm; eluent: Hex/EA = 7/3). The desired fraction (R_f = 0.26, Hex/EA = 3/1) was collected and the solvent was evaporated to give colorless oil. The white foam was generated in vacuo to give **14** (1.43 g, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.24 (s, 3 H), 3.59 (d, J = 11 Hz, 2 H), 3.69 (s, 3 H), 3.71 (d, J = 11 Hz, 2 H), 3.89 (s, 6 H), 5.15 (s, 2 H), 5.32 (s, 1 H), 6.79 (d, J = 9 Hz, 1 H), 7.00 (s, 1 H), 7.19 (s, 1 H), 7.21 (d, J = 2 Hz, 1 H), 7.26 (d, J = 4 Hz, 1 H), 7.32−7.34 (m, 2 H), 7.38 (d, J = 8 Hz, 2 H), 7.55 (d, J = 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.2, 23.4, 30.5, 56.2, 56.4, 71.1, 78.0, 101.3, 101.3, 111.7, 111.9, 112.3, 118.7, 126.4, 127.6, 128.4, 129.0, 131.0, 134.3, 134.8, 136.6, 147.3, 149.8, 152.9, 153.0, 194.8; MS (ESI) *m/z* 493 ($M + H^+$). Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.31; H, 6.67.

1-(4-Benzyloxy-3-methoxyphenyl)-2-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)acetylene (15). To a solution of trimethylsilyldiazomethane (2.0 M, 2 mL) in THF (30 mL) was added *n*-BuLi (1.5 M, 2.5 mL) at −78 °C under argon. After the mixture was stirred for 30 min at the same conditions, the resulting lithium salt solution was added to the solution of **14** (0.98 g, 2.0 mmol) in THF at −78 °C under argon via cannula. After being stirred at −78 °C under argon for 5 h, the reaction mixture was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL). The resulting solution was partitioned between ether (150 mL) and water (10 mL). The organic layer was washed with saturated $NaHCO_{3(aq)}$ (20 mL), water (20 mL), and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 9 cm; eluent: Hex/EA = 3/1). The desired fraction (R_f = 0.34, Hex/EA = 3/1) was collected and the solvent was evaporated to give the white solid that was recrystallized from EtOH to yield **15** (958 mg, 98%). Mp 106−109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 3 H), 1.26 (s, 3 H), 3.59 (d, J = 11 Hz, 2 H), 3.73 (d, J = 11 Hz, 2 H), 3.84 (s, 6 H), 3.96 (s, 3 H), 5.10 (s, 2 H), 5.29 (s, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.05−7.07 (m, 3 H), 7.25−7.28 (m, 2 H), 7.32 (t, J = 7 Hz, 2 H), 7.39 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 22.0, 23.3, 30.3, 56.1, 61.1, 71.0, 77.8, 84.5, 93.8, 101.1, 110.7, 113.9, 115.0, 116.3, 118.0, 123.0, 125.1, 127.5, 128.1, 128.8, 134.6, 137.0, 148.9, 149.5, 150.6, 152.8; MS (ESI) *m/z* 489 ($M + H^+$). Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.76; H, 6.71.

2-(4-Benzyloxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (17). To a solution of **15** (7.84 g, 16.1 mmol) in glacial acetic acid (300 mL) was added $Hg(OAc)_2$ (6.51 g, 20.4 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h and room temperature for an additional 1 h. The resulting mixture was poured into an iced saturated NaCl solution (300 mL) with vigorous stirring. After the mixture was stirred until it warmed to room temperature, the resulting mixture was filtered and the residue was washed with water (100 mL) and hexane (20 mL). The residue was dried with the aid of air flow overnight. The residue was dissolved in boiling $CHCl_3$. The chloroform mixture was filtered through Celite 545. The filtrate was concentrated in vacuo to give **16**, which was used for the next step without further purification as a white solid in quantitative yield. To the solution of **16** (7.10 g, 10.0 mmol) in dry THF (200 mL) was added $NaBH_4$ (1.25 g, 32.8 mmol). After 12.5 h of being stirred at room temperature, the resulting solution was saturated by adding NaCl and stirred for another 30 min. The resulting reaction mixture was filtered through Celite 545 to give a solution with a green solid. The mixture was purified by column chromatography (silica gel: ϕ 4 × 10.5 cm; eluent: Hex/EA = 7/3). The desired fraction (R_f = 0.42, Hex/EA = 3/1) was collected and the solvent was evaporated to give a solid that was recrystallized from MeCN to obtain **17** (4.07 g, 85% from **15**). Mp 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 1.33 (s, 3 H), 3.67 (d, J = 11 Hz, 2 H), 3.79 (d, J = 11 Hz, 2 H), 3.97 (s, 3 H), 4.05 (s, 3 H), 5.17 (s, 2 H), 5.44 (s, 1 H), 6.85 (s, 1 H), 6.91 (d, J = 8 Hz, 1 H), 6.98 (s, 1 H), 7.30 (s, 2 H), 7.34−7.39 (m, 4 H), 7.44 (d, J = 8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.6, 30.7, 56.5, 56.7, 71.5, 78.2, 101.2, 102.6, 104.9, 109.2, 111.6, 114.5, 118.5, 124.3, 127.8, 128.4, 129.0, 131.3, 134.9, 137.3, 144.6, 145.5, 149.2, 150.3, 157.0; HRMS calcd for $C_{29}H_{30}O_6$ 474.2042, found 474.2042. Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 72.37; H, 6.37.

2-(4-Hydroxy-3-methoxyphenyl)-7-methoxybenzofuran-5-carbaldehyde (18). To a solution of **17** (1.75 g, 3.7 mmol) in CH_2Cl_2 (100 mL) was added active palladium (10%, 387.5 mg) with shaking in Parr-Shaker equipment under 60 psi of H_2 for 30 h. The reaction mixture was filtered through Celite 545 and the filtrate was concentrated to give a yellow oil. The mixture was purified by column chromatography (silica gel: ϕ 3.5 × 9.5 cm; eluted by Hex/EA = 6/4). The desired fraction (R_f = 0.15, Hex/EA = 1/1) was collected and the solvent was evaporated to give a solid that was recrystallized from EtOH to obtain 2-(4-hydroxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (1.25 g, 88%). Mp 183−185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.32 (s, 3 H), 3.67 (d, J = 11 Hz, 2 H), 3.79 (d, J = 11 Hz, 2 H), 3.96 (s, 3H), 4.05 (s, 3H), 5.44 (s, 1 H), 5.75 (s, 1 H, exchangeable), 6.83 (s, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.97 (s, 1 H), 7.29 (d, J = 2 Hz, 1 H), 7.38 (dd, J = 8, 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 23.6, 30.7, 56.5, 56.7, 78.3, 100.9, 102.6, 104.9, 108.1, 111.6, 115.1, 115.2, 119.4, 123.4, 131.3, 134.9, 144.5, 145.4, 146.9, 147.2, 157.2. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.77; H, 6.23. A solution of 2-(4-hydroxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran in acetone (100 mL) was added to $HCl_{(aq)}$ (6 N, 10 mL) and the mixture was stirred at room temperature for 5 h. The resulting solution was neutralized with $NaOH_{(aq)}$ (1 N, 60 mL) and the aqueous solution was extracted with $CHCl_3$ (200 mL × 2). The organic layer was washed with water (50 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give black oil. The mixture was subjected to column chromatography (silica gel: ϕ 3.5 × 8 cm; eluted by Hex/EA = 1/1) to give the product that was recrystallized from EtOH to yield **18** (792 mg, 72%). Mp 178−180 °C; ^1H NMR (400 MHz, acetone-d_6) δ 3.99 (s, 3 H), 4.07 (s, 3 H), 5.55 (s, 1 H, exchangeable proton), 6.81 (s, 1 H), 6.97 (s, 1 H), 7.15 (d, J = 8 Hz, 1 H), 7.22 (s, 1 H), 7.29 (d, J = 2 Hz, 1 H), 7.39 (dd, J = 8, 2 Hz, 1 H), 10.02 (s, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 56.7, 56.9, 105.0, 108.5, 111.6, 115.1, 115.2, 119.3, 123.3, 131.3, 134.9, 144.5, 145.4, 146.9, 147.3, 157.2, 191.1. HRMS calcd for $C_{17}H_{14}O_5$ 298.0841, found 298.0840.

2-(4-Hydroxy-3-methoxyphenyl)-5-(carbethoxyethylene)-7-methoxybenzofuran (19). To a solution of **18** (4.44 g, 14.9 mmol) in THF (250 mL) was added a solution of the lithium salt of carbethylmethyltriphenylphosphine bromide (6.76 g, 15.8 mmol) at −78 °C under argon. The resulting solution was stirred at −78 °C under argon for 1 h and room temperature for 5 h. After being quenched with saturated $NH_4Cl_{(aq)}$ (30 mL), the reaction mixture was partitioned between ether (150 mL) and water (20 mL). The organic layer was washed with water (50 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 3.5 × 13 cm; eluted by Hex/EA = 1/1). The desired fraction (R_f = 0.41, Hex/EA = 1/1) was collected and the solvent was evaporated to give a solid that was recrystallized from EtOH to yield **19** (325.6 mg, 97%). Mp 149−151 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 3.95 (s, 3H), 4.03 (s, 3H), 4.26 (q, J = 7 Hz, 2H), 5.90 (s, 1 H, exchangeable proton), 6.38 (d, J = 16 Hz, 1 H), 6.81 (s, 1H), 6.92 (s, 1H), 6.96 (d, J = 8 Hz, 1 H), 7.27 (s, 1H), 7.32 (d, J = 2 Hz, 1H), 7.37 (dd, J = 2, 8 Hz, 1 H), 7.72 (d, J = 16 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 56.5, 56.6, 60.9, 100.6, 105.6, 108.1, 114.9, 115.3, 117.3, 117.4, 119.5, 122.9, 131.0, 131.9, 145.6, 145.9, 147.1, 147.3, 157.8, 167.7. Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.63; H, 5.52.

2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxypropenyl)-7-methoxybenzofuran (1). To a solution of **19** (1.25 g, 3.0 mmol) in THF (120 mL) was added DIBAL-H (1.0 M in hexane, 6 mL) at −78 °C under argon. After being stirred at the same conditions for 2 h, the reaction was quenched with saturated $Na_2SO_4 \cdot 10H_2O_{(aq)}$ (30 mL). The resulting solution was partitioned between ether (200 mL) and water (20 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give yellow oil. The mixture was purified by column chromatography (silica gel: ϕ 3.5 × 13 cm; eluted by Hex/EA = 1/1). The desired fraction (R_f = 0.60, Hex/EA = 1/3) was collected and the solvent was evaporated to give a solid that was recrystallized from EtOH to yield **1** (325.6 mg, 97%). Mp 195−197 °C [lit.[3] mp 199−201 °C]; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 3.98 (s, 3 H), 4.13 (t, J = 5 Hz, 2 H), 4.83 (t, J = 5 Hz, 1 H), 6.37 (td, J = 5, 16 Hz, 1 H), 6.60 (d, J = 16 Hz, 1 H), 6.87 (dd, J = 1, 8 Hz, 1 H), 6.99 (s, 1 H), 7.16 (s, 1 H), 7.17 (d, J = 1 Hz, 1 H), 7.32 (dd, J = 2, 8 Hz, 1 H), 7.37 (s, 1 H), 9.41 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 61.6, 100.2, 104.4, 108.7, 110.9, 115.9, 117.9, 121.1, 129.1, 129.6, 130.8, 133.3, 142.5, 144.6, 147.7, 1148.0, 156.3; HRMS calcd for $C_{19}H_{18}O_5$ 326.1154, found 326.1154.

2-Bromo-6-methoxy-4-(5,5-dimethyl-1,3-dioxan-2-yl)-phenol (20). To the bottle with **4** (1.09 g, 4.8 mmol) was added 2,2-dimethylpropan-1,3-diol (2.37 g, 22.8 mmol), *p*-toluenesulfonic acid (165.2 mg, 0.9 mmol), and benzene (150 mL), respectively. The resulting solution was heated to reflux with Dean−Stark apparatus for 20 h. The resulting solution was partitioned between CH_2Cl_2 (100 mL) and water (20 mL). The organic layer was washed with water (20 mL × 5) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow liquid. The liquid was purified by column chromatography (silica gel: ϕ 3.5 × 15.5 cm; eluent: Hex/EA = 7/3). The desired fraction (R_f = 0.36, Hex/EA = 7/3) was collected and the solvent was evaporated to give **20** (1.10 g, 73%) as oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3 H), 1.25 (s, 3 H), 3.60 (d, J = 11 Hz, 2 H), 3.73 (d, J = 11 Hz, 2 H), 3.88 (s, 3 H), 5.26 (s, 1 H), 6.02 (br s, 1 H), 6.96 (s, 1 H), 7.22 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.5, 30.6, 56.8, 78.1, 101.2, 108.4, 123.2, 131.9, 143.9, 147.5; MS (ESI) *m/z* 317 ($M^+ + H$), 319 ($M^+ + 2 + H$); HRMS calcd for $C_{13}H_{17}BrO_4$ 316.0310, found 316.0311.

(4-Benzyloxy-3-methoxyphenyl)(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2-hydroxy-3-methoxyphenyl)carbinol (21). To a solution of **20** (1.57 g, 5.0 mmol) in THF (20 mL) was added *n*-BuLi (1.20 M, 4.5 mL) at −78 °C under argon. After the mixture was stirred at the same conditions for 70 min, the resulting solution was added to a solution of **10** (1.35 g, 5.6 mmol) in THF (20 mL) via cannula at −78 °C under argon. Without removal of the ice trap, the resulting solution was stirred under argon for 6 h. After the mixture was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL), the resulting solution was partitioned between ether (200 mL) and water (10 mL). The organic layer was washed with saturated $NaHCO_{3(aq)}$ (20 mL), water (30 mL), and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 12 cm; eluent: Hex/EA = 1/1). The desired fraction (R_f = 0.31, Hex/EA = 1/1) was collected and the solvent was evaporated to give **21** (1.72 g, 72%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.25 (s, 3 H), 3.31 (d, J = 3 Hz, 1 H), 3.56 (d, J = 11 Hz, 2 H), 3.69 (d, J = 11 Hz, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 5.23 (s, 1 H), 5.89 (d, J = 3 Hz, 1 H), 6.75 (br s, 3 H), 6.87 (d, J = 2 Hz, 1 H), 6.98 (d, J = 2 Hz, 1 H), 7.00 (br s, 1H), 7.25−7.27 (m, 1 H), 7.32 (t, J = 8 Hz, 2 H), 7.39 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 56.3, 71.4, 73.1, 78.0, 102.1, 102.2, 108.1, 111.1, 114.0, 118.3, 119.3, 127.6, 127.6, 128.1, 128.7, 128.8, 128.9, 130.4, 136.5, 137.6, 144.1, 147.3, 147.8, 149.8; HRMS calcd for $C_{28}H_{32}O_7$ 480.2149, found 480.2148. Anal. Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 69.81; H, 6.63.

(4-Benzyloxy-3-methoxyphenyl)-3-methylcarbonyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (22) and 2-(4-Benzyloxy-3-methoxyphenyl)-5-(5,5-dimethyl-

1,3-dioxan-2-yl)-7-methoxybenzofuran (17). Compound **16** prepared by the same approach as described in the preparation of **17** starting from **15** (7.84 g, 16.1 mmol) was used directly without further purification. To the bottle with MgO (240 mg, 6.0 mmol), $LiCl_2$ (216.4 mg, 2.8 mmol), and $PdCl_2$ (562.5 mg, 3.2 mmol) was added dry MeOH (80 mL) at −78 °C under CO. After the mixture was stirred at the same conditions for 30 min, to the resulting mixture was added **16** (2.18 g, 2.8 mmol) at the same conditions. The resulting solution was stirred at the same conditions for an additional 5 h. The reaction was quenched with active palladium (85 mg). The resulting mixture was filtered and the filtrate was concentrated in vacuo to remove MeOH. The residue was dissolved in ether (300 mL) and the mixture was washed with water (30 mL) and brine (50 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 11 cm; eluent: Hex/EA = 3/1). The slow moving band (R_f = 0.2, Hex/EA = 3/1) was collected and the solvent was evaporated. The solid was recrystallized from EtOH to yield **22** (1.04 g, 69%). Mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 1.34 (s, 3 H), 3.73 (d, J = 11 Hz, 2 H), 3.86 (s, 3 H), 3.86 (d, J = 11 Hz, 2 H), 3.92 (s, 3 H), 4.02 (s, 3 H), 5.21 (s, 2 H), 5.48 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.07 (s, 1 H), 7.24 (s, 1 H), 7.29 (d, J = 2 Hz, 1 H), 7.32 (dd, J = 2, 5 Hz, 2 H), 7.36 (t, J = 8 Hz, 2 H), 7.43 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.7, 30.0, 51.9, 56.0, 56.1, 70.8, 78.0, 102.9, 107.0, 109.0, 112.8, 113.0, 122.5, 122.9, 127.1, 127.9, 128.5, 131.2, 133.5, 136.4, 140.7, 143.0, 145.1, 148.8, 149.9, 162.0, 165.0; MS (FAB) m/z 532 (M^+). Anal. Calcd for $C_{31}H_{32}O_8\ HgCl_2$: C, 46.31; H, 4.01. Found: C, 46.25; H, 4.37. The fast moving band (R_f = 0.42, Hex/EA = 3/1) was collected and the solvent was evaporated. The solid was recrystallized from MeCN to yield **17** (12 mg, 9%).

2-(4-Benzyloxy-3-methoxyphenyl)-3-methylcarbonyl-7-methoxybenzofuran-5-carboxaldehyde (23). To a solution of **22** (705 mg, 1.3 mmol) in acetone (50 mL) was added $HCl_{(aq)}$ (6 N, 50 mL) and the mixture was stirred at room temperature for 4 h. The resulting black mixture was concentrated to remove acetone. The resulting solution was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layer was washed with saturated $NaHCO_{3(aq)}$ (30 mL), water (30 mL), and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 10 cm; eluent: Hex/EA = 3/1). The desired fraction (R_f = 0.37, Hex/EA = 3/1) was collected and the solvent was evaporated. The solid was recrystallized from EtOH to yield **23** (571 mg, 97%). Mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3 H), 3.97 (s, 3 H), 4.04 (s, 3 H), 5.22 (s, 2 H), 6.96 (d, J = 9 Hz, 1 H), 7.31 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 2 H), 7.38 (s, 2 H), 7.44 (d, J = 7 Hz, 2 H), 7.65 (dd, J = 2, 8 Hz, 1 H), 7.76 (d, J = 2 Hz, 1 H), 8.10 (s, 1 H), 10.03 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 56.6, 56.7, 71.3, 105.2, 108.8, 113.4, 113.5, 121.5, 122.0, 123.5, 127.7, 128.5, 129.1, 129.6, 134.6, 137.0, 146.3, 146.7, 149.5, 150.9, 162.7, 164.4, 192.3; HRMS calcd for $C_{26}H_{22}O_7$ 446.1366, found 446.1365.

2-(4-Benzyloxy-3-methoxyphenyl)-3-methylcarbonyl-5-(ethylcarbethenyl)-7-methoxybenzofuran (24). To a solution of **23** (316.7 mg, 0.7 mmol) in THF (100 mL) was added a solution of the lithium salt of carbethylmethyltriphenylphosphine bromide (330 mg 0.8 mmol) at −78 °C under argon. The resulting solution was stirred at −78 °C under argon for 3 h. After being quenched with saturated NH_4Cl (30 mL), the resulting solution was partitioned between ether (150 mL) and water (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 3.5 × 8 cm; eluted by Hex/EA = 2/1). The desired fraction (R_f = 0.45, Hex/EA = 3/1) was collected and the solvent was evaporated. The solid was recrystallized from EtOH to yield **24** (284.7 mg, 78%). Mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 4.27 (q, J = 7 Hz, 2 H), 5.22 (s, 2 H), 6.44 (d, J = 16 Hz, 1 H), 6.78 (dd, J = 2, 9 Hz, 1 H), 6.95 (d, J = 9 Hz, 1 H), 7.00 (s, 1 H), 7.30 (d, J = 7 Hz, 1 H), 7.36 (t, J = 8 Hz, 1 H), 7.44 (d, J = 7 Hz, 2 H), 7.73 (d, J = 2 Hz, 1 H), 7.76 (d, J = 4 Hz, 1 H), 7.80 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 50.3, 54.6, 54.7, 59.0, 69.4, 75.7, 104.4, 106.6, 111.5, 111.6, 114.6, 116.1, 120.5, 121.5, 125.7, 126.5, 127.1, 127.8, 130.0, 135.1, 142.6, 143.7, 147.5, 148.8, 160.2, 162.8, 165.5; MS (FAB) m/z 516. Anal. Calcd for $C_{30}H_{28}O_8$: C, 69.76; H, 5.46. Found: C, 69.70; H, 5.54.

2-(4-Benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-5-(3-hydroxyprop-1-en-1-yl)-7-methoxybenzofuran (25). To a solution of **24** (420.0 mg, 0.8 mmol) in THF (50 mL) was added a solution of DIBAL-H (1.0 M in CH_2Cl_2, 4 mL) at room temperature under argon. After the mixture was stirred at room temperature for 1.5 h, the reaction was quenched with saturated $Na_2CO_3{\cdot}10H_2O_{(aq)}$ (20 mL). The resulting mixture was partitioned between CH_2Cl_2 (150 mL) and water (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (silica gel: 4 × 9 cm; eluted by Hex/EA = 1/1). The desired fraction (R_f = 0.22, Hex/EA = 1/1) was collected and the solvent was evaporated. The solid was recrystallized from EtOH with drops of $CHCl_3$ to yield **25** (174 mg, 49%). Mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3 H), 4.00 (s, 3 H), 4.23 (s, 2 H), 4.70 (s, 2 H), 5.17 (s, 2 H), 6.30 (dt, J = 21, 6 Hz, 1 H), 6.62 (d, J = 16 Hz, 1 H), 6.83 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.20 (s, 1 H), 7.30 (d, J = 21 Hz, 1 H), 7.31 (s, 1 H), 7.33 (d, J = 2 Hz, 2 H), 7.43 (d, J = 7 Hz, 3 H); ^{1}H NMR (400 MHz, $CDCl_3$ + MeOH-d_4) δ 3.78 (s, 3 H), 3.85 (s, 3 H), 4.65 (s, 2 H), 5.01 (s, 2 H), 6.15 (dt, J = 16, 6 Hz, 1 H), 6.49 (d, J = 16 Hz, 1 H), 6.71 (s, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.08 (s, 1 H), 7.15 (d, J = 12 Hz, 1 H), 7.19 (d, J = 6 Hz, 3 H), 7.25 (d, J = 6 Hz, 1 H), 7.28 (d, J = 6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 54.6, 54.7, 62.3, 69.5, 103.6, 108.7, 109.5, 112.3, 112.5, 118.9, 121.7, 125.8, 126.1, 126.5, 127.1, 129.7, 130.2, 131.4, 135.3, 141.3, 143.6, 147.5, 148.3, 153.0; MS (FAB) m/z 446 (M^+). Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 71.60; H, 5.90.

2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran-3-carbaldehyde (2). To a solution of **25** (785 mg, 1.8 mmol) in EtOH (50 mL) was added active palladium (10%, 105 mg) and the mixture was stirred at room temperature for 15 h. After being filtered through Celite 545, the filtrate was concentrated in vacuo to give a brown oil. The oil was dissolved in CH_2Cl_2 (100 mL) and the solution was added to active MnO_2 (1.02 g, 90%) and stirred at room temperature for 5 h. The resulting solution was filtered through Celite 545. The filtrate was concentrated in vacuo to give a yellowish oil. The oil was purified by column chromatography (silica gel: ϕ 3.5 × 13 cm; eluted by Hex/EA = 1/3). The desired fraction (R_f = 0.18, Hex/EA = 1/9) was collected and evaporated to give a solid that was recrystallized from EtOH to yield **2** (154 mg, 24%). Mp 77−79 °C [lit.[2] mp 78−80 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (m, 2 H), 2.80 (t, J = 8 Hz, 2 H), 3.70 (t, J = 8 Hz, 2 H), 3.98 (s, 3 H), 4.00 (s, 3 H), 6.05 (br s, 1 H), 6.73 (d, J = 1 Hz, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.30 (d, J = 1 Hz, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.64 (s, 1 H), 10.26 (s, 1 H).

2-(4-Benzyloxy-3-methoxyphenyl)-3-hydroxymethyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (27). To thae solution of **23** (346.3 mg, 0.7 mmol) in THF (30 mL) was added DIBAL-H (1.0 M in CH_2Cl_2) at room temperature. After the mixture was stirred at room temperature for 5 h, the reaction was quenched with saturated $Na_2SO_4{\cdot}10H_2O$ (10 mL). The resulting mixture was partitioned between CH_2Cl_2

(150 mL) and water (20 mL). The organic layer was washed with water (30 mL × 2) and saturated NaCl solution (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (silica gel: ϕ 3 × 8 cm; eluted by Hex/EA = 3/1) to give a solid that was recrystallized form EtOH to yield **27** (138.5 mg, 43%). Mp 221−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3 H), 1.32 (s, 3 H), 1.73 (t, J = 6 Hz, 1 H), 3.67 (d, J = 11 Hz, 2 H), 3.79 (d, J = 11 Hz, 2 H), 3.96 (s, 3 H), 4.03 (s, 3 H), 4.88 (d, J = 6 Hz, 2 H), 5.19 (s, 2 H), 5.45 (s, 1 H), 6.94 (d, J = 8 Hz, 1 H), 6.99 (d, J = 1 Hz, 1 H), 7.30 (d, J = 7 Hz, 1 H), 7.35 (d, J = 2 Hz, 2 H), 7.37 (d, J = 2 Hz, 1 H), 7.40 (d, J = 1 Hz, 7 H), 7.43 (d, J = 7 Hz, 2 H), 7.46 (d, J = 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.6, 54.7, 62.3, 64.4, 69.5, 99.0, 99.1, 103.1, 104.3, 107.3, 110.0, 110.2, 112.5, 116.6, 125.8, 125.9, 126.4, 127.1, 129.6, 129.8, 130.4, 135.2, 135.3, 143.3, 143.6, 143.7, 147.3, 148.3, 155.1; MS (FAB) *m/z* 504 (M^+); HRMS calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2148.

2-(4-Benzyloxy-3-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxy-3-methylbenzofuran (29) and 2-(4-Benzyloxy-3-methoxyphenyl)-3-methyl-7-methoxybenzofuran-5-carbaldehyde (28). To a solution of **27** (420.7 mg, 0.8 mmol) in a mixture of $CHCl_3$ (30 mL) and THF (30 mL) was added PdO (24 mg) and the mixture was stirred at 85 °C under 50 psi of H_2. After being stirred at the same conditions for 3 d, the reaction mixture was filtered through Celite 545 and the residue was washed with $CHCl_3$ (150 mL) and water (20 mL). The filtered was partitioned between $CHCl_3$ (30 mL) and water (30 mL). The water layer was extracted with $CHCl_3$ (30 mL × 2). The combined organic layer was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (silica gel: ϕ 2.5 × 8 cm; eluted by Hex/EA = 3/1) to give two products. The slower moving band (R_f = 0.21, Hex/EA = 3/1) was collected and the solvent was evaporated to afford solid that was recrystallized from 2-propanol to yield **28** (179.9 mg, 52%). Mp 180−181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3 H), 3.97 (s, 3 H), 4.04 (s, 3 H), 5.22 (s, 2 H), 6.96 (d, J = 9 Hz, 1 H), 7.30 (d, J = 7 Hz, 1 H), 7.35 (d, J = 6 Hz, 1 H), 7.37 (d, J = 5 Hz, 1 H), 7.38 (s, 1 H), 7.44 (d, J = 7 Hz, 2 H), 7.65 (dd, J = 2, 8 Hz, 1 H), 7.76 (d, J = 2 Hz, 1 H), 8.09 (d, J = 1 Hz, 1 H), 10.03 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 56.2, 56.2, 70.8, 104.8, 108.3, 112.9, 113.1, 121.0, 121.6, 123.1, 127.2, 128.0, 128.6, 129.1, 134.1, 136.5, 145.8, 146.2, 149.0, 150.5, 162.2, 164.0, 191.8; HRMS calcd for $C_{24}H_{20}O_4$ 372.1362, found 372.1361. The faster moving band (R_f = 0.25, Hex/EA = 3/1) was collected and the solvent was evaporated to afford a solid that was recrystallized from EtOH to yield **29** (55 mg, 13%). Mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 1.34 (s, 3 H), 3.73 (d, J = 11 Hz, 2 H), 3.84 (s, 3 H), 3.83 (d, J = 11 Hz, 2 H), 3.92 (s, 3 H), 4.02 (s, 3 H), 5.21 (s, 2 H), 5.48 (s, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.07 (s, 1 H), 7.30 (s, 1 H), 7.32−7.38 (m, 5 H), 7.43 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.8, 30.1, 52.0, 56.0, 56.2, 70.9, 78.1, 103.0, 107.1, 109.0, 112.9, 113.2, 122.6, 123.0, 127.3, 128.0, 128.6, 131.3, 133.6, 136.6, 140.8, 143.1, 145.2, 148.9, 150.1, 162.1, 165.1; HRMS calcd for $C_{30}H_{32}O_6$ 372.2199, found 372.2198.

4,5-Dibenzyloxy-3-methoxybenzaldehyde (30). To a solution of 4,5-dihydroxy-3-methoxybenzaldehyde (2.27 g, 3.5 mmol) in *N*,*N*-dimethylacetamide (100 mL) was added K_2CO_3 (6.2 g) and the mixture was stirred at room temperature for 30 min. To the resulting solution was added benzyl bromide (1 mL, 8.4 mmol) at room temperature. After the solution was stirred at room temperature for 21 h, the resulting mixture was concentrated in vacuo to give a deep brown liquid. The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and water (50 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a brown mixture. The mixture was purified by column chromatography (silica gel: ϕ 4.5 × 11 cm; eluted by Hex/EA = 1/1) to give a solid that was recrystallized from 2-propanol to yield **30** (1.15 g, 94%). Mp 156−158 °C [lit.[36] mp 158 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 5.11 (s, 2 H), 5.15 (s, 2 H), 7.12 (s, 1 H), 7.17 (s, 1 H), 7.29−7.39 (m, 6 H), 7.41−7.46 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 71.4, 75.3, 106.9, 109.0, 127.8, 128.3, 128.3, 128.5, 128.7, 128.8, 132.1, 136.7, 137.6, 143.3, 153.2, 154.4, 191.2; MS (FAB) *m/z* 349 (M + H^+); HRMS calcd for $C_{22}H_{21}O_4$ 349.1440, found 349.1439.

2-(3,4-Dibenzyloxy-5-methoxyphenyl)-1-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)carbinol (31). To a solution of **7** (4.47 g, 13.5 mmol) in THF (300 mL) was added *n*-BuLi (1.4 M, 11 mL) at −78 °C under argon. After the mixture was stirred at the same conditions for 30 min, to the resulting solution was added thae solution of **30** (3.43 g, 9.9 mmol) in THF (100 mL) via cannula at −78 °C under argon. Without removal of the ice trap, the resulting solution was stirred under argon for 4 h. After the solution was quenched with saturated $NH_4Cl_{(aq)}$ (50 mL), the resulting mixture was partitioned between ether (300 mL) and water (20 mL). The organic layer was washed with water (30 mL) and brine (50 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 5 × 11 cm; eluent: Hex/EA = 7/3). The desired fraction (R_f = 0.23, Hex/EA = 3/1) was collected and evaporated to give a product that was recrystallized from 2-propanol to yield **31** (4.34 g, 77%). Mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 1.29 (s, 3 H), 3.00 (br s, 1 H), 3.43 (s, 3 H), 3.63 (d, J = 11 Hz, 2 H), 3.75 (d, J = 11 Hz, 2 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 5.01 (s, 2 H), 5.03 (s, 2 H), 5.33 (s, 1 H), 5.87 (d, J = 5 Hz, 1 H), 6.64 (d, J = 14 Hz, 2 H), 7.06 (d, J = 12 Hz, 2 H), 7.24−7.33 (m, 8 H), 7.41−7.44 (m, 2 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.8, 23.1, 30.1, 55.7, 56.1, 60.3, 70.9, 72.0, 74.9, 77.6, 101.4, 104.2, 105.8, 109.4, 117.7, 127.5, 127.7, 127.8, 128.0, 128.4, 128.5, 134.4, 136.5, 137.2, 137.9, 139.7, 146.5, 152.2, 152.5, 153.5; MS (FAB) *m/z* 601 (M + H^+); HRMS calcd for $C_{36}H_{41}O_8$ 601.2802, found 601.2803.

3,4-Dibenzyloxy-5-methoxyphenyl 5-(5,5-Dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl Ketone (32). To a solution of **31** (4.34 g, 7.2 mmol) in CH_2Cl_2 (270 mL) was added active MnO_2 (90%, 12.13 g). After the mixture was stirred at the same conditions for 24 h, the resulting solution was filtered through Celite 545 to give a yellow liquid. The mixture was purified by column chromatography (silica gel: ϕ 4 × 10 cm; eluent: Hex/EA = 6/4) to give a colorless oil. The desired fraction (R_f = 0.28, Hex/EA = 3/1) was collected and evaporated. The white foam was generated in vacuo to afford **32** (4.14 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 1.27 (s, 3 H), 3.75 (d, J = 11 Hz, 2 H), 3.80 (s, 3 H), 3.77 (d, J = 11 Hz, 2 H), 3.92 (s, 3 H), 5.02 (s, 2 H), 5.11 (s, 2 H), 5.36 (s, 1H), 7.05 (d, J = 2 Hz, 1 H), 7.13 (d, J = 2 Hz, 2 H), 7.24−7.34 (m, 9 H), 7.40−7.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 23.0, 30.1, 55.8, 56.1, 61.5, 71.8, 74.9, 77.5, 100.7, 107.3, 109.6, 111.7, 118.3, 127.5, 127.8, 128.0, 128.3, 128.3, 132.6, 133.4, 136.5, 137.3, 142.1, 147.0, 152.1, 152.5, 153.3, 194.5; MS (FAB) (*m/z*) 599 (M + H^+); HRMS calcd for $C_{36}H_{39}O_8$ 599.2645, found 599.2645. Anal. Calcd for $C_{36}H_{38}O_8$: C, 72.22; H, 6.40. Found: C, 72.22; H, 6.38.

2-(3,4-Benzyloxy-5-methoxyphenyl)-1-(5-(5,5-dimethyl-1,3-dioxan-2-yl)-2,3-dimethoxyphenyl)acetylene (33). To a solution of trimethylsilyldiazomethane (2 M, 2.6 mL) in THF (30 mL) was added *n*-BuLi (1.5 M, 3.6 mL) at −78 °C under argon. After the mixture was stirred for 30 min at the same conditions, the resulting lithium salt solution was added to a solution of **32** (2.11 g, 3.5 mmol) in THF (100 mL) at −78 °C under argon via cannula. After the mixture was stirred at −78 °C under argon for 3 h, the resulting solution was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL). The resulting solution was partitioned between ether (150 mL) and water (10 mL). The organic layer was washed with saturated NaHCO$_{3(aq)}$ (20 mL), water (20 mL), and brine (50 mL), dried over MgSO$_4$, and concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 5 × 8 cm; eluent: Hex/EA = 3/1). The desired fraction (R_f = 0.30, Hex/EA = 3/1) was collected and the solvent was evaporated to give the **33** (2.07 g, 99%) as an oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.78 (s, 3 H), 1.29 (s, 3 H), 3.62 (d, J = 11 Hz, 2 H), 3.76 (d, J = 11 Hz, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 5.06 (s, 2 H), 5.08 (s, 2H), 5.33 (s, 1 H), 6.80 (d, J = 2 Hz, 1 H), 6.85 (d, J = 2 Hz, 1 H), 7.08 (d, J = 1 Hz, 1 H), 7.27−7.41 (m, 7 H), 7.42−7.46 (m, 4 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.0, 23.3, 30.4, 56.2, 56.4, 60.6, 61.2, 71.4, 75.4, 78.0, 84.9, 93.7, 101.1, 109.6, 110.9, 111.1, 117.8, 118.7, 123.1, 127.7, 128.1, 128.2, 128.4, 128.7, 134.7, 137.1, 137.9, 138.7, 150.7, 152.8, 152.8, 153.8; MS (FAB) m/z 595 (M + H$^+$); HRMS calcd for C$_{37}$H$_{39}$O$_7$ 595.2696, found 595.2696.

2-(3,4-Dibenzyloxy-5-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (35). Compound **34** prepared by the same approach as described in the preparation of **17** starting from **33** (2.07 g, 3.5 mmol) was used directly without purification. The resulting mixture of chloromercurio intermediate, MgO (295 mg, 7.3 mmol), PdCl$_2$ (631 mg, 3.6 mol), and LiCl (310 mg, 7.3 mmol) was dissolved in dry MeOH (80 mL) and stirred at 0 °C for 1 h and at room temperature for another 1.5 h. After the reaction was quenched by water (20 mL), the resulting solution was filtered through Celite 545. The filtrate was partitioned between CHCl$_3$ (150 mL) and water (30 mL). The organic layer was washed with water (20 mL) and brine (50 mL), dried over MgSO$_4$, and concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4.5 × 11 cm; eluent: Hex/EA = 3/1). The desired fraction (R_f = 0.32, Hex/EA = 3/1) was collected and the solvent was evaporated to give a solid that was recrystallized from 2-propanol to yield **35** (1.43 g, 89%). Mp 128−130 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.81 (s, 3 H), 1.34 (s, 3 H), 3.68 (d, J = 11 Hz, 2 H), 3.80 (d, J = 11 Hz, 2 H), 3.91 (s, 3 H), 4.06 (s, 3 H), 5.07 (s, 2 H), 5.16 (s, 2 H), 5.46 (s, 1H), 6.89 (s, 1 H), 7.00 (d, J = 1 Hz, 1 H), 7.10 (d, J = 2 Hz, 1 H), 7.15 (d, J = 2 Hz, 1 H), 7.27−7.30 (m, 3 H), 7.32−7.40 (m, 4 H), 7.43−7.46 (m, 4 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.1, 23.4, 56.3, 56.6, 71.7, 75.4, 78.0, 101.8, 102.3, 103.2, 104.8, 104.9, 111.5, 126.1, 127.8, 128.1, 128.2, 128.3, 128.7, 128.8, 130.8, 134.7, 137.1, 137.9, 138.6, 144.4, 145.2, 153.2, 154.3, 156.6. Anal. Calcd for C$_{36}$H$_{36}$O$_7$: C, 74.46; H, 6.25. Found: C, 74.15; H, 6.32.

3-Bromo-2-(3,4-dibenzyloxy-5-methoxyphenyl)-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (37). Compound **34** prepared by the same approach as described in the preparation of **17** starting from **33** (7.34 g, 12.4 mmol) was used directly without further purification. Two methods were applied for the preparation of **37**. **Method 1:** To a solution of **34** (8.98 g, 11.0 mmol) in CHCl$_3$ (200 mL) was added Br$_2$ (0.58 mL, 11.3 mmol) in CHCl$_3$ (20 mL) dropwise at −15 °C. The resulting solution was stirred at −15 °C for 30 min and then filtered through Celite 545. The filtrate was partitioned between CH$_2$Cl$_2$ (150 mL) and saturated NaHCO$_{3(aq)}$ (30 mL). The organic layer was washed with water (30 mL) and saturated NaCl (30 mL) and dried over MgSO$_4$. The MgSO$_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (silica gel: ϕ 5 × 10 cm; eluted by Hex/EA = 3/1). The desired fraction (R_f = 0.48, Hex/EA = 3/1) was collected and the solvent was evaporated to give a solid that was recrystallized form EtOH and ethyl acetate to yield **37** (4.52 g, 64%). Mp 222−224 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.80 (s, 3 H), 1.32 (s, 3 H), 3.65 (d, J = 11 Hz, 2 H), 3.75 (d, J = 11 Hz, 2 H), 3.93 (s, 3 H), 4.05 (s, 3 H), 5.10 (s, 4 H), 5.72 (s, 1 H), 7.10 (s, 1 H), 7.30 (s, 1 H), 7.31 (d, J = 2 H, 1 H), 7.32 (d, J = 2 Hz, 1 H), 7.34−7.36 (m, 3 H), 7.37 (br s, 1 H), 7.39−7.44 (m, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 21.7, 23.1, 30.1, 56.4, 61.2, 71.4, 75.6, 77.8, 100.6, 106.7, 110.1, 112.4, 127.4, 127.5, 128.2, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 132.6, 135.9, 136.8, 143.5, 144.0, 145.2, 1521, 152.4, 158.7. Anal. Calcd for C$_{36}$H$_{35}$BrO$_7$HgBr$_2$: C, 42.39; H, 3.46. Found: C, 42.74; H, 3.37.

Method 2: To a solution of **33** (2.71 g, 4.6 mmol) in CHCl$_3$ (200 mL) was added a solution of Br$_2$ (0.23 mL, 4.5 mmol) in CHCl$_3$ (20 mL) at −15 °C dropwise over a period of 30 min. After the mixture was stirred at the same conditions for another 3 h, the reaction was quenched with saturated NaHCO$_{3(aq)}$ (50 mL). The resulting solution was partitioned between CHCl$_3$ (200 mL) and water (20 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over MgSO$_4$, and concentrated in vacuo to give a yellow oil. The resulting residue was purified by column chromatography (silica gel: ϕ 5 × 7 cm; eluted by Hex/EA = 3/1) to give a yellow solid that was recrystallized from EtOH to yield **37** (2.52 g, 84%).

(3,4-Dibenzyloxy-5-methoxyphenyl)-3-methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-7-methoxybenzofuran (38). To a solution of **37** (1.33 g, 2.0 mmol) in THF (40 mL) was added n-BuLi (1.48 M, 1.4 mL) at −78 °C under argon. After the mixture was stirred at the same conditions for 30 min, to the resulting solution was added methyl iodide and the mixture was stirred for an additional 3 h. The reaction was quenched with saturated NH$_4$Cl$_{(aq)}$ (30 mL). The resulting mixture was partitioned between ether (300 mL) and water (20 mL). The organic layer was washed with water (20 mL × 2) and brine (30 mL) and dried over MgSO$_4$. The MgSO$_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 12 cm; eluted by Hex/EA = 8/2). The desired fraction (R_f = 0.45, Hex/EA = 3/1) was collected and the solvent was evaporated to give **38** (1.08 mg, 90%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.82 (s, 3 H), 1.36 (s, 3 H), 2.56 (s, 3 H), 3.74 (d, J = 11 Hz, 2 H), 3.81 (d, J = 11 Hz, 2 H), 3.90 (s, 3 H), 4.04 (s, 3 H), 5.11 (s, 2 H), 5.16 (s, 2 H), 5.85 (s, 1 H), 6.95 (d, J = 4 Hz, 2 H), 7.25 (s, 1 H), 7.29−7.32 (m, 3 H), 7.34 (d, J = 7 Hz, 2 H), 7.38 (d, J = 7 Hz, 2 H), 7.43 (d, J = 8 Hz, 2 H), 7.48 (d, J = 7 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.3, 21.8, 28.7, 54.8, 54.8, 69.8, 73.7, 81.4, 99.7, 107.9, 108.6, 1098.6, 110.9, 115.0, 116.5, 125.8, 126.1, 126.4, 126.5, 126.7, 127.0, 127.1, 127.3, 128.1, 135.3, 136.1, 137.3, 144.5, 146.8, 151.0, 152.1; MS (FAB) m/z 594 (M$^+$); HRMS calcd for C$_{37}$H$_{38}$O$_7$ 595.2618, found 595.2617.

2-(3,4-Dibenzyloxy-5-methoxyphenyl)-3-methyl-7-methoxybenzofuran-5-carbaldehyde (39). A solution of **38** (649.9 mg, 1.1 mmol) in acetone (50 mL) was added to 6 N HCl$_{(aq)}$ (10 mL) at room temperature and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to give a yellow oil. The oil was dissolved in CHCl$_3$ (200 mL), washed with water (30 mL) and brine (30 mL), and dried over MgSO$_4$. The MgSO$_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow oil. The oil was purified by column chromatography (silica gel: ϕ 2.5 × 7 cm; eluted by Hex/EA = 4/1), the desired fraction (R_f = 0.3, Hex/EA = 3/1) was collected, and the solvent was evaporated to give **39** (423.2 mg, 77%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.56 (s, 3 H), 3.91 (s, 3 H), 4.01 (s, 3 H), 5.09 (s, 2 H), 5.17 (s, 2 H), 6.92 (d, J = 4 Hz, 2 H), 7.25 (s, 1 H), 7.22−7.34 (m, 5 H), 7.35 (d, J = 7 Hz, 2 H), 7.41 (d, J = 8 Hz, 2 H), 7.51 (d, J = 7 Hz, 2 H), 10.45 (s, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 50.4, 54.7, 69.4, 103.3, 111.5, 119.6, 121.6, 125.8, 125.8, 126.5, 126.5, 127.2, 127.6, 132.6, 135.1, 144.4, 147.5, 149.0, 162.5, 190.4; HRMS calcd for C$_{32}$H$_{28}$O$_6$ 595.1886, found 595.1880.

2-(3,4-Dihydroxy-5-methoxyphenyl)-3-methyl-5-(prop-1-en-1-yl)-7-methoxybenzofuran (3). To a solution of **39** (422 mg, 1.0 mmol) in THF (20 mL) was added the lithium salt of ethyltriphenylphosphine iodide (655 mg, 1.6 mmol) in THF (20 mL) at −78 °C under argon. After the mixture was stirred at the same conditions for 5 h, the saturated NH$_4$Cl$_{(aq)}$ (30 mL) was added to quench the reaction. The resulting solution was partitioned between $CHCl_3$ (100 mL) and water (30 mL). The organic layer was washed sequentially with water (20 mL) and brine (20 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellow solid. To a solution of the yellow solid in THF (100 mL) was added BBr_3 (0.1 mL, 1 M in THF) dropwise at −78 °C under argon. After the mixture was stirred for another 5 min, the resulting solution was neutrilized with saturated $NaHCO_{3(aq)}$. The resulting solution was partitioned between $CHCl_3$ (150 mL) and water (10 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The residue was subjected to column chromatography (silica gel: ϕ 4 cm × 8 cm; eluent: Hex/EA = 1/1). The desired fraction (R_f =0.21, Hex/EA = 1/3) was collected and the solvent was evaporated to give **39** (108 mg, 31%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (dd, J = 6, 2 Hz 3 H), 2.50 (s, 3 H), 3.97 (s, 3 H), 4.06 (s, 3 H), 6.19−6.32 (m, 1 H), 6.49 (dd, J = 16, 2 Hz, 1 H), 6.83 (s, 1 H), 6.97 (s, 1 H), 7.03 (s, 1 H), 7.07 (s, 1 H); MS (EI) m/z 340 (M^+); HRMS calcd for $C_{20}H_{20}O_5$ 340.1311, found 340.1310.

2-(4-Benzyloxy-3-methoxyphenyl)-3-bromo-7-methoxybenzofuran-5-carbaldehyde (42). To a solution of **15** (4.12 g, 8.4 mmol) in $CHCl_3$ (300 mL) was added a solution of Br_2 (450 μL, 8.8 mmol) in $CHCl_3$ (20 mL) at −15 °C. The resulting solution was stirred at −15 °C under argon for 2 h. The resulting solution was concentrated in vacuo to give a yellow oil. The oil was dissolved in acetone. To the resulting solution was added HCl (6 N, 30 mL) and the mixture was stirred at room temperature for an additional 3 h. After being quenched with $NaOH_{(aq)}$ (3 N), the resulting solution was partitioned between $CHCl_3$ (200 mL) and saturated $NaHCO_{3(aq)}$ (50 mL). The organic layer was washed with water (30 mL × 2) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 12 cm; eluted by Hex/EA = 4/1). The desired fraction (R_f = 0.42, Hex/EA = 3/1) was collected and the solvent was evaporated to give a yellowish solid that was recrystallized from EtOH to yield **40** (3.41 g, 86%). Mp 104−106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3 H), 4.06 (s, 3 H), 5.21 (s, 2 H), 6.97 (d, J = 9 Hz, 1 H), 7.31 (d, J = 7 Hz, 1 H), 7.35 (d, J = 6 Hz, 1 H), 7.37 (d, J = 7 Hz, 1 H), 7.38 (s, 1 H), 7.45 (d. J = 7 Hz, 1 H), 7.64 (d, J = 1 Hz, 1 H), 7.68 (d, J = 2 Hz, 1 H), 7.70 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2 56.3, 70.9, 92.7, 105.3, 110.3, 113.5, 117.5, 120.2, 121.8, 127.3, 128.0, 128.6, 131.5, 133.7, 136.6, 145.8, 149.4, 149.5, 152.2, 191.3; MS (FAB) m/z 467 ($M + H^+$), 469 ($M + 2 + H^+$); HRMS calcd for $C_{24}H_{19}BrO_5$ 466.0416, found 466.0415.

2-(4-Benzyloxy-3-methoxyphenyl)-3-bromo-7-methoxy-5-(ethylcarbethenyl)benzofuran (43). To a solution of **42** (924.8 mg, 1.9 mmol) in THF (20 mL) was added a solution of the lithium salt of carbethylmethyltriphenylphosphine bromide (956.3 mg, 2.3 mmol) at −78 °C under argon. The resulting solution was stirred at −78 °C under argon for 2 h. After the mixture was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL), the resulting solution was partitioned between ether (200 mL) and water (30 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish mixture. The mixture was purified by column chromatography (silica gel: ϕ 4 × 8 cm; eluted by Hex/EA = 3/1). The desired fraction (R_f = 0.22, Hex/EA = 3/1) was collected and the solvent was evaporated to give a solid that was recrystallized from MeCN to yield **43** (897 mg, 88%). Mp 183−185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7 Hz, 3 H), 3.96 (s, 3 H), 4.01 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 5.21 (s, 2 H), 6.33 (d, J = 16 Hz, 1 H), 6.96 (d, J = 8 Hz, 1 H), 7.01 (s, 1 H), 7.24 (s, 1 H), 7.31 (d, J = 7 Hz, 1 H), 7.36 (t, J = 7 Hz, 2 H), 7.44 (d, J = 7 Hz, 2 H), 7.65 (br s, 2 H), 8.24 (d, J = 16 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 54.7, 54.8, 59.2, 60.4, 104.5, 109.7, 111.9, 119.0, 119.5, 120.3, 125.8, 126.5, 127.1, 141.9, 143.1, 147.9, 148.0, 165.0; HRMS calcd for $C_{28}H_{25}BrO_6$ 536.0835, found 536.0835.

2-(4-Benzyloxy-3-methoxyphenyl)-3-bromo-5-(3-hydroxyprop-1-en-1-yl)-7-methoxybenzofuran (44). To a solution of **43** (1.38 g, 2.6 mmol) in THF (50 mL) was added a solution of DIBAL-H in CH_2Cl_2 (1.0 M, 10 mL) at room temperature under argon. After the mixture was stirred at room temperature for 21 h, the reaction was quenched with saturated $Na_2CO_3{\cdot}10H_2O_{(aq)}$. The resulting solution was partitioned between $CHCl_3$ (200 mL) and water (20 mL). The organic layer was washed with water (30 mL × 3) and brine (30 mL) and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the filtrate was concentrated in vacuo to give a yellowish oil. The residue was purified by column chromatography (silica gel: ϕ 4.5 × 9 cm; eluted by Hex/EA = 2/3). The desired fraction (R_f = 0.35, Hex/EA = 1/1) was collected and the solvent was evaporated to give a solid that was recrystallized from EtOH to yield **44** (918.2 mg, 73%). Mp 185−187 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 4.02 (s, 3 H), 4.33 (dd, J = 6, 1 Hz, 2 H), 5.20 (s, 2 H), 6.36 (dt, J = 6, 16 Hz, 1 H), 6.67 (d, J = 16 Hz, 1 H), 6.88 (d, J = 1 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 7.09 (d, J = 1 Hz, 1 H), 7.31 (d, J = 7 Hz, 1 H), 7.36 (t, J = 7 Hz, 2 H), 7.44 (d, J = 8 Hz, 2 H), 7.67 (dd, J = 6, 8 Hz, 1 H), 7.70 (d, J = 2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 56.2, 63.7, 70.9, 92.6, 105.8, 110.1, 110.3, 113.5, 120.0, 122.5, 127.2, 127.9, 128.1, 128.6, 131.2, 131.4, 133.4, 136.7, 142.0, 144.9, 148.9, 149.4, 151.0. Anal. Calcd for $C_{26}H_{23}BrO_5$: C, 63.04; H, 4.68. Found: C, 62.80; H, 4.41.

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