The synthesis of natural products containing the benzofuran skeleton via halogen-metal exchange/cyclization

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The synthesis of natural products containing the benzofuran skeleton via halogen-metal exchange/cyclization

by

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in partial fulfillment of the requirements for the degree of

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2005

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This is to certify that the master's thesis of

Jacob Daniel Schroeder

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy
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INTRODUCTION

Numerous natural products exist containing a benzofuran subunit. These compounds show potent biological activity including anticancer, antiviral, antifungal, and immunosuppressive activity. The benzofuran skeleton is found in several flavones, flavonoids, oligomeric isoflavonoids, and many other families of compounds. The biological activity exhibited by many of these compounds has resulted in a number of synthetic approaches. Many routes suffer from long reaction times, the use of expensive catalysts or polymer support systems, or simply low yields. However, a few well designed syntheses have been shown to proceed in good yields, and in most cases with high purity. In the recent literature, the most common approaches to the benzofuran skeleton are (1) cyclodehydration of ketones under basic or acidic conditions, (2) intramolecular Heck cyclization, (3) palladium-catalyzed cyclization of arylacetylenes, (4) radical cyclization of β-(aryloxy)acrylates, (5) an intramolecular Wittig reaction, and (6) intramolecular solvomercuration of a substituted arylacetylene. These approaches are depicted in Scheme 1.

Depending on the substituents in the starting materials, treatment with p-toluenesulfonic acid seems to be the most common approach for cyclodehydration. Yields have been reported in the 90% range, decreasing when the aromatic ring contains electron withdrawing groups. Intramolecular Heck cyclization has proceeded in modest yields with organic based solvents, and now shows yields in the 80% range using ionic liquids. In this approach, yields decreased with less hindrance on the double bond and with increasing substituents on the aryl group. A variety of substituted benzofurans were prepared using radical cyclization with yields ranging from 93 – 99%. Substitutions on the aromatic ring (R^3
and $R^4$ in Scheme 1) had no negative effect on yields. The intramolecular Wittig reaction has shown promise, although the scope and limitations remain to be determined. The three step approach with solvomercuration has generally shown yields from 60 – 90%, although this specific approach in preparing benzofurans is now not very common.

Scheme 1. Representation of Various Synthetic Approaches
Recently, our group has shown the use of the halogen-metal exchange reaction in a synthesis of malibatol A, a natural product exhibiting cytotoxic activity and HIV-inhibitory activity. As shown below, the aryl iodoketone cyclized to the benzofuran by treatment with methyl lithium followed by dehydration of the resulting alcohol in a 75% overall yield.

The halogen-metal exchange reaction has become a key reaction in both organic and organometallic methodologies since its discovery by Wittig and Gilman. The reaction is used extensively to form carbon-carbon bonds between an alkyl or aryl halide and an electrophilic carbon center. By using alkyl lithium reagents such as methyl lithium or n-butyl lithium, the anion of the alkyl or aryl halide is formed followed by the addition to a reactive carbon center.

\[
R-X \xrightarrow{n-BuLi} \left[ \begin{array}{c} - \\ R-Li \end{array} \right] +E \rightarrow R-E
\]

The halogen needs to be either iodine or bromine. Various electrophiles have been examined, examples of which include other functionalized halides or carbonyl compounds. Nevertheless, this specific reaction had never been used to prepare benzofurans. Prior to our synthesis, Kihara and co-workers used this procedure to synthesize substituted indoles.
They reported modest yields ranging from 20 – 60% with various substituents. To our knowledge, this protocol has remained unexplored, leaving in question the versatility of the halogen-metal exchange reaction for preparing benzofurans. The key questions to be evaluated are the effect of steric bulk and functionality present in the starting material, the halogen involved, and whether the reaction works for aldehydes in addition to ketones.
METHODOLOGY

Our approach has been used to synthesize both known and unknown compounds. The known compounds were synthesized for comparison with previous reported cyclizations. Only the yields for the cyclization step are being used for comparison. Our first eight results are reported in Table 1. The iodoketone precursors (entries 1a – 8a) were prepared in consistently high yields by coupling the desired α-bromoketone with a suitable iodophenol in boiling acetone. The resulting ketone was then treated with methyl lithium followed by dehydration using PTSA to afford the substituted benzofuran. The product in entry 1 is commercially available 3-phenylbenzofuran. Many previous preparations of this compound are known with yields ranging between 65 – 95%, with the higher yields being obtained by using microwave irradiation or solid support systems. A variety of methoxy-substituted aryl compounds as indicated in entries 2 – 5 were also cyclized. The results show no clear pattern between yields and position or number of methoxy groups present. Compound 2b has been cyclized previously in 14% yield using photolysis of the β-(o-methoxyphenyl)vinyl bromide. Our method generated the compound in 84% yield. Compound 3b has also been cyclized in 79% yield by a reaction with an Amberlyst resin. Our results show a modest improvement to 97%. The trimethoxyphenyl benzofuran (entry 4) was previously unknown but the yield of the cyclization is similar to that found with the other methoxyphenyl compounds. Substituting a methoxy group on the iodophenol produced compound 5b. Previous cyclizations reacted methanesulfonic acid with the (3-methoxyphenoxy)ketone in yields from 70 – 74%. Our approach produced the compound in 81% yield. It should be
noted that entries 3 and 4 did not require dehydration by PTSA following the cyclization as the work-up provided the benzofuran exclusively.

Table 1. Results of the Halogen-Metal Exchange/Cyclization Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R_1 )</th>
<th>( R_2 )</th>
<th>( \text{Ar} )</th>
<th>% Yield(^a)</th>
<th>% Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Phenyl</td>
<td>97</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>2’-MeOC(_6)H(_5)</td>
<td>99</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>4’-MeOC(_6)H(_5)</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>2’,4’,5’-MeOC(_6)H(_5)</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>5-OMe</td>
<td>H</td>
<td>( C_6H_5 )</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Me</td>
<td>( C_6H_5 )</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>H</td>
<td>Thiophen-2-yl</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>H</td>
<td>Furan-2-yl</td>
<td>75</td>
<td>79</td>
</tr>
</tbody>
</table>

\(^a\) Yield of coupled product; \(^b\) Yield of cyclized product
To test for steric interactions we introduced a methyl group in the α position to the carbonyl (entry 6). This compound has been previously synthesized from a reaction of an o-hydroxyphenyl ketone with a benzotriazol-1-ylalkyl chloride. This procedure required 3 steps with the cyclization taking place in 55%.\textsuperscript{2c} Our method provided the compound in 97% yield.

With entries 7 and 8, we explored how heterosubstitution in the aryl group affected the cyclization. With a thiophenyl group, we observed a 77% yield for the cyclization. This compound shows biological activity as a blood platelet aggregation inhibitor.\textsuperscript{14} The authors noted that this compound has a two-fold higher effect than aspirin. The furan analog was cyclized in 79% yield.

From the above results, we found that the halogen-metal exchange/cyclization was competitive with some of the known methods used for the synthesis of benzofurans. In a few instances we saw dramatic yield increases compared to known procedures. To extend this study, we prepared an aliphatic iodoketone. Coupling chloroacetone with 2-iodophenol afforded compound 9a in 95% yield. The cyclization protocol provided 3-methylbenzofuran 9b in 88% yield. This compound is commercially available, and numerous preparations have also been reported, generally with high yields.
To determine whether an aldehyde would participate, we synthesized 10a in 89% overall yield by coupling 2-iodophenol with allyl bromide, followed by oxidative cleavage with osmium tetroxide and sodium periodate. Treatment with methyl lithium produced a mixture of the addition products shown below.

\[
\text{I} \quad \text{Br}^+ \quad \text{OH}
\]

\[
\text{I} \quad \text{O}^+ \quad \text{H}
\]

\[
\text{I} \quad \text{O}^+ \quad \text{Me}
\]

From our results, we conclude that the substitution pattern of methoxy groups in various positions on the precursors had no affect on the cyclization reaction. We also conclude that addition of a methyl group \(\alpha\) to the carbonyl group had no detrimental effect on the cyclization. With the substituted phenyls the yields of benzofurans were slightly higher. We can also conclude that this procedure does not work for aldehydes. Finally, in comparison to other methods for obtaining benzofurans, the halogen-metal exchange/cyclization protocol provided higher yields in all cases.
NATURAL PRODUCT SYNTHESIS

Compounds 1 and 2 were extracted from *Dalbergia cochinchinensis*, a perennial tree that mainly grows in Iran, Vietnam, and Indonesia. These two compounds have been classified as antiandrogenic, showing moderate inhibitory activity against testosterone 5α-reductase, an enzyme responsible for converting testosterone into 5α-dihydrotestosterone (DHT). When in excess, DHT can lead to prostatomegaly, prostate cancer, male pattern baldness, hirsutism, and acne.

In addition to these two compounds, it has been reported that the stems of this plant contain 12 other phenolic compounds. Two of these, 9-hydroxy-6,7-dimethoxydalbergiquinol and 6-hydroxy-2,7-dimethoxyneoflavene, show potent inhibitory activity against the binding of 5α-dihydrotestosterone (DHT) to its receptor.
To our knowledge, compounds 1 and 2 have never been synthesized. There are no stereogenic centers in either of the two compounds and given the results of our halogen-metal exchange methodology study, we believed we could obtain the benzofuran half of the molecule in a similar fashion. The retrosynthetic analysis is shown in scheme 2.

Scheme 2: Retrosynthetic Analysis
We believed compound 1 could be obtained via Claisen rearrangement of compound 2. Compound 2 could be obtained by coupling the anion of benzofuran 16 with aldehyde 19, followed by deoxygenation of the resulting alcohol and deprotection of the benzyl ether. Benzofuran 16 could be obtained following the methodological study previously described, starting from compound 11. Aldehyde 19 could be obtained by a simple $S_N2$ reaction between the $\alpha$-hydroxyaldehyde 18 and cinnamyl bromide.

Compound 11 is a known compound obtained from commercially available vanillin in three steps.\textsuperscript{18} In parallel with our previous methodology, the next step was to iodinate the ring. Several conditions are known for iodination of phenols such as $N$-iodosuccinimide with trifluoroacetic acid\textsuperscript{119} and without acid,\textsuperscript{20} iodine monochloride with acetic acid\textsuperscript{21} and without acid,\textsuperscript{22} and a tetrabutylammonium iodinedichloride salt.\textsuperscript{23} Multiple runs under all of the above conditions, however, failed to generate the iodophenol, instead leaving a complex mixture. Iodine monochloride instead chlorinated the ring. Later attempts to generate the benzofuran from the chlorophenol failed.
Bromination of the phenol proved much more beneficial as we were able to obtain the known compound 12 in quantitative yield. Using the general coupling procedure with phenacyl bromide, compound 13 was obtained in 77% yield. Treatment of 13 with methyl lithium failed to produce the desired benzofuran. The $^1$H NMR showed a singlet at 1.60 ppm, indicating methyl addition to the ketone. An internal Grignard reaction was attempted using both lithium metal and magnesium metal, but both of these trials were unsuccessful.

With the unfavorable results obtained at the beginning of the synthesis, we went back to the drawing board with 11. It was envisioned that the problems we encountered would be solved if we did not have the free hydroxy group interfering with the reaction. By changing the order of steps we were able to obtain 14 in 90% yield by coupling the phenol with phenacyl bromide. With the coupled product in hand, iodination was then achieved using N-iodosuccinimide and catalytic trifluoroacetic acid to give 15 in 89% yield. Compound 15 was then subjected to the halogen-metal exchange/cyclization conditions with methyl lithium to obtain the benzofuran 16 in 94% yield.
With the key benzofuran in hand, attention was turned toward the synthesis of the aldehyde. Starting from commercially available trimethoxybenzaldehyde, selective demethylation using boron trichloride gave the known α-hydroxyaldehyde 18 in 86% yield. The general coupling procedure with cinnamyl bromide then afforded 19 in 86% yield.

The addition reaction was carried out by treatment of benzofuran 16 with \( n \)-butyl lithium, followed by quenching with aldehyde 19, to afford 20 in 63% yield.
With 20 in hand, only two steps remained: deprotection of the benzyl ether and deoxygenation. Given the conditions, we focused first on removing the hydroxyl group. The primary methods for deoxygenation are either radical-based, using tri-n-butyltin hydride$^{26}$ or carbocation-based using a hydride donor with acid catalyst.$^{27}$ With the double bond from the cinnamyl group present, the radical cyclization might compete with hydrogen abstraction to yield the 6-exo-trig adduct.

Under ionic conditions, our first attempt was with triethylsilane and a catalytic amount of trifluoroacetic acid.$^{27b}$ Addition of the acid to 20 immediately produced a dark blue color, but after work-up no product was detected. Instead, we were left with a complex mixture. In our next attempt, we used sodium borohydride with catalytic trifluoroacetic
Once again, treatment with the acid produced a dark blue color, but the reaction failed to produce any desirable product. Other attempts with these conditions involved changing the acid. Substituting boron trifluoride etherate produced the same results with no desirable product. After looking through the literature, alternative approaches surfaced. One protocol used a Birch-type reduction with either sodium or lithium metal. The second involved the in situ generation of iodotrimethylsilane. These routes seemed attractive since they are also known conditions for the deprotection of the benzyl ether. This led us to believe that it was possible to reach the target compound in one step from 20. Unfortunately, all three trials provided the same results as our previous attempts, consuming the starting material and leaving a complex, unidentifiable mixture.

With these disappointing results, it was clear that we needed to go back a few steps and perhaps alter our precursors to see if there was some structural feature that was interfering in the above reactions. Our strategy involved modifying the oxidation state of the aldehyde. Although the anion coupling was proceeding with good yields, the resulting alcohol was difficult to remove. We envisioned first reducing the aldehyde, then converting...
the resultant alcohol into a halide, and finally coupling the benzofuran with the halide. This would afford the desired methylene group, leaving only the deprotection as the last step.

The literature does show precedent for converting a benzyl alcohol similar to ours into the corresponding halide by using thionyl chloride\(^\text{32}\) or phosphorous tribromide\(^\text{33}\).

![Chemical Structures](attachment:image.png)

With this precedent, we reduced aldehyde 19 with sodium borohydride, which gave benzyl alcohol 21 in nearly quantitative yield.

![Chemical Structures](attachment:image.png)

Since bromine is a better leaving group than chlorine and the literature bromination was reported to work well it was a logical first choice. However, attempted bromination with phosphorous tribromide resulted in a complex mixture. Iodination was attempted using
triphenylphosphine and imidazole. The spectral data of the crude product showed the formation of the iodinated compound; however, the compound decomposed in the chromatography column. With the failed attempts of bromination and iodination, we focused on chlorination. Using thionyl chloride we were unable to obtain the chlorinated product. Another attempt involved forming the mesylate with subsequent chlorination by lithium chloride. However this protocol failed, as cinnamyl alcohol was identified in the $^1$H NMR spectrum of the crude product. Attempts to form the tosylate or the mesylate showed no product. Once again, cinnamyl alcohol was identified in the spectral data of the crude product.

With no success in making the $S_N2$ precursor, we moved our attention to the benzofuran half of the compound. The deoxygenation of 20 may have failed because the benzyl ether was interfering with the reaction. Our focus was to remove the benzyl ether prior to coupling and then try the conditions necessary for deoxygenation. Standard conditions for debenzylation are catalytic hydrogenation; however, when 16 was subjected to
these conditions, reduction of the furan double bond took place rather than debenzylolation. This resulted in a high yield of the saturated compound, but none of the desired compound. Fortunately, by treating 16 with iodos(trimethyl)silane generated in situ, we were able to obtain the hydroxy-benzofuran 22 in very good yield. With 22, the dianion was made with two equivalents n-butyl lithium, followed by the addition of aldehyde 19 to produce the dihydroxy compound 23 in good yield.

![Chemical Structures](image)

Observation of the $^1$H NMR spectrum for this compound revealed five extra protons present in the aromatic region along with three extra protons around 3.90 ppm. This possibly is due to isomerization about the cinnamyl group double bond or an impurity with the same $R_f$ as 23. Precedent for isomerization has recently been observed in the literature. When Gennari
and co-workers added deuterated chloroform to a compound with a \textit{trans} double bond, it isomerized to a \textit{cis} double bond.\textsuperscript{35} They hypothesized that deuterated chloroform promoted an equilibrium that favored the \textit{cis} isomer.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Diagram showing the isomerization of a compound with deuterated chloroform.}
\end{figure}

It should also be noted that \textsuperscript{23} was obtained as a tan solid after purification. When deuterated chloroform was added for \textsuperscript{1}H NMR analysis, the resulting solution immediately turned a deep, dark green color, similar to the change that was observed when trifluoroacetic acid was added before. The \textsuperscript{13}C NMR spectrum of \textsuperscript{23} shows a peak at 37.7 ppm. One would normally expect to see a carbinol carbon in the 60-65 ppm range, but this compound did not show any peaks in this range.

Despite these questions, compound \textsuperscript{23} was subjected to the conditions for deoxygenation. Using all of the conditions mentioned before produced the same results. No desirable products were obtained and the starting material was consumed, leaving a complex mixture that was unidentifiable by \textsuperscript{1}H NMR analysis. A final attempt was made using zinc iodide with sodium cyanoborohydride,\textsuperscript{36} but these conditions returned the starting material. Longer reaction times made little difference, with 80% of the starting material recovered after two days of reaction time.
The benzyl-protected compound 20 underwent the same color changes as 23 did, but examination of the $^{13}$C NMR spectrum showed no peak near 37 ppm. After taking the $^1$H NMR, the NMR tubes were always rinsed with reagent-grade chloroform, with the rinse added to the product. After a solution of 20 in chloroform had been stored for nearly one week, thin layer chromatography analysis revealed a new compound in addition to the original one. The $^1$H NMR was taken, only to show a mixture, but after purification of 20, $^1$H NMR analysis showed a new compound, the ethyl ether 24.

The ether 24 was easily identified by the multiplet around 3.50 ppm and the triplet around 1.20 ppm. The initial reactions produced poor yields of 24. This can be attributed to the fact that reagent grade chloroform does contain 1% ethanol as a stabilizing agent. After several trials trying to exploit this unusual reaction, it was found that the optimum conditions
to generate 24 were simply deuterated chloroform and ethanol. After stirring the solution overnight, compound 24 was obtained in 73% yield. Furthermore, all spectral data were in agreement with the new structure, and a high-resolution mass spectrum was obtained. The only similarity between benzyl ether 20 and the diol 23 was the fact that the color of the solution changed when deuterated chloroform was added. With 24 in hand, we subjected it to triethylsilane and catalytic trifluoroacetic acid to find that now the ethoxy group was removed readily, providing compound 25 in very good yield.

The deprotection of the benzyl ether was attempted using iodonitrtrimethylsilane generated \textit{in situ}; however these conditions did not provide the natural product. An attempt was made using boron trifluoride etherate\textsuperscript{37} however, these conditions also failed.
With these failed attempts, attention was refocused on diol 23. Using the optimized conditions for the preparation of 24, we were able to convert 23 into 26, in 78% yield.

As evidenced by NMR integrations, compound 26 lacked the impurity present in 23. The ethyl ether was then readily removed by treatment with triethylsilane and catalytic trifluoroacetic acid to obtain the natural product 2 in 73% yield. All spectral data obtained for the natural product were in agreement with that reported in the literature.

The natural product 2 was then placed in a sealed tube and heated to 150 °C in toluene, but after several trials with differing reaction times, no evidence of 1 was obtained. Instead, the natural product decomposed, with cinnamyl alcohol and the benzofuran visible in the spectral data of the crude reaction product.
Despite the failed attempts to obtain 1 we were able to synthesize the natural product 2 in seven steps, with a 17% overall yield from known phenol 11. This synthesis further demonstrates the utility of the halogen-metal exchange/cyclization conditions and also brings to light an intriguing reaction with deuterated chloroform.

During the course of this work a natural product was found that has only been synthesized once since its original isolation. Isoparvifuran 27 was isolated from another Dalbergia species, Dalbergia parviflora in 1981.

Parvifuran 28, the structural isomer of 27 was also isolated and had been once synthesized. Both of these compounds show antifungal activity, and contain the same structural skeletons that many of our benzofurans do.

The previous synthesis of isoparvifuran used photooxidation of the phenol giving isoparvifuran in 66% yield in two days. Using our protocol starting from 11, coupling with 2-bromo-1-phenylpropanone afforded 29 in excellent yield.
Treatment of 29 with N-iodosuccinimide afforded 30 which cyclized to 31 when treated with methyl lithium. Deprotection of the benzyl ether using iodoniumtrimethylsilane gave isoparvifuran 27.

This synthesis required four steps, yielding the natural product in 54% overall yield from 11. With the high yield of the cyclization, this synthesis further demonstrates the use of the cyclization reaction.
GENERAL SUMMARY

This work has shown the synthesis of a total of 11 benzofurans ranging in yields from 77% to 97%. One attractive feature of this protocol is the short reaction time, generally requiring only 15 – 30 minutes for complete cyclization to occur. The limitations of this procedure are the requirement for a ketone and for the halogen involved to be iodine. In comparison to previous cyclization steps for known compounds, the halogen-metal exchange/cyclization shows considerable improvements in both percent yield as well as reaction times. With these improvements, this process could be used to synthesize other benzofuran natural products efficiently.

This work has also shown the first reported synthesis of 2-[4,5-dimethoxy-2-(3-phenyl-trans-allyloxy)benzyl]-5-hydroxy-6-methoxy-3-phenylbenzofuran, 2. In addition, we were able to produce an improved synthesis of isoparvifuran.

The etherification reaction involving deuterated chloroform came as a surprise. This could open the door toward further research to study this particular reaction since this work seems to demonstrate the first time this reaction has ever been attempted.
EXPERIMENTAL SECTION

Unless otherwise noted, materials were obtained from commercial sources and were used without further purification. Tetrahydrofuran (THF) and methylene chloride were distilled from sodium prior to use. All reactions were done under an argon atmosphere. Flash chromatography was performed using standard grade silica gel (60 Å, 32-63 µm). The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sgc represents silica gel flash chromatography. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Varian VXR 300 spectrophotometer. All chemical shifts are reported in δ relative to CDCl₃ (7.26). Splitting patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); a br suffix indicates a broadened pattern. Carbon-13 NMR spectra (75 MHz) were obtained on the same spectrophotometer and chemical shifts are reported in δ relative to CDCl₃ (77.0). High resolution mass spectra were obtained on a Kratos model MS-50 mass spectrometer. Low resolution mass spectra were obtained on a Finnegan model TSQ700 mass spectrometer. Prepared compounds that are known in the literature were compared and referenced to the article in which they were previously characterized.

General Procedure for Coupling Reaction. One millimole of starting iodosphenol, 1 millimole of α-bromoketone, and 1.5 millimoles of potassium carbonate were dissolved in 10 mL of acetone and stirred at 85 ºC for 4 h. After completion of the reaction, the acetone was evaporated and the crude product was dissolved in ethyl acetate, washed with brine, dried
over MgSO₄, filtered, and concentrated. It was then purified by chromatography on silica gel to yield the pure compound.

2-(2-Iodophenoxy)-1-(2-methoxyphenyl)ethanone (2a). ¹H NMR (CDCl₃ 300MHz) δ 7.91 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 8.6 Hz, 1H), 7.22 (t, J = 8.6 Hz, 1H), 7.05-6.97 (m, 2H), 6.71-6.63 (m, 2H), 5.27 (s, 2H), 3.90 (s, 3H); ¹³C NMR (CDCl₃) δ 195.0, 159.6, 157.4, 139.8, 135.1, 131.1, 129.6, 125.0, 123.1, 121.3, 112.7, 111.9, 86.6, 75.4, 56.0; HRMS m/z Calcd for C₁₃H₁₃I₀₃ 367.9910, found 367.9914.

2-(2-Iodophenoxy)-1-(4-methoxyphenyl)ethanone (3a). ¹H NMR (CDCl₃) δ 8.06 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 6.2 Hz, 1H), 7.24 (t, J = 6.6 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 6.75-6.69 (m, 2H), 5.24 (s, 2H), 3.87 (s, 3H); ¹³C NMR (CDCl₃) δ 192.9, 164.3, 157.1, 139.9, 131.1, 129.7, 127.7, 123.6, 114.2, 121.8, 86.6, 72.2, 55.8; HRMS m/z Calcd for C₁₃H₁₃I₀₃ 367.9910, found 367.9914.

2-(2-Iodophenoxy)-1-(2,4,5-trimethoxyphenyl)ethanone (4a). ¹H NMR (CDCl₃) δ 7.77 (d, J = 6.2 Hz, 1H), 7.51 (s, 1H), 7.21 (t, J = 7.3 Hz, 1H), 6.65 (t, J = 9.4 Hz, 2H), 6.49 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H); ¹³C NMR (CDCl₃) δ 192.5, 157.5, 156.1, 155.1, 143.7, 139.8, 129.5, 122.5, 116.0, 115.4, 112.7, 95.9, 86.7, 75.4, 56.5, 56.4, 56.3; HRMS m/z Calcd for C₁₇H₁₇I₀₅ 428.0121, found 428.0127.

2-(2-Iodo-5-methoxyphenoxy)-1-phenylethanone (5a). ¹H NMR (CDCl₃) δ 7.99 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 8.7 Hz, 2H), 7.47 (t, J = 7.8 Hz 2H), 6.34 (s, 1H), 6.34 (d, J = 6.6 Hz, 1H), 5.27 (s, 2H), 3.72 (s, 3H); ¹³C NMR (CDCl₃) δ 194.1, 161.4, 157.7, 139.7, 134.5, 134.2, 129.1, 128.6, 108.4, 101.0, 75.4, 72.2, 55.8; HRMS m/z Calcd for C₁₃H₁₃I₀₃ 367.9910, found 367.9914.
2-(2-Iodophenoxy)-1-phenylpropan-1-one (6a). $^1$H NMR (CDCl$_3$) δ 8.14 (d, J = 7.0 Hz, 2H), 7.76 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.17 (t, J = 6.2 Hz, 2H), 6.67 (t, J = 8.0 Hz, 1H), 5.41 (q, J = 6.8 Hz, 1H), 1.82 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (CDCl$_3$) δ 198.8, 156.4, 140.0, 134.0, 129.7, 129.3, 129.0, 123.5, 113.3, 87.2, 78.9, 58.6, 19.2; HRMS m/z Calc for C$_{15}$H$_{13}$I$_{2}$O$_2$ 351.9960, found 351.9966.

2-(2-Iodophenoxy)-1-(thiophen-2-yl)ethanone (7a). $^1$H NMR (CDCl$_3$) δ 8.09 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 5.0 Hz, 1H), 7.71 (d, J = 5.7 Hz, 1H), 7.17 (t, J = 4.3 Hz, 1H), 6.77 (t, J = 8.5 Hz, 2H), 5.13 (s, 2H); $^{13}$C NMR (CDCl$_3$) δ 188.1, 156.9, 140.1, 135.1, 134.1, 130.0, 128.9, 123.9, 115.4, 112.7, 86.4, 72.7; HRMS m/z Calc for C$_{12}$H$_{9}$I$_{2}$O$_2$ 343.9368, found 343.9372.

1-(Furan-2-yl)-2-(2-iodophenoxy)ethanone (8a). $^1$H NMR (CDCl$_3$) δ 7.80 (d, J = 6.0 Hz, 1H), 7.64 (s, 1H), 7.54 (d, J = 3.7 Hz, 1H), 7.24 (t, J = 7.0 Hz, 1H), 6.74 (t, J = 10.3 Hz, 2H), 6.59 (d, J = 1.7 Hz, 1H), 5.11 (s, 2H); $^{13}$C NMR (CDCl$_3$) δ 183.4, 157.0, 150.6, 147.4, 140.1, 129.8, 123.8, 120.1, 115.1, 112.8, 86.5, 71.9; HRMS m/z Calc for C$_{12}$H$_{9}$I$_{2}$O$_2$ 327.9597, found 327.9600.

1-(2-Iodophenoxy)propan-2-one (9a). Prepared using the general coupling procedure as outlined above with chloroacetone as the α-halo ketone. $^1$H NMR (CDCl$_3$) δ 7.80 (d, J = 7.7 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 4.50 (s, 2H), 2.40 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ 205.9, 156.6, 140.1, 129.9, 123.8, 112.2, 86.4, 74.0, 27.6; HRMS m/z Calc for C$_{9}$H$_{9}$I$_{2}$O$_2$ 275.9667, found 275.9652.

2-(2-Iodophenoxy)acetaldehyde (10a). A catalytic amount of osmium tetroxide (2 mol%) was added to a mixture of the known 1-(allyloxy)-2-iodobenzene (1.5 mmol, 390 mg),
diethyl ether (12 mL), and distilled water (12 mL) and stirred for 10 min at rt. Powdered sodium periodate (3.3 mmol, 706 mg) was added over a 30 min period with continued stirring for 2.5 h at rt. After reaction, the mixture was poured into water and extracted with ether (3 x 10 mL). The combined extracts were dried over Na₂SO₄, filtered, and evaporated to give the crude aldehyde, which was purified by sgc (1:1 H/EA) to afford pure aldehyde as a pale yellow oil (349 mg, 89% yield). ¹H NMR (CDCl₃) δ 9.91 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 6.4 Hz, 1H), 6.81 (t, J = 7.8 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 4.60 (s, 2H); ¹³C NMR (CDCl₃) δ 199.2, 156.6, 140.2, 129.9, 124.1, 112.7, 86.6, 73.9; HRMS m/z Calcd for C₈H₆O₂ 261.9691, found 261.9697.

**General Procedure for the Halogen-Metal Exchange/Cyclization.** Five equivalents of methyl lithium (1.6M solution in diethyl ether) were added via syringe to 4 mL of THF at 78 °C. To this solution was added 1 equivalent of starting halide (in 4 mL of THF) drop wise via syringe. After complete addition, the reaction was allowed to stir at -78 °C for 15 min. The reaction was allowed to slowly warm to rt, and was immediately quenched by the addition of 4 mL of aqueous NH₄Cl solution. After 5 min, the reaction was extracted into ethyl acetate, washed with brine (2 x 10 mL), dried over MgSO₄, filtered, and concentrated. The crude product was then dissolved in 10 mL of acetone, and 5 mL of a 10% aqueous PTSA solution was added with continued stirring for 4 h. Removal of acetone, followed by aqueous workup and extraction into ethyl acetate, afforded the crude benzofuran, which was purified via sgc.

**3-(2-methoxyphenyl)benzofuran (2b).** ¹H NMR (CDCl₃) δ 7.99 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.39-7.31 (m, 3H), 7.14-7.06 (m, 2H), 3.90 (s, 3H); ¹³C NMR (CDCl₃) δ 157.1, 155.4, 144.0, 130.2, 128.8, 127.4, 124.3,
122.9, 121.4, 121.2, 121.0, 117.8, 117.7, 111.8, 55.7; HRMS m/z Calcd for C\textsubscript{15}H\textsubscript{12}O\textsubscript{2} 224.0837, found 224.0839.

3-(4-methoxyphenyl)benzofuran (3b). $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 7.87 (d, $J = 7.3$ Hz, 1H), 7.76 (s, 1H), 7.59 (t, $J = 8.7$ Hz, 3H), 7.41-7.31 (m, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 3.89 (s, 3H); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$ 159.4, 156.0, 140.9, 131.6, 128.9, 127.3, 127.0, 124.7, 123.1, 122.1, 120.6, 114.7, 113.7, 111.9, 55.7; HRMS m/z Calcd for C\textsubscript{15}H\textsubscript{12}O\textsubscript{2} 224.0839.

3-(2,4,5-Trimethoxyphenyl)benzofuran (4b). $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 7.89 (s, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.31 (t, $J = 8.8$ Hz, 2H), 7.17 (s, 1H), 6.68 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$ 155.4, 151.6, 149.2, 143.5, 127.5, 124.4, 122.9, 122.8, 121.1, 117.6, 114.1, 112.6, 111.8, 98.5, 57.0, 56.7, 56.4; HRMS m/z Calcd for C\textsubscript{17}H\textsubscript{16}O\textsubscript{4} 284.1048, found 284.1053.

3-Phenyl-5-methoxybenzofuran (5b). $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 7.72 (s, 1H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.65 (d, $J = 7.3$ Hz, 2H), 7.47 (t, $J = 7.2$ Hz, 2H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.08 (s, 1H), 6.97 (dd, $J = 2.3$, 6.4 Hz, 1H), 3.89 (s, 3H); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$ 158.4, 157.1, 140.6, 132.4, 129.1, 128.2, 127.6, 122.3, 120.8, 120.0, 112.3, 96.4, 56.0; HRMS m/z Calcd for C\textsubscript{15}H\textsubscript{12}O\textsubscript{2} 224.0837, found 224.0839.

3-(Thiophen-2-yl)benzofuran (7b). $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 7.92 (d, $J = 9.2$ Hz, 1H), 7.87 (s, 1H), 7.57 (d, $J = 9.4$ Hz, 1H), 7.37-7.33 (m, 4H), 7.16 (t, $J = 3.5$ Hz, 1H); $^{13}$C NMR (CDCl\textsubscript{3}) $\delta$ 155.8, 141.4, 133.6, 127.9, 126.3, 125.1, 124.6, 124.5, 123.4, 120.7, 116.5, 112.0; HRMS m/z Calcd for C\textsubscript{12}H\textsubscript{8}SO 200.0296, found 200.0298.

3-(Furan-2-yl)benzofuran (8b). $^1$H NMR (CDCl\textsubscript{3}) $\delta$ 7.95 (s, 1H), 7.90 (d, $J = 6.6$ Hz, 1H), 7.54-7.50 (m, 2H), 7.39-7.31 (m, 2H), 6.67 (d, $J = 3.4$ Hz, 1H), 6.54 (d, $J = 1.8$ Hz, 1H); $^{13}$C
NMR δ 147.4, 141.7, 141.1, 137.9, 125.1, 124.8, 123.4, 121.0, 113.7, 111.9, 111.5, 106.2; HRMS m/z Calcd for C₁₂H₈O₂ 184.0524, found 184.0527.

2-(4-(Benzyloxy)-2-bromo-5-methoxyphenoxy)-1-phenylethanone (13). Prepared using the general coupling procedure as outlined above. Purification via sgc (2:1 H/EA) gave the product as a cream-colored solid in 77% yield (m.p. 97-99 °C). ¹H NMR (CDCl₃) δ 8.01 (d, J = 7.1 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.42-7.32 (m, 5H), 7.07, (s, 1H), 6.63 (s, 1H), 5.26 (s, 2H), 5.04 (s, 2H), 3.79 (s, 3H); ¹³C NMR (CDCl₃) δ 194.8, 150.1, 149.9, 144.4, 136.9, 134.7, 134.2, 129.0, 128.8, 128.5, 128.3, 127.8, 119.5, 102.8, 102.7, 73.9, 72.2, 56.6; HRMS m/z Calcd for C₂₂H₁₉BrO₄ 426.0467, found 426.0473.

2-(4-(Benzyloxy)-3-methoxyphenoxy)-1-phenylethanone (14). Prepared using the general coupling procedure as outlined above. Purification via sgc (2:1 H/EA) gave the product as an orange oil in 90% yield. ¹H NMR (CDCl₃) δ 8.00 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.43-7.28 (m, 5H), 6.77 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 2.8 Hz, 1H), 6.33-6.29 (dd, J = 2.8, 5.8 Hz, 1H), 5.21 (s, 2H), 5.07 (s, 2H), 3.85 (s, 3H); ¹³C NMR (CDCl₃) δ 194.9, 153.4, 151.1, 137.6, 134.8, 134.1, 129.1, 128.7, 128.3, 128.0, 127.6, 115.5, 104.3, 101.9, 82.3, 72.2, 71.6, 56.2; HRMS m/z Calcd for C₂₂H₂₀O₄ 348.1362, found 348.1368.

2-(4-(Benzyloxy)-2-iodo-5-methoxyphenoxy)-1-phenylethanone (15). Trifluoroacetic acid (0.3 mmol, 0.023 mL) was added to N-iodosuccinimide (1.1 mmol, 247 mg) with stirring at rt. A solution of 14 (1 mmol, 348 mg) in acetonitrile (5.15 mL) was added dropwise via syringe. After stirring at rt for 15 min, ethyl acetate was added and the mixture was washed with aqueous NaHSO₃ (10 mL), aqueous NaHCO₃ (10 mL), and brine (10 mL). The organic extract was dried over MgSO₄, filtered, and concentrated to yield a dark red oil. The crude
product was purified by sgc (2:1 H/EA) to yield 15 as a cream-colored solid (422 mg, 89% yield, m.p. 90-91 °C). $^1$H NMR (CDCl$_3$) $\delta$ 8.03 (d, $J$ = 7.2 Hz, 2H), 7.61 (t, $J$ = 7.4 Hz, 1H), 7.49 (t, $J$ = 8.0 Hz, 2H), 7.42-7.30 (m, 6H), 6.55 (s, 1H), 5.24 (s, 2H), 5.03 (s, 2H), 3.80 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 194.8, 152.7, 151.2, 144.6, 136.9, 134.6, 134.1, 129.0, 128.7, 128.6, 128.2, 127.8, 125.1 101.1, 82.3, 72.3, 68.2, 56.4; HRMS m/z Calc for C$_{22}$H$_{19}$IO$_4$ 476.0328, found 476.0336.

5-(Benzyloxy)-6-methoxy-3-phenylbenzofuran (16). Prepared using the cyclization procedure as outlined above with 1.24 mmol of 15. Purification via sgc (3:1 H/EA) yielded 16 as a pale yellow oil (383 mg, 94%). $^1$H NMR (CDCl$_3$) $\delta$ 7.70 (s, 1H), 7.69-7.47 (m, 5H), 7.44-7.32 (m, 5H), 7.13 (s, 1H), 5.19 (s, 2H), 3.96 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 151.3, 149.4, 145.9, 140.6, 137.6, 132.5, 129.2, 128.8, 128.2, 127.9, 127.6, 127.5, 122.6, 118.6, 105.8, 96.2, 72.5, 56.6; HRMS m/z Calc for C$_{22}$H$_{18}$O$_3$ 330.1256, found 330.1259.

2-(Cinnamyloxy)-4,5-dimethoxybenzaldehyde (19). Prepared using the general coupling procedure as outlined above with 4.32 mmol 18. Purification via sgc (2:1 H/EA) yielded 19 as a white solid (1.10 g, 86%, mp 118-120 °C). $^1$H NMR (CDCl$_3$) $\delta$ 10.4 (s, 1H), 7.40 (d, $J$ = 6.8 Hz, 2H), 7.35-7.28 (m, 4H), 6.77 (d, $J$ = 16.0 Hz, 1H), 6.54 (s, 1H), 6.45-6.35 (m, 1H), 4.79-4.77 (dd, $J$ = 1.4, 4.4 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 188.2, 157.9, 155.8, 144.1, 136.2, 133.9, 128.9, 128.4, 126.8, 123.7, 118.2, 109.0, 97.9, 70.5, 56.5, 56.4; HRMS m/z Calc for C$_{18}$H$_{18}$O$_4$ 298.1205, found 298.1211.

(E)-(5-(Benzyloxy)-6-methoxy-3-phenylbenzofuran-2-yl)(2-(cinnamyloxy)-4,5-dimethoxyphenyl)methanol (20). To 5 mL of THF at -78 °C, 1.2 mmol n-BuLi (0.48 mL, 2.5M in hexanes) was added via syringe. A solution of 16 (330 mg, 1 mmol) in THF (4 mL)
was added producing a dark red color. The reaction was allowed to warm to -5 °C over 2.5 h. The temperature was lowered to -78 °C and a solution of 19 (298 mg, 1 mmol) in THF (4 mL) was added dropwise. After complete addition, the reaction was allowed to warm to rt with continued stirring for 6 h. The reaction was quenched by the addition of 5 mL of aqueous NH₄Cl. The reaction mixture was washed with water and extracted with ethyl acetate (3 x 20 mL). The aqueous layer was acidified by the addition of 10% HCl and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated. The crude product was purified by sgc (1:1 H/EA) to yield 20 as an orange oil (394 mg, 63% yield). ¹H NMR (CDCl₃) δ 7.50 (d, J = 7.0 Hz, 2H), 7.42 (t, J = 6.6 Hz, 3H), 7.37-7.28 (m, 10H), 7.25 (s, 1H), 7.04 (s, 1H), 7.03 (s, 1H), 6.53 (s, 1H), 6.49 (d, J = 12.9 Hz, 1H), 6.32 (s, 1H), 6.14-6.07 (m, 1H), 5.08 (s, 2H), 4.56 (d, J = 5.9 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H); ¹³C NMR (CDCl₃) δ 151.7, 150.0, 149.7, 149.3, 148.3, 146.9, 142.3, 141.2, 136.3, 135.2, 129.7, 129.3, 129.0, 128.8, 128.7, 128.0, 127.7, 127.5, 127.1, 127.0, 126.4, 126.1, 123.8, 113.1, 110.7, 105.4, 101.6, 97.3, 71.6, 71.1, 67.7, 56.2, 56.1, 56.0; HRMS m/z Calcd for C₄₀H₃₆O₁ 628.2461.

(E)-(2-(Cinnamyloxy)-4,5-dimethoxyphenyl)methanol (21). To a solution of 19 (1 mmol, 298 mg) in methanol (7 mL) was added NaBH₄ powder (1 mmol, 37.8 mg). The mixture was allowed to stir for 30 min. After evaporation of the methanol, the crude product was dissolved in CH₂Cl₂ (15 mL), washed with brine, dried over MgSO₄, filtered, and concentrated. The product was obtained as a pale yellow oil (296 mg, 98% yield), requiring no further purification. ¹H NMR (CDCl₃) δ 7.41 (d, J = 7.6 Hz, 2H), 7.35-7.28 (m, 3H), 6.88 (s, 1H), 6.74 (d, J = 15.9 Hz, 1H), 6.58 (s, 1H), 6.44-6.37 (m, 1H), 4.70 (dd, J = 3.1, 4.5 Hz, 2H), 4.67 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H); ¹³C NMR (CDCl₃) 150.8, 149.2, 143.5, 136.5,
133.4, 128.9, 128.3, 126.8, 124.7, 121.7, 113.1, 99.4, 70.4, 61.5, 56.7, 56.5; HRMS m/z Calcd for C₁₈H₂₀O₄ 300.1362, found 300.1365.

5-Hydroxy-6-methoxy-3-phenylbenzofuran (22). NaI (3.59 mmol, 539 mg) was dissolved in acetonitrile (6 mL) with stirring at rt. To this solution was added chlorotrimethylsilane (3.59 mmol, 0.456 mL) and the resultant mixture was allowed to stir for 20 min. A solution of 16 (1.44 mmol, 475 mg) in 8 mL of acetonitrile was slowly added. The mixture was warmed to 60 °C and allowed to continue stirring for 2 h. Water (8 mL) was then added with continued stirring for 15 min. The mixture was then extracted with ethyl acetate (3 x 20 mL) and the organic layer was washed with aqueous sodium bisulfite (2 x 20 mL) and brine (2 x 20 mL), followed by drying over MgSO₄, filtering, and removing the solvent in vacuo. The crude product was purified by sgc (2:1 H/EA) to afford a cream-colored solid (248 mg, 72% yield, m.p. 100-101 °C). ¹H NMR (CDCl₃) δ 7.71 (s, 1H), 7.65 (d, J = 7.0 Hz, 2H), 7.47 (t, J = 7.2 Hz, 2H), 7.38 (s, 1H), 7.36 (t, J = 4.4 Hz, 1H), 7.08 (s, 1H), 5.63 (s, 1H), 3.96 (s, 3H); ¹³C NMR (CDCl₃) δ 150.3, 145.7, 143.1, 140.7, 132.5, 129.2, 127.5, 127.4, 122.4, 119.3, 104.4, 95.1, 56.6; HRMS m/z Calcd for C₁₅H₁₂O₃ 240.0786, found 240.0789.

(5-Hydroxy-6-methoxy-3-phenylbenzofuran-2-yl)(2-cinnamyloxy-4,5-dimethoxyphenyl)methanol (23). n-BuLi (1.1 mmol, 2.5M in hexanes, 0.44 mL) was added to 5 mL of THF at -78 °C, followed by addition of 22 (0.5 mmol, 120 mg) in 5 mL of THF. The mixture was allowed to warm to -5 °C over 2.5 h and then 19 (0.5 mmol, 149 mg) in 5 mL of THF was added. The mixture was cooled to -78 °C and allowed to stir for 6 h. The solution was quenched by the addition of 4 mL aqueous ammonium chloride and extracted with ethyl acetate (3 x 15 mL). The aqueous layer was acidified by 2N HCl and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over MgSO₄,
filtered, and the solvent was removed in vacuo. The crude compound was purified by sgc (1:1 H/EA) to afford 23 as a mixture of inseparable isomers (152 mg, 57% yield, mp 196 °C).  

$^1$H NMR (CDCl$_3$) $\delta$ 7.43 (s, 1H), 7.32-7.25 (m, 6H), 7.17 (bs, 8H), 7.09 (s, 2H), 7.08 (s, 2H), 6.52 (s, 1H), 6.40 (s, 1H), 6.35 (d, J = 16.0 Hz, 1H), 5.75-5.67 (dt, J = 6.1, 15.9 Hz, 1H), 5.54 (s, 2H), 4.33 (dd, J = 5.1, 4.7 Hz, 2H), 3.91 (s, 6H), 3.89 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 151.3, 150.0, 148.8, 145.3, 143.7, 142.9, 136.6, 132.8, 132.4, 129.2, 128.7, 128.6, 128.0, 127.2, 126.9, 124.8, 121.3, 120.1, 118.0, 115.1, 109.6, 104.1, 99.8, 95.1, 71.0, 57.1, 56.6, 56.3, 37.7; HRMS m/z Calcd for C$_{33}$H$_{30}$O$_1$ 538.1992.

(5-Benzylxy-6-methoxy-3-phenylbenzofuran-2-yl)(2-cinnamyloxy-4,5-dimethoxyphenyl)(ethoxy)methane (24). Four mL of CDCl$_3$ was added to 20 (0.63 mmol, 396 mg) immediately producing a dark green color. To this mixture, 5 mL ethanol was added and the mixture was allowed to stir overnight (9 h). The solvent was then evaporated, and the crude product was dissolved in ethyl acetate. The mixture was washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by sgc (1:1 H/EA) to afford 24 as a dark red oil (302 mg, 73% yield).  

$^1$H NMR (CDCl$_3$) $\delta$ 7.55 (d, J = 7.0 Hz, 2H), 7.48-7.44 (m, 4H), 7.39-7.29 (m, 11H), 7.06 (s, 1H), 7.04 (s, 1H), 6.53 (s, 1H), 6.51 (d, J = 16.0 Hz, 1H), 6.10-6.05 (m, 1H), 6.07 (s, 1H), 5.09 (s, 2H), 4.51-4.48 (dd, J = 4.2 Hz, 2H), 3.96 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.51-3.45 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 150.8, 149.9, 149.8, 149.3, 147.1, 145.7, 144.0, 137.5, 136.5, 133.0, 132.5, 129.5, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.8, 127.4, 126.8, 124.8, 120.3, 120.1, 105.5, 96.2, 77.5, 72.3, 70.8, 68.9, 64.4, 60.6, 56.8, 56.6, 56.3, 15.5; HRMS m/z Calcd for C$_{42}$H$_{40}$O$_7$ 656.2774, found 656.2786.
(5-Benzylxy-6-methoxy-3-phenylbenzofuran-2-yl)(2-cinnamyloxy-4,5-dimethoxyphenyl)methane (25). To a solution of 24 (0.262 mmol, 172 mg) in 10 mL of CH₂Cl₂ was added triethylsilane (0.786 mmol, 0.126 mL) with stirring at rt. Trifluoroacetic acid (0.079 mmol, 6 µL) was slowly added and the mixture was allowed to stir at rt for 2 hr. The mixture was poured into cold saturated NaHCO₃ (15 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organic layer was dried over MgSO₄, filtered, and evaporated to give the crude product which was purified by sgc (1:1 H/EA) to afford 25 as a pale white oil (130 mg, 81% yield). ^1^H NMR (CDCl₃) δ 7.46-7.26 (m, 15H), 7.09 (s, 1H), 7.03 (s, 1H), 6.72 (s, 1H), 6.65 (d, J = 16.0 Hz, 1H), 6.59 (s, 1H), 6.31-6.24 (m, 1H), 5.12 (s, 2H), 4.62 (dd, J = 4.4 Hz, 2H), 4.20 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H); ^1^3^C NMR (CDCl₃) δ 151.9, 150.0, 148.3, 147.8, 147.7, 146.9, 142.0, 141.2, 136.3, 135.1, 129.7, 129.3, 129.0, 128.8, 128.7, 128.0, 127.9, 127.7, 127.0, 126.8, 126.6, 123.4, 117.1, 116.0, 108.9, 107.4, 102.2, 98.6, 72.2, 71.8, 56.4, 56.2, 56.1, 27.9; HRMS m/z Calcd for C₄₀H₃₆O₆ 612.2512, found 612.2523.

(5-Hydroxy-6-methoxy-3-phenylbenzofuran-2-yl)(2-cinnamyloxy-4,5-dimethoxyphenyl)(ethoxy)methane (26). Prepared from 23 following the procedure for the preparation of 24. The product was obtained as a dark red oil (78% yield). ^1^H NMR (CDCl₃) δ 7.59 (d, J = 7.0Hz, 2H), 7.38 (t, J = 7.2 Hz, 3H), 7.31-7.28 (m, 9H), 7.07 (s, 1H), 7.00 (s, 1H), 6.52 (s, 1H), 6.50 (d, J = 16.2 Hz, 1H), 6.10-6.03 (m, 1H), 6.06 (s, 1H), 5.49 (s, 1H), 4.49 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.50-3.44 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H); ^1^3^C NMR (CDCl₃) δ 150.9, 150.0, 149.3, 148.8, 145.7, 144.0, 143.0, 136.5, 133.1, 132.5, 129.6, 128.8, 128.7, 128.1, 127.5, 126.8, 124.8, 121.1, 120.1, 112.2, 104.2, 99.4, 95.1, 70.8, 69.0, 64.5, 56.8, 56.5, 56.3, 15.5; HRMS m/z Calcd for C₃₅H₃₄O₇ 566.2305, found 566.2315.
2-[4,5-dimethoxy-2-(3-phenyl-trans-allyloxy)benzyl]-5-hydroxy-6-methoxy-3-phenylbenzofuran (2). Prepared following the procedure for the preparation of 25, starting with 26 (73% yield). $^1$H NMR (CDCl₃) δ 7.55 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 7.2 Hz, 3H), 7.32-7.30 (m, 5H), 7.11 (s, 1H), 6.97 (s, 1H), 6.70 (s, 1H), 6.65 (d, J = 16.0 Hz, 1H), 6.58 (s, 1H), 6.31-6.21 (dt, J = 5.9, 15.8 Hz, 1H), 5.50 (s, 1H), 4.63-4.60 (dd, J = 1.3, 4.4 Hz, 2H), 4.19 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (CDCl₃) δ 152.1, 150.5, 148.5, 145.0, 143.6, 142.8, 137.0, 136.7, 133.1, 132.9, 129.1, 128.9, 128.8, 128.1, 127.2, 126.8, 125.1, 121.6, 118.9, 118.0, 114.3, 109.6, 103.9, 99.9, 94.8, 70.8, 56.8, 56.6, 56.4, 27.2; HRMS m/z Calcd for C₃₃H₃₀O₆ 522.2042, found 522.2031.

2-(4-Benzyloxy-3-methoxyphenoxy)-1-phenylpropan-1-one (29). Prepared using the general coupling procedure with 11 (1.23 mmol, 283 mg), 2-bromo-1-phenylpropanone, and potassium carbonate. The crude product was purified via sgc (3:1 H/EA) to afford 29 as a transparent oil (405 mg, 90% yield). $^1$H NMR (CDCl₃) δ 8.06 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.47-7.28 (m, 7H), 6.69 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 2.9 Hz, 1H), 6.22 (dd, J = 2.9, 5.9 Hz, 1H), 5.45 (q, J = 6.8 Hz, 1H), 5.01 (s, 2H), 3.79 (s, 3H), 1.67 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (CDCl₃) δ 199.3, 152.8, 151.2, 151.1, 151.0, 143.2, 143.1, 137.6, 134.5, 133.9, 129.0, 128.7, 128.0, 127.6, 115.5, 104.8, 102.1, 72.1, 56.1, 18.9; HRMS m/z Calcd for C₂₃H₂₂O₄ 362.1518, found 362.1522.

2-(4-Benzyloxy-2-iodo-5-methoxyphenoxy)-1-phenylpropan-1-one (30). Trifluoroacetic acid (0.311 mmol, 24 µL) was added to a flask containing N-iodosuccinimide (1.14 mmol, 256 mg). A solution of 29 (1.04 mmol, 375 mg) in 10 mL acetonitrile was added slowly, and the resultant mixture was allowed to stir at rt for 15 min. Ethyl acetate was added and the mixture was washed with aqueous sodium bisulfite (2 x 20 mL) and brine (2 x 20 mL),...
followed by drying over MgSO₄, filtering, and evaporating the solvent in vacuo. The crude product was purified by sgc (3:1 H/EA) to afford 30 (443 mg, 87% yield) as a pale-yellow oil. ¹H NMR (CDCl₃) δ 8.12 (d, J = 7.1 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.37-7.30 (m, 5H), 7.24 (s, 1H), 6.44 (s, 1H), 5.33 (q, J = 6.8 Hz, 1H), 4.99 (s, 1H), 3.69 (s, 3H), 1.79 (d, J = 6.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 199.4, 152.0, 151.1, 144.4, 137.0, 134.3, 134.0, 129.3, 128.9, 128.7, 128.2, 127.8, 125.2, 101.5, 80.4, 74.8, 72.3, 56.3, 19.4; HRMS m/z Calcd for C₂₃H₂₁O₄ 488.0485, found 488.0492.

5-Benzyloxy-6-methoxy-2-methyl-3-phenylbenzofuran (31). Prepared using the halogen-metal exchange/cyclization procedure with 30 (0.907 mmol, 443 mg) and methyl lithium (4.54 mmol, 1.6 M in Et₂O, 2.84 mL) to give 31 as a white solid (291 mg, 94% yield, m.p. 115-117 °C). ¹H NMR (CDCl₃) δ 7.49-7.47 (m, 5H), 7.44-7.36 (m, SH), 7.11 (s, 1H), 7.07 (s, 1H), 5.14 (s, 2H), 3.95 (s, 3H), 2.51 (s, 3H); ¹³C NMR (CDCl₃) δ 150.5, 149.3, 148.6, 145.6, 137.7, 133.3, 129.0, 128.9, 128.7, 128.1, 127.9, 127.1, 120.9, 120.8, 117.0, 105.3, 95.9, 72.5, 56.7, 13.1; HRMS m/z Calcd for C₂₃H₂₀O₃ 344.1412, found 344.1416.

Isoparvifuran (27). Sodium iodide (1.37 mmol, 205 mg) was dissolved in 5 mL of acetonitrile. Chlorotrimethylsilane (1.37 mmol, 0.173 mL) was added and the solution was allowed to stir at rt for 20 min. A solution of 31 (0.621 mmol, 214 mg) in 7 mL acetonitrile was added and the resultant solution was warmed to 60 °C and allowed to stir for 90 min. The reaction was cooled to rt and water was added with additional stirring for 15 min. The mixture was extracted into ethyl acetate (3 x 20 mL) and the organic layer was washed with aqueous sodium bisulfite (2 x 20 mL) and brine (2 x 20 mL) followed by drying over MgSO₄, filtering, and evaporating the solvent in vacuo. The crude product was purified by sgc (3:1 H/EA) to yield isoparvifuran as a white solid (117 mg, 74% yield, m.p. 120 °C).
NMR (CDCl₃) δ 7.48 (bs, 1H), 7.12 (s, 1H), 7.01 (s, 1H), 5.55 (s, 1H), 3.94 (s, 3H), 2.51 (s, 3H); ¹³C NMR (CDCl₃) δ 150.3, 148.2, 144.8, 142.8, 133.2, 129.0, 128.9, 127.0, 121.6, 117.0, 103.8, 94.6, 56.6, 13.1; HRMS m/z Calcd for C₁₆H₁₄O₃ 254.0943, found 254.0947.
REFERENCES


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