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A Convergent Total Synthesis of the Biologically Active Benzofurans Ailanthoidol, Egonol and Homoegonol from Biomass-Derived Eugenol

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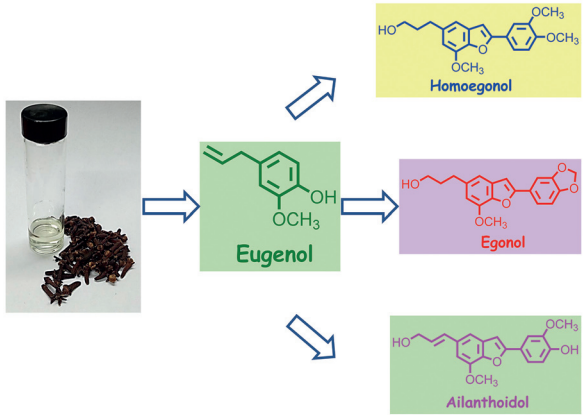

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Abstract An efficient, general synthetic protocol for the synthesis of the biologically active benzofurans ailanthoidol, egonol and homoegonol was developed. The key starting material, eugenol, is a naturally occurring and abundant precursor. The protocol, involving sequential acylation and intramolecular Wittig reaction, provides a convenient method for building the benzofuran moiety in good yield.

Key words benzofurans, ailanthoidol, egonol, homoegonol, sustainable synthesis, total synthesis, natural products

Benzofuran compounds are an important class of natural and synthetic products.[1] Their wide-ranging biological activities include antiviral,[2] anticancer,[3] antimicrobial[4] and antifungal activity,[5] among others.[6] For instance, egonol (**1**) and homoegonol (**2**) (Figure 1) are benzofuran lignans isolated from plants of the *Styrax* genus, such as *S. officinalis*,[7] *S. americana*[8] and *S. obassia*.[9] These substances exhibit cytostatic activity against human leukemic HL60 cells.[10] Another benzofuran lignan, ailanthoidol (**3**), has been isolated from the Chinese medicinal plants *Zanthoxylum ailanthoides* and *Salvia miltiorrhiza* Bunge.[11] This compound suppresses NF-κB activation, which is associated with various inflammation-associated mediators.[12] The naturally occurring egonol linoleate **4**, derived from **1** and linoleic acid, inhibits acetylcholinesterase. The latter enzyme is involved in the hydrolysis of acetylcholine, which promotes Aβ peptide aggregation, a process that leads to neural death and is associated with Alzheimer's disease.[13]

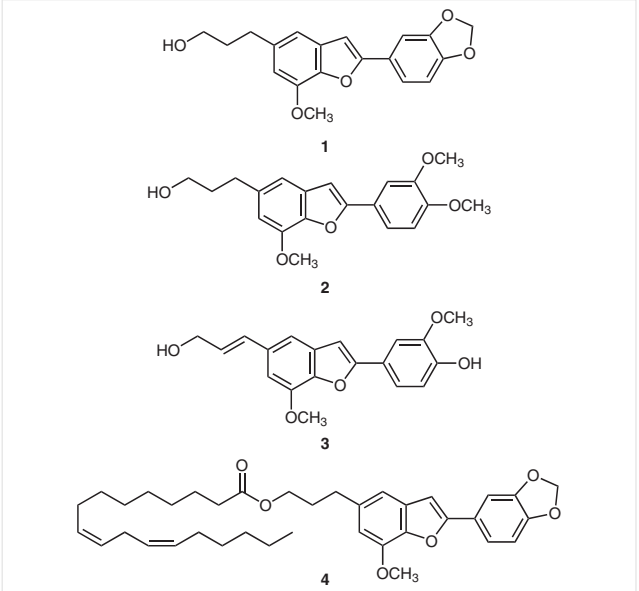

Figure 1 Structures of biologically active benzofurans

Due to the importance of the benzofuran scaffold as a potential source of novel therapeutic agents, insights into the synthesis of **1**–**4**, their analogues and other benzofuran lignans is a relevant field of research.[14,15] Thus, intense research efforts in organic synthesis have recently aimed to develop new and efficient synthetic strategies as well as improve known methods for access to these compounds. One effective and convergent strategy involves starting materials containing a common scaffold that can react with diverse structural partners to provide a wide range of ana-

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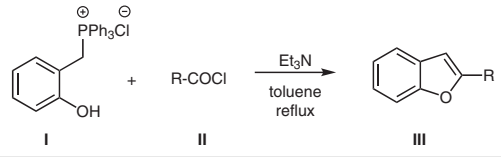
logues.[16] Based on several methodologies, many approaches have been designed for the construction of the benzofuran core,[17] one example being palladium-mediated reactions.[18] However, the drawbacks of some of these methods preclude or limit a large-scale application.

One of the methods for obtaining benzofurans **III** is the intramolecular Wittig reaction of an (*o*-hydroxybenzyl)triphenylphosphonium halide **I** with an acid chloride **II** or acid anhydride in the presence of triethylamine (Scheme 1).[19] Due to the efficiency of this methodology and the availability of starting materials, it is conceivable to achieve a total synthesis of natural products **1–3** by using adequately functionalized (*o*-hydroxybenzyl)triphenylphosphonium halides and acid chlorides.

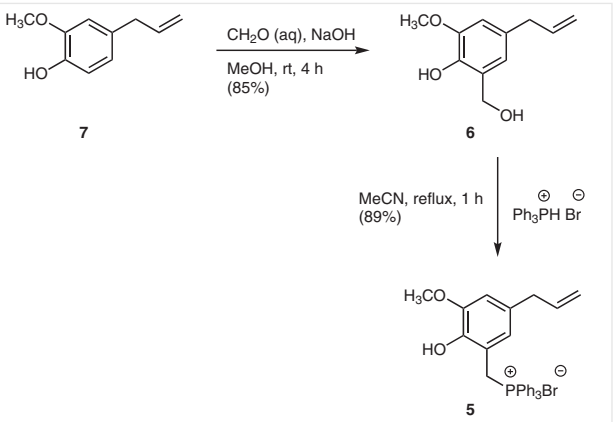


Scheme 1 General synthesis of the benzofuran ring system via the intramolecular Wittig reaction

The structural analogy between compounds **1–3** is likely derived from a common starting material. The retrosynthetic analysis of compounds **1–3** is illustrated in Scheme 2, showing that they can be prepared from (*o*-hydroxybenzyl)triphenylphosphonium bromide **5** as the common precursor. It is possible to obtain the latter compound by starting from alcohol **6**, which in turn is easily furnished from a biomass-derived chemical such as eugenol (**7**).[20] The aforementioned alcohol was previously produced from *o*-vanillin through a sequence beginning with O-allylation, followed by a Claisen rearrangement and finally a hydride reduction of the resulting aldehyde to afford (hydroxymethyl)eugenol (**6**).[21]

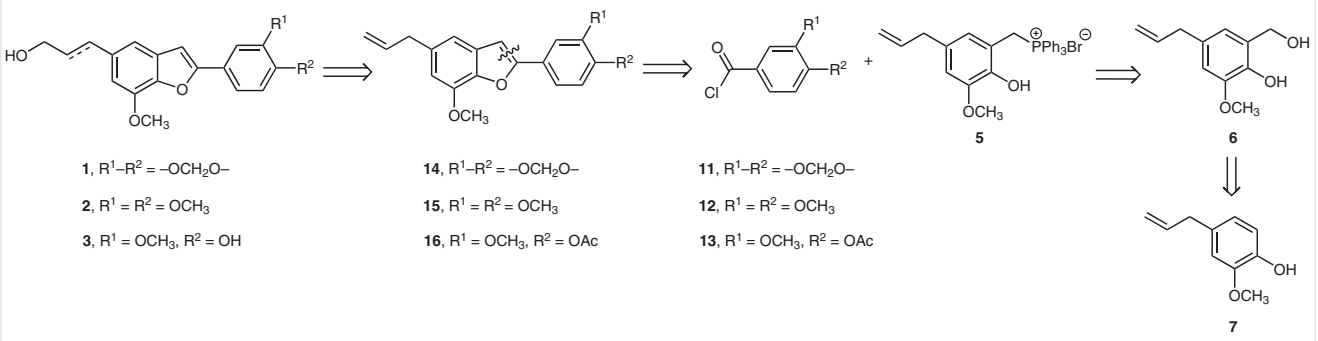
The use of biomass-derived organic compounds as starting materials constitutes one of the main objectives of green chemistry.[22] In recent years, important organic targets have been synthesized from a starting material obtained from biomass.[23] Accordingly, the main constituent of clove oil, eugenol (**7**), has been employed as the starting material for the synthesis of diverse organic compounds.[22] Therefore, we explored the preparation of compounds **1–3** by starting from this inexpensive and abundant compound. All these compounds are functionalized benzofurans of potential biological importance.

The aforementioned retrosynthetic analysis indicated that (hydroxymethyl)eugenol (**6**) should be the key intermediate leading to the formation of benzofurans **1–3**. Thus, eugenol (**7**) was reacted with formalin solution in a basic medium (NaOH) to produce the desired allylic alcohol **6** in 85% yield (Scheme 3).[24] Treatment of **6** with triphenylphosphonium bromide in acetonitrile, as reported by Hamanaka and co-workers,[25] gave phosphonium salt **5** in 89% yield. The latter salt was used in the next step without further purification.



Scheme 3 Preparation of the key phosphonium salt intermediate **5** from eugenol (**7**)

The design of the synthetic approach to generate the precursor of the benzofuran ring depended on which of the natural products **1–3** was targeted (Scheme 4). The synthesis of egonol (**1**) and homoegonol (**2**) was achieved by reacting the corresponding acid chlorides **11** and **12**, respectively, in the presence of phosphonium salt **5** in toluene at reflux, with triethylamine as the base. The allylbenzofuran



Scheme 2 Retrosynthetic analysis of the propyl/propenyl-substituted benzofuran system

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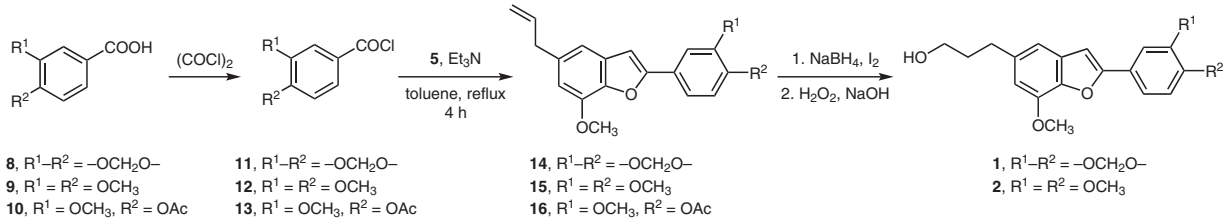


Scheme 4 General scheme for synthesis of the benzofuran system by the intramolecular Wittig reaction

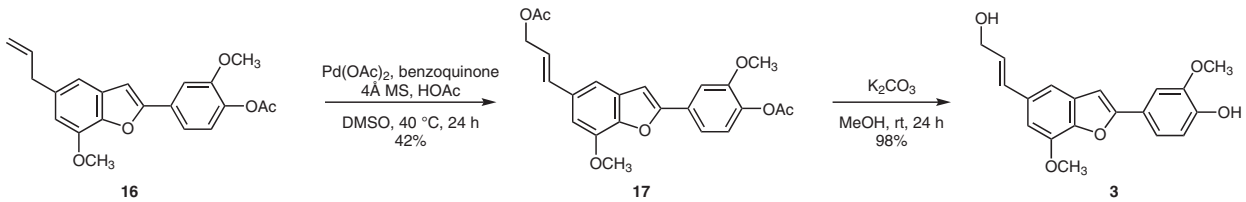
products **14** and **15** were furnished in 69% and 58% yield, respectively. Utilizing the procedure of Periasamy and co-workers,[26] hydroboration–oxidation of the allyl chain of **14** and **15** resulted in egonol (**1**) and homoegonol (**2**) in 53% and 83% yield, respectively.

The availability of acid chloride **13** was required for the synthesis of ailanthoidol (**3**). The former compound was obtained from *O*-acetylvanillic acid (**10**), which in turn was prepared from commercially available vanillic acid, by a two-step sequence. Firstly, acetylation of vanillic acid with acetic anhydride and sulfuric acid as the catalyst afforded **10**.[27] Then, reaction of **10** with oxalyl chloride provided acid chloride **13**, which was used without further purification. Finally, a mixture of phosphonium salt **5** and **13** in toluene was heated to reflux with triethylamine (3 equiv), delivering 5-allylbenzofuran **16** in 59% yield as a crystalline solid after purification by chromatography (Scheme 4).

Once the key precursor **16** was in hand, the oxidation conditions for the allylic chain were explored. Initially, the procedure reported by Le Bras and co-workers for the allylic acetoxylation of alkenes[28] was tested. Thus, **16** was reacted with palladium(II) acetate (5 or 10 mol%), benzoquinone (2 equiv) and sodium acetate (2 equiv) in acetic acid at 40 °C for 24 hours. Analysis of the reaction mixture showed no conversion into the desired allylic acetate, only a recovery of the starting substrate **16**. In contrast, the method reported by Chen and White was more efficient.[29] This method consists of similar palladium-catalyzed conditions, but in the presence of dimethyl sulfoxide as the solvent. Consequently, allylbenzofuran **16** was treated with palladium(II) acetate (10 mol%), benzoquinone (2 equiv) and acetic acid in DMSO at 40 °C for 24 hours, in the presence of molecular sieves. The desired ailanthoidol diacetate (**17**) was generated in 42% yield. Hydrolysis of both acetyl groups of **17** with potassium carbonate in methanol furnished ailanthoidol (**3**) in 98% yield (Scheme 5). With the aim of improving the yield of the oxidation step, some variations on the procedure were carried out,[30] either by increasing the palladium(II) acetate concentration to 20 mol% or modifying the equivalents of benzoquinone or acetic acid; however, the yield of the process was not increased. Indeed, there was no reaction at all in some experiments.

In summary, we have accomplished the total synthesis of the biologically active benzofurans egonol (**1**), homoegonol (**2**) and ailanthoidol (**3**) by using eugenol (**7**), which is a readily available, inexpensive and biomass-derived starting material. The acylation/intramolecular Wittig reaction cascade process proved to be an efficient method for the formation of the benzofuran scaffold. Furthermore, the palladium(II)-catalyzed allylic acetoxylation of the propenyl side chain of precursor **16** is a convenient method for the final key step in the synthesis of **3**, albeit in modest yield. Therefore, this approach may be an expedient strategy for the synthesis of a variety of substituted 2-arylbenzofurans with potential biological activity.

All reagents were obtained from commercial suppliers (Sigma-Aldrich and Oakwood Chemical) unless otherwise stated, and solvents were used as received. All moisture-sensitive reactions were performed under an argon atmosphere. Reactions were monitored by analytical TLC (E. Merck 0.25 mm silica gel 60 F254). TLC plates were visualized by exposure to UV light (254 nm). Benzofuran products were spotted by their fluorescence under these conditions. Flash column chromatography was performed with silica gel (Natland 230–400 mesh). All spectra were recorded at 25 °C. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer using $CDCl_3$ as solvent. Tetramethylsilane was the reference (0.00 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR acquisitions. HRMS data were recorded on a Jeol JSM-GC Mate-II spectrometer in EI$^+$ mode.



Scheme 5 Palladium-catalyzed allylic oxidation of the propenyl side chain of **16** and hydrolysis to give ailanthoidol (**3**)

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4-Allyl-2-(hydroxymethyl)-6-methoxyphenol (6)

To a solution of NaOH (1 g, 25 mmol) in H_2O (25 mL) was added eugenol (**7**; 5.00 g, 30.5 mmol), and then the mixture was stirred until complete dissolution was achieved. Subsequently, 35% aqueous formaldehyde solution (15 mL, 6.00 g, 200 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 4 h. Thereafter, the resulting mixture was acidified (pH 5) with HOAc and extracted with $CHCl_3$ (2 × 35 mL). The combined organic extracts were washed with H_2O (4 × 40 mL) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography over silica gel (hexane/EtOAc, 3:2) to afford **6** (5.03 g, 85%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.63 (br s, 1 H, O*H*), 3.30 (dm, *J* = 6.7 Hz, 2 H, ArCH_2CH=), 3.86 (s, 3 H, OCH_3), 4.70 (s, 2 H, CH_2OH), 5.04–5.09 (m, 2 H, CH_2=), 5.93 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1 H, CH_2C*H*=), 6.15 (s, 1 H, O*H*), 6.65 (br s, 1 H, H-3), 6.67 (br s, 1 H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 39.8 (Ar*C*H_2CH=), 56.0 (O*C*H_3), 61.8 (*C*H_2OH), 110.7 (C-3), 115.6 (*C*H_2=), 120.6 (C-5), 126.1 (C-1), 131.4 (C-4), 137.6 (CH_2*C*H=), 141.9 (C-2), 146.5 (C-6).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{11}H_{14}O_3$: 194.0943; found: 194.0934.

(5-Allyl-2-hydroxy-3-methoxybenzyl)triphenylphosphonium Bromide (5)

A solution of **6** (2.64 g, 13.6 mmol) and triphenylphosphine hydrobromide (4.70 g, 13.6 mmol) in MeCN (70 mL) was stirred under reflux for 1 h. The reaction mixture was concentrated to half-volume and diluted with Et_2O (100 mL). The solid was collected by filtration and washed with Et_2O to give **5** (6.3 g, 89%) as a brownish powder; mp 269–273 °C (Lit.[14f] 277–278 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.08 (d, *J* = 6.6 Hz, 2 H, CH_2PPh_3Br), 3.78 (s, 3 H, OCH_3), 4.85–4.92 (m, 2 H, CH_2=), 4.99 (d, *J* = 13.7 Hz, 2 H, ArCH_2CH=), 5.66 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1 H, CH_2C*H*=), 6.31 (br s, 1 H, H-5), 6.57 (br s, 1 H, H-3), 7.64–7.66 (m, 12 H, Ph-H), 7.78–7.79 (m, 3 H, Ph-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 39.4 (Ar*C*H_2CH=), 51.6 (O*C*H_3), 65.8 (*C*H_2PPh_3Br), 111.6 (ArC), 111.6 (ArC), 112.5 (ArC), 112.6 (ArC), 115.7 (*C*H_2=), 117.3 (ArC), 118.2 (ArC), 123.1 (C-1), 123.2 (ArC), 129.9 (ArC), 130.0 (C-3), 131.7 (ArC), 131.8 (C-4), 134.0 (ArC), 134.1 (C-5), 134.9 (CH_2*C*H=), 135.0 (ArC), 136.9 (ArC), 142.9 (ArC), 143.0 (C-2), 147.0 (C-6), 147.0 (ArC).

4-Acetoxy-3-methoxybenzoic Acid (*O*-Acetylvanillic Acid, 10)[27]

Ac_2O (10 mL, 106 mmol) and vanillic acid (10 g, 59.5 mmol) were placed in a 100-mL round-bottom flask equipped with a magnetic stirring bar. A catalytic amount of H_2SO_4 (2 drops) was added and the mixture was heated to 80 °C for 6 h. After the mixture was cooled to 0 °C and H_2O (100 mL) was added, the resulting yellow solid was collected by filtration, washed with H_2O (4 × 10 mL) and air-dried at room temperature to obtain **10** (9.63 g, 77%) as a light-brown powder; mp 140–142 °C (Lit.[27] 143–145 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, OCOCH_3), 3.91 (s, 3 H, OCH_3), 7.15 (d, *J* = 8.2 Hz, 1 H, H-5), 7.71 (d, *J* = 1.9 Hz, 1 H, H-2), 7.77 (dd, *J* = 8.2, 1.9 Hz, 1 H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.8 (ArOCO*C*H_3), 56.2 (ArO*C*H_3), 113.9 (C-2), 123.1 (C-5), 123.6 (C-6), 128.0 (C-1), 144.5 (C-4), 151.3 (C-3), 168.6 (ArCO*C*H_3), 171.3 (COOH).

Acid Chlorides 11, 12 and 13; General Procedure

In a one-necked 50-mL round-bottom flask equipped with a magnetic stirring bar, the corresponding carboxylic acid **8**, **9** or **10** (11.55 mmol) was placed in CH_2Cl_2 (10 mL). Subsequently, addition was made of a drop of DMF and oxalyl chloride (4 mL, 47 mmol) in one portion. A vigorous gas emission was immediately released. Stirring was continued until the gas emission stopped (about 25–30 min), and then the mixture was heated to reflux for 1 h. The solvent and excess oxalyl chloride were removed under reduced pressure to furnish the corresponding acid chloride as a dark-brown syrup. The syrup was used in the next step without further purification.

Benzofurans 14, 15 and 16; General Procedure

Phosphonium salt **5** (5.50 g, 10.5 mmol) was suspended in toluene (60 mL); then, the corresponding acid chloride **11**, **12** or **13** (11.55 mmol) and freshly distilled Et_3N (4.4 mL, 31.5 mmol) were added sequentially. The mixture was heated to reflux under an argon atmosphere for 4 h, and then the solid was removed by filtration and the solvent evaporated. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 9:1) to deliver the corresponding benzofuran as a solid.

5-(5-Allyl-7-methoxybenzofuran-2-yl)benzo[*d*][1,3]dioxole (14)

Yield: 2.25 g (69%); white solid; mp 67–71 °C (Lit.[14f] 69–71 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (d, *J* = 6.7 Hz, 2 H, ArCH_2CH=), 4.03 (s, 3 H, OCH_3), 5.08–5.15 (m, 2 H, CH_2=), 6.00 (s, 2 H, OCH_2O), 5.97–6.07 (m, 1 H, CH_2C*H*=), 6.62 (br s, 1 H, H-4), 6.79 (s, 1 H, H-3), 6.87 (d, *J* = 8.1 Hz, 1 H, H-5′), 6.97 (br s, 1 H, H-6), 7.32 (d, *J* = 1.6 Hz, 1 H, H-2′), 7.40 (dd, *J* = 8.1, 1.6 Hz, 1 H, H-6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 40.5 (Ar*C*H_2CH=), 56.0 (O*C*H_3), 100.4 (C-3), 101.3 (OCH_2O), 105.5 (C-2′), 107.3 (C-4), 108.6 (C-5′), 112.5 (C-6), 115.6 (*C*H_2=), 119.1 (C-6′), 124.6 (C-1′), 131.0 (C-3a), 135.6 (C-5), 137.9 (CH_2*C*H=), 142.5 (C-7a), 144.7 (C-7), 147.9 (C-3′ or C-4′), 148.0 (C-3′ or C-4′), 156.0 (C-2).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{19}H_{16}O_4$: 308.1049; found: 308.1041.

5-Allyl-2-(3,4-dimethoxyphenyl)-7-methoxybenzofuran (15)[14f]

Yield: 1.88 g (58%); white solid; mp 90–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 (d, *J* = 6.7 Hz, 2 H, ArCH_2CH=), 3.93 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 5.08–5.15 (m, 2 H, CH_2=), 6.03 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1 H, CH_2C*H*=), 6.62 (br s, 1 H, H-4), 6.84 (s, 1 H, H-3), 6.92 (d, *J* = 8.4 Hz, 1 H, H-5′), 6.98 (br s, 1 H, H-6), 7.36 (d, *J* = 1.9 Hz, 1 H, H-2′), 7.45 (dd, *J* = 8.4, 1.9 Hz, 1 H, H-6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 40.5 (Ar*C*H_2CH=), 56.0 (O*C*H_3), 56.0 (O*C*H_3), 56.0 (O*C*H_3), 100.3 (C-3), 107.2 (C-4), 108.0 (C-2′), 111.1 (C-5′), 112.5 (C-6), 115.7 (*C*H_2=), 118.0 (C-6′), 123.4 (C-1′), 131.1 (C-3a), 135.7 (C-5), 137.9 (CH_2*C*H=), 142.5 (C-7a), 144.7 (C-7), 149.0 (C-3′), 149.4 (C-4′), 156.3 (C-2).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{20}H_{20}O_4$: 324.1362; found: 324.1364.

4-(5-Allyl-7-methoxybenzofuran-2-yl)-2-methoxyphenyl Acetate (16)

Yield: 1.89 g (51%); light-yellow crystals; mp 123–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, OCOCH_3), 3.46 (d, *J* = 6.7 Hz, 2 H, ArCH_2CH=), 3.94 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 5.09–5.16 (m, 2 H, CH_2=), 6.03 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1 H, CH_2C*H*=), 6.65 (br s, 1 H, H-4′), 6.93 (s, 1 H, H-3′), 7.00 (br s, 1 H, H-6′), 7.10 (d, *J* = 8.4 Hz, 1 H, H-6), 7.44–7.46 (m, 2 H, H-5, H-3).

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^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.7 ($OCOCH_3$), 40.5 ($ArCH_2CH$=), 55.8 (OCH_3), 56.1 (OCH_3), 101.8 (C-3′), 107.6 (C-4′), 108.9 (C-3), 112.7 (C-6′), 115.7 (CH_2=), 117.6 (C-5), 123.1 (C-6), 129.3 (C-4), 130.8 (C-3a), 135.8 (C-5′), 137.8 (CH_2CH=), 139.8 (C-1), 142.8 (C-7a), 144.8 (C-7′), 151.2 (C-2), 155.5 (C-2′), 169.0 ($OCOCH_3$).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{21}H_{20}O_5$: 352.1311; found: 352.1301.

Hydroboration–Oxidation of 14 and 15; General Procedure[26]

Pulverized $NaBH_4$ (115 mg, 3 mmol) and anhydrous THF (20 mL) were placed in a 100-mL round-bottom flask equipped with a septum and a magnetic stirring bar. The flask was cooled in an ice–salt bath, which was followed by the dropwise addition (via syringe) of a solution of iodine (0.306 g, 1.20 mmol) dissolved in THF (5 mL). The addition rate was controlled according to the disappearance of the color. After the mixture was stirred in the cooling bath for 30 min, a solution of the corresponding alkene **14** or **15** (6.48 mmol) in anhydrous THF (10 mL) was added dropwise via syringe (during 10 min). The mixture was stirred at 25 °C for 2 h, then the reaction was quenched with aqueous 3 N NaOH (12 mL). Subsequently, 30% H_2O_2 (1.4 mL) was added dropwise and the mixture was stirred at room temperature for 1 h, followed by dilution with EtOAc (25 mL) and brine solution (20 mL). The aqueous phase was extracted with EtOAc (1 × 20 mL) and the combined organic extracts were washed with H_2O (2 × 20 mL) and brine (1 × 20 mL), then dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude purified by flash column chromatography over silica gel (hexane/EtOAc, 3:2, 1:1) to provide the corresponding alcohol **1** or **2** as a solid.

3-(2-(Benzo[*d*][1,3]dioxol-5-yl)-7-methoxybenzofuran-5-yl)propan-1-ol (Egonol, 1)

Yield: 1.13 g (53%); white powder; mp 105–107 °C (Lit.[14e] 100–103 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63 (br s, 1 H, O*H*), 1.94 (quin, *J* = 6.5 Hz, 2 H, $ArCH_2CH_2CH_2OH$), 2.76 (t, *J* = 7.6 Hz, 2 H, $ArCH_2CH_2CH_2OH$), 3.70 (t, *J* = 6.4 Hz, 2 H, $ArCH_2CH_2CH_2OH$), 4.02 (s, 3 H, OCH_3), 5.99 (s, 2 H, OCH_2O), 6.63 (br s, 1 H, H-4), 6.78 (s, 1 H, H-3), 6.86 (d, *J* = 8.4 Hz, 1 H, H-5′), 6.96 (s, 1 H, H-6), 7.31 (d, *J* = 1.2 Hz, 1 H, H-2′), 7.39 (dd, *J* = 8.1, 1.4 Hz, 1 H, H-6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 32.4 ($ArCH_2CH_2CH_2OH$), 34.6 ($ArCH_2CH_2CH_2OH$), 56.1 (OCH_3), 62.2 ($ArCH_2CH_2CH_2OH$), 100.3 (C-3), 101.3 (OCH_2O), 105.5 (C-2′), 107.2 (C-4), 108.6 (C-5′), 112.2 (C-6), 119.1 (C-6′), 124.6 (C-1′), 130.9 (C-3a), 137.5 (C-5), 142.3 (C-7a), 144.7 (C-7), 147.9 (C-3′ or C-4′), 148.0 (C-3′ or C-4′), 156.0 (C-2).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{19}H_{18}O_5$: 326.1154; found: 326.1144.

3-(2-(3,4-Dimethoxyphenyl)-7-methoxybenzofuran-5-yl)propan-1-ol (Homoegonol, 2)

Prepared from 0.332 g (1.02 mmol) of **15**.

Yield: 0.285 g (83%); white powder; mp 115–118 °C (Lit.[14d] 118–119 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (br s, 1 H, O*H*), 1.88–2.01 (m, 2 H, $ArCH_2CH_2CH_2OH$), 2.73–2.83 (m, 2 H, $ArCH_2CH_2CH_2OH$), 3.71 (t, *J* = 6.4 Hz, 2 H, $ArCH_2CH_2CH_2OH$), 3.92 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 6.64 (d, *J* = 1.2 Hz, 1 H, H-4), 6.83 (s, 1 H, H-3), 6.92 (d, *J* = 8.4 Hz, 1 H, H-5′), 6.96–7.00 (m, 1 H, H-6), 7.36 (d, *J* = 1.9 Hz, 1 H, H-2′), 7.45 (dd, *J* = 8.4, 2.0 Hz, 1 H, H-6′).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 32.6 ($ArCH_2CH_2CH_2OH$), 34.8 ($ArCH_2CH_2CH_2OH$), 56.1 (OCH_3), 56.2 (OCH_3), 56.2 (OCH_3), 62.4 ($ArCH_2CH_2CH_2OH$), 100.4 (C-3), 107.3 (C-4), 108.2 (C-2′), 111.3 (C-5′), 112.4 (C-6), 118.2 (C-6′), 123.6 (C-1′), 131.2 (C-3a), 137.6 (C-5), 142.6 (C-7a), 144.9 (C-7), 149.2 (C-3′ or C-4′), 149.6 (C-3′ or C-4′), 156.4 (C-2).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{20}H_{22}O_5$: 342.1467; found: 342.1474.

(*E*)-3-(2-(4-Acetoxy-3-methoxyphenyl)-7-methoxybenzofuran-5-yl)allyl Acetate (Ailanthoidol Diacetate, 17)

A 40-mL Schlenk tube equipped with a stirring bar was charged with $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%), benzoquinone (217 mg, 2 mmol), **16** (352 mg, 1 mmol) and 4 Å molecular sieves (217 mg). After sequential addition of DMSO (2 mL) and HOAc (3 mL) via syringe, the mixture was heated to 40 °C for 24 h. A saturated aqueous solution of NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried over Na_2SO_4, filtered and then concentrated *in vacuo* to give a brown oil, which was purified by flash column chromatography over silica gel (hexane/EtOAc, 4:1) to furnish **17** (0.172 g, 42%) as a dark-brown solid; mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, C3″-OCO*CH*$_3$), 2.24 (s, 3 H, C1-OCO*CH*$_3$), 3.83 (s, 3 H, O*CH*$_3$), 3.94 (s, 3 H, O*CH*$_3$), 4.66 (d, *J* = 6.4 Hz, 2 H, *CH*$_2$OAc), 6.17 (dt, *J* = 15.8, 6.6 Hz, 1 H, ArCH=*CH*), 6.62 (d, *J* = 15.8 Hz, 1 H, Ar*CH*=CH), 6.78 (br s, 1 H, H-4′), 6.83 (s, 1 H, H-3′), 7.00 (d, *J* = 8.8 Hz, 1 H, H-6), 7.06 (br s, 1 H, H-6′), 7.34–7.35 (m, 2 H, H-3, H-5).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.6 (C3″-OCO*CH*$_3$), 21.0 (C1-OCO*CH*$_3$), 55.9 (O*CH*$_3$), 56.0 (O*CH*$_3$), 65.2 (*CH*$_2$OAc), 101.9 (C-3′), 104.6 (C-4′), 108.8 (C-3), 112.2 (C-6′), 117.6 (C-5), 121.9 (ArCH=CH), 123.1 (C-6), 128.9 (C-4), 130.8 (C-7a), 132.3 (C-5′), 134.7 (Ar*CH*=CH), 139.9 (C-1), 144.0 (C-3a), 145.0 (C-7′), 151.2 (C-2), 155.8 (C-2′), 168.9 (C1-O*CO*CH$_3$), 170.9 (C3″-O*CO*CH$_3$).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{23}H_{22}O_7$: 410.1366; found: 410.1370.

4-(5-((*E*)-3-Hydroxyprop-1-en-1-yl)-7-methoxybenzofuran-2-yl)-2-methoxyphenol (Ailanthoidol, 3)

Diacetate **17** (0.100 g, 0.243 mmol) in anhydrous MeOH (20 mL) was placed in a 100-mL round-bottom flask equipped with a stirring bar. Subsequently, K_2CO_3 (1.000 g, 7.24 mmol) was poured into the mixture, which was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue diluted with EtOAc (20 mL) and H_2O (15 mL). The phases were separated, the aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with H_2O (2 × 25 mL) and brine (1 × 25 mL), then dried (Na_2SO_4). Solvent removal *in vacuo* afforded **3** (0.0775 g, 98%) as a yellow solid; mp 193–195 °C (Lit.[14a] 199–201 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3 H, C3′-O*CH*$_3$), 3.96 (s, 3 H, C7-O*CH*$_3$), 4.13 (d, *J* = 4.4 Hz, 2 H, *CH*$_2$OH), 5.02 (br s, 1 H, O*H*), 6.36 (dt, *J* = 15.9, 5.2 Hz, 1 H, ArCH=*CH*), 6.59 (d, *J* = 15.9 Hz, 1 H, Ar*CH*=CH), 6.88 (d, *J* = 8.2 Hz, 1 H, H-5′), 6.98 (d, *J* = 1.1 Hz, 1 H, H-6), 7.16 (br s, 2 H, H-3, H-4), 7.31 (dd, *J* = 8.2, 2.0 Hz, 1 H, H-6′), 7.36 (d, *J* = 2.0 Hz, 1 H, H-2′), 9.60 (br s, 1 H, O*H*).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 55.7 (C7-O*CH*$_3$), 55.8 (C3′-O*CH*$_3$), 61.5 (*CH*$_2$OH), 100.0 (C-3), 104.6 (C-6), 108.9 (C-2′), 110.8 (C-4), 115.9 (C-5′), 118.0 (C-6′), 121.0 (C-1′), 129.1 (C-3a), 129.6 (ArCH=CH), 130.9 (ArCH=*CH*), 133.2 (C-5), 142.5 (C-7a), 144.6 (C-7), 147.9 (C-4′), 148.0 (C-3′), 156.3 (C-2).

HRMS (EI$^+$): *m*/*z* [M$^+$] calcd for $C_{19}H_{18}O_5$: 326.1154; found: 326.1142.

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Supporting Information

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