Total Synthesis of Ailanthoidol, Egonol, and Related Analogues

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Abstract: Efficient and general synthetic protocols were developed for the total synthesis of ailanthoidol, egonol, and some related analogues. The key transformations describe here involve a two-step construction of the benzofuran and a Sonogashira coupling, and proved to be convenient and effective, starting from readily available reagents.

Key words: benzofurans, cross-coupling, McMurry reaction, Sonogashira coupling, natural products

Benzofurans and their analogues constitute a major group of naturally occurring compounds.[1] They are of particular interest for their broad range of biological activities and significant pharmacological potential.[2] Ailanthoidol (**1**) and XH14 (**1a**) (Figure 1) were isolated from the Chinese traditional herbal medicines *Zanthoxylum ailanthoides*[3] and danshen,[4] respectively, which demonstrated interesting pharmacological activities.[5] A few other 2-arylbenzofurans, egonol (**2a**), homoegonol (**2b**), and demethoxyegonol (**2c**) (Figure 1) were isolated from *Styrax japonicum*, *Styrax officinalis* L., and *Styrax obassia*.[6–8] These compounds have been reported to have cytostatic activity against human leukemic HL-60 cells.[9]

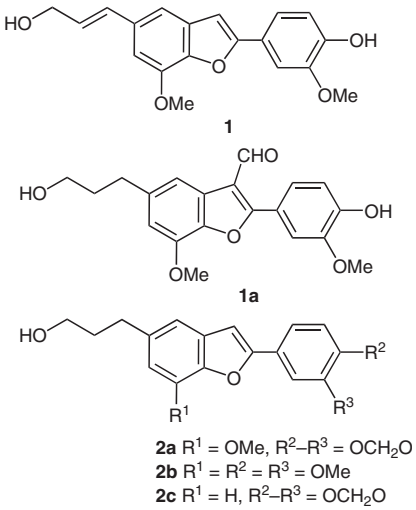

Figure 1 Structures of ailanthoidol (**1**), XH14 (**1a**), egonol (**2a**), and analogues **2b** and **2c**

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Various methodologies have been developed for the synthesis of the benzofuran nucleus, including the following: (a) metal-mediated Sonogashira coupling[10] and C–C[11] or C–O[12] arylation reactions, (b) oxidative cyclization of *o*-vinylphenols,[13] (c) dehydration of α-phenoxy ketones,[14] and (d) intramolecular McMurry coupling[15] or Wittig reactions.[16]

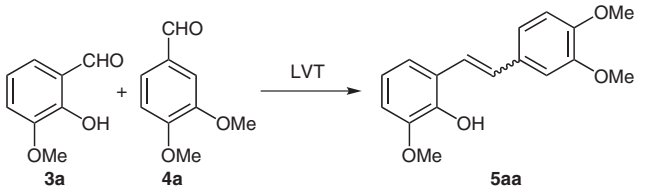
To date, many methods have been developed for the preparation of ailanthoidol (**1**), egonol (**2a**), and analogues **2b** and **2c** (Figure 1). The number of reported preparation approaches includes six for ailanthoidol (**1**),[3a,17] seven for egonol (**2a**),[18] and three each for homoegonol (**2b**)[18d,f,g] and demethoxyegonol (**2c**).[18f,g,19] Most of these syntheses are based on the construction of the benzofuran ring by a Sonogashira coupling of *o*-bromo- or iodophenols with copper–alkynes.

We report herein a general approach to the total synthesis of ailanthoidol (**1**), egonol (**2a**), and analogues **2b** and **2c** (Figure 1). It involves a stepwise reaction: the synthesis of bromobenzofurans by selective cross McMurry coupling is followed by sequential oxidative cyclization, Sonogashira coupling, reduction, and hydrolysis. This method proved to be convenient and effective, as the starting materials are the readily available salicylaldehyde as well as aromatic aldehydes, and the operations are simple.

Recently we reported various selective cross McMurry couplings of structurally similar diaryl or aryl ketones and aromatic aldehydes.[20] A two-step synthetic strategy for benzofurans based on selective cross McMurry coupling has been developed as well.[20b] During our synthesis of benzofurans,[20b] the cross McMurry couplings were mediated by $TiCl_4$ and Zn in THF. Most recently, our laboratory has made good progress in further improving the yield of this cross-coupling reaction when $TiCl_4$/Mn/THF was used in the place of $TiCl_4$/Zn/THF (Table 1). Other types of low-valent-titanium reagents were also tested, but $TiCl_4$/Mn/THF gave the best results (Table 1). Although $[TiCp_2Cl_2]$/Mn has previously been reported to promote pinacol-type coupling of aldehydes,[21] this is the first time that alkenes were generated by the use of $TiCl_4$ and Mn in THF. This can serve as an improved and alternative protocol for our previously reported selective cross-McMurry couplings and two-step construction of benzofurans.[20b]

The oxidative cyclization of *o*-vinylphenols to form benzofurans is usually achieved by the use of one of the following three reagents: (a) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[13b,c] (b) *m*-chloroperoxybenzoic

Table 1 Selective Cross-McMurry Coupling of **3a** and **4a** Promoted by Various Low-Valent Titanium Systems[a]



Entry	Titanium promoter (LVT)[b]	Reaction time (h)	Yield[c] (%)
1	$TiCl_4$/Mn (1:2)	6.0	78
2	$TiCl_4$/Zn (1:2)	6.0	70
3	$TiCl_4$/Zn/CuCl (1:2:0.1)	6.0	48
4	$TiCl_4$/Sm (1:2)	8.0	64
5	$TiCl_4$/LAH (1:2)	6.0	45

[a] Reaction conditions: **3a** (1 equiv), **4a** (1.2 equiv), LVT (2.5 equiv). For the investigation of other types of low-valent-titanium promoters, see ref. 16.
[b] Molar ratio given in parentheses.
[c] Isolated yield.

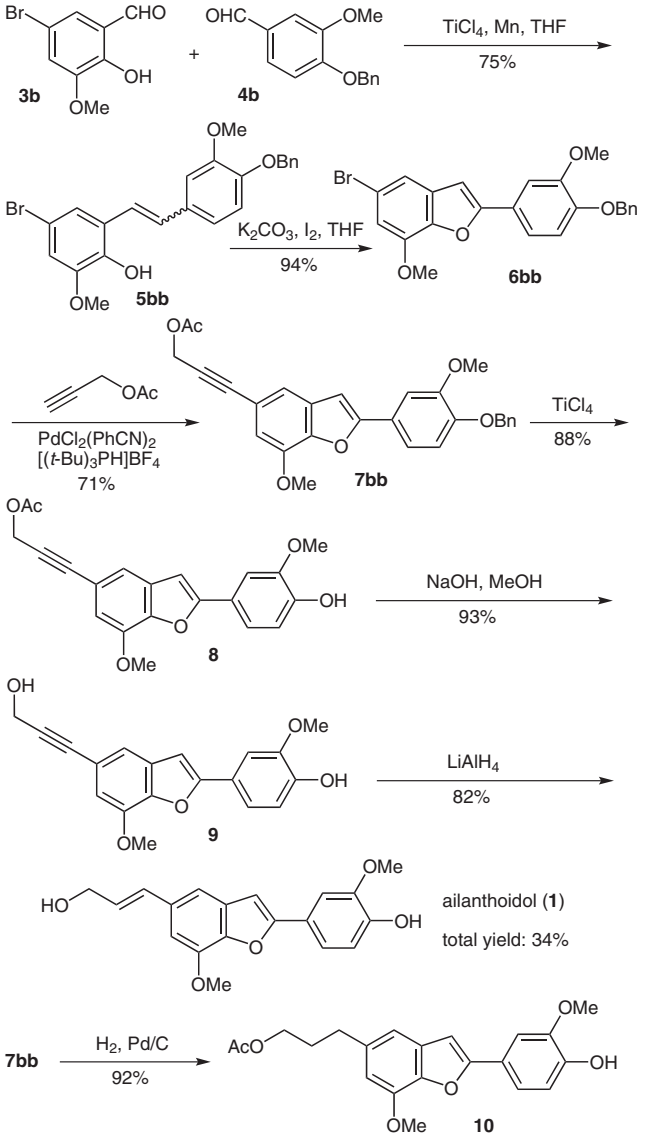
acid/*p*-toluenesulfonic acid,[13d] and (c) iodine/potassium carbonate.[13a] Here, we demonstrate that *o*-vinylphenols were cyclized by using iodine/potassium carbonate to furnish benzofurans in high yields (>90%).

The standard procedures[3a,22] used for Sonogashira coupling of propargyl acetate with bromobenzofurans catalyzed by tetrakis(triphenylphosphine)palladium led to only low yields (<35%) in our hands. The yields of the couplings were, finally, significantly improved (all >70%) when $[PdCl_2(NCPh)_2]$ with $[t\text{-}Bu_3PH]BF_4$ was used as the palladium catalyst.

As illustrated in Scheme 1, the synthesis of ailanthoidol (**1**) started with the two readily available compounds **3b** and **4b**. Bromobenzofuran **6bb** was obtained in an overall yield of 71% via a selective cross McMurry coupling, followed by oxidative cyclization. The bromobenzofuran was coupled with propargyl acetate by a palladium-catalyzed Sonogashira reaction to generate **7bb**. By debenzylation and hydrolysis, **7bb** was converted into compound **9**. Reduction of propargyl alcohol **9** to give the corresponding *trans*-allyl alcohol by the use lithium aluminum hydride[23] finally gave ailanthoidol (**1**), after a six-step synthesis with a total yield of 34%.

It should be noted that our synthetic strategy can be conveniently employed in the formal synthesis of XH14 (**1a**). Compound **7bb** (Scheme 1) was smoothly hydrogenated and debenzylated under the catalysis of palladium on carbon under one atmosphere of hydrogen to generate **10** in 92% yield. Obviously, this key precursor **10** can be regioselectively formylated according to a reported procedure[24] to afford XH14 (**1a**).

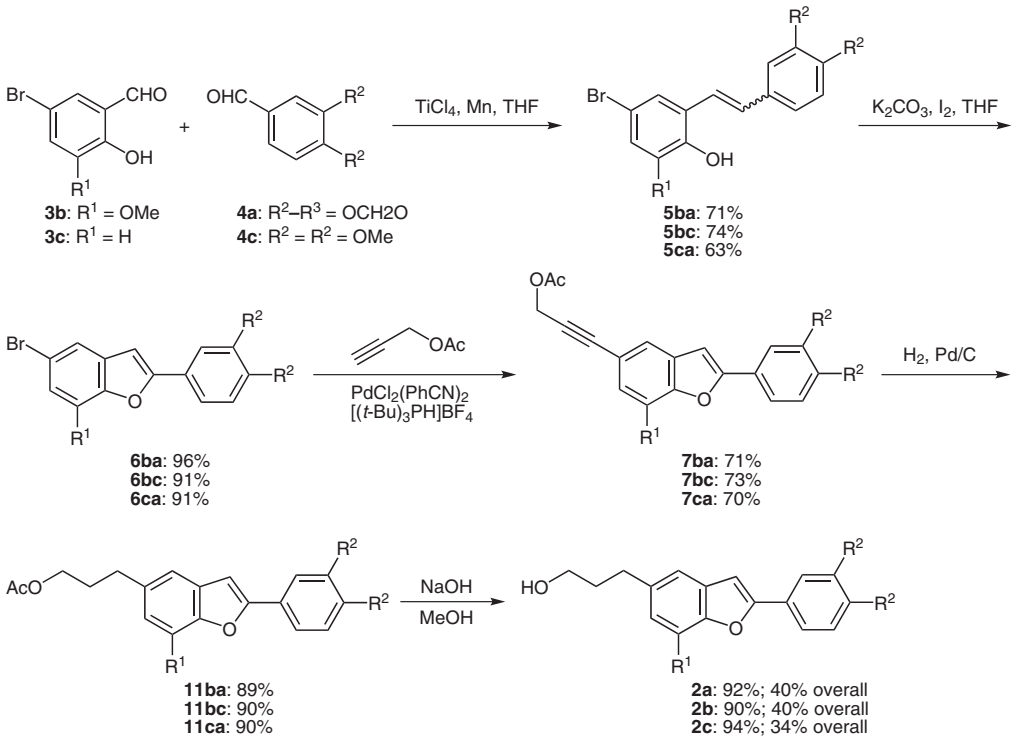
As illustrated in Scheme 2, egonol (**2a**), homoegonol (**2b**), and demethoxyegonol (**2c**) were each synthesized in five steps with overall yields of 40, 40, and 34%, respec-



Scheme 1 Total synthesis of ailanthoidol (**1**) and precursor **10** of XH14 (**1a**)

tively. The bromobenzofurans **6ba**, **6bc**, and **6ca** were also each prepared in two steps by means of selective cross McMurry coupling in overall yields of 57–68%. The 3-hydroxypropyl side chain was introduced on the benzofuran rings by Sonogashira coupling, followed by hydrogenation and hydrolysis.

To sum up, ailanthoidol (**1**) was synthesized from readily available 5-bromo-3-methoxysalicylaldehyde (**3b**) and 4-(benzyloxy)-3-methoxybenzaldehyde (**4b**) in six steps in 34% overall yield. In addition, egonol (**2a**), homoegonol (**2b**), and demethoxyegonol (**2c**) were prepared in five steps in 40, 40, and 34% overall yield, respectively. This method uses a modified reaction with a new low-valent-titanium reagent ($TiCl_4$ and Mn in THF) in the selective cross McMurry coupling. It represents an improvement to our previously reported protocol for the two-step construction of the benzofuran ring. The tethered three-carbon side chain at the 5-position of these benzofurans is



Scheme 2 Total synthesis of egonol (**2a**), homoegonol (**2b**), and demethoxyegonol (**2c**)

completed by a palladium-catalyzed Sonogashira coupling.

In conclusion, we have developed an effective and general synthetic strategy for the preparation of ailanthoidol, egonol, and analogues. On the whole, this can be accomplished with readily available reagents.

All glassware was oven-dried (120 °C) and cooled under a stream of argon gas. The reagents and solvents used for the pinacol-type couplings were freshly distilled or dehydrated before use. All other starting materials were obtained from commercial suppliers and used without further purification. Analytical TLC was conducted by using QDHY GF254 plates. Column chromatography was performed on QDYD silica gel (200–300 mesh). Melting points were recorded on a TECH X-4 microscopic instrument and are uncorrected. IR spectra were obtained on a Vaatar 360 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker Avance 400 spectrometer; TMS was used as internal standard. Mass spectra were recorded on a Traces MS spectrometer. Elemental analyses were obtained by using an Elementar Vario EL instrument.

2-(3,4-Dimethoxystyryl)-6-methoxyphenol (5aa); Typical Procedure for the Synthesis of *o*-Vinylphenols 5 by McMurry Coupling

Under an argon atmosphere, a four-necked flask equipped with a magnetic stirrer was charged with Mn powder (1.4 g, 24 mmol) and THF (80 mL). The mixture was cooled to –5 to 0 °C, and $TiCl_4$ (1.3 mL, 12 mmol) was slowly added by syringe, while the temperature was kept at <0 °C. The suspension was warmed to r.t. and stirred for 0.5 h, then heated at reflux for 2.5 h. The mixture was again cooled to –5 to 0 °C, and a soln of 2-hydroxy-3-methoxybenzaldehyde (**3a**; 0.73 g, 4.8 mmol) and 3,4-dimethoxybenzaldehyde (**4a**; 0.96 g, 5.8 mmol) in THF (30 mL) was added slowly. After addition, the reaction mixture was heated at reflux until the carbonyl compounds were consumed (as monitored by TLC). The reaction mixture was quenched with 10% aq $NaHCO_3$ (90 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and dried (Na_2SO_4). The solvent was removed and the residue was purified by flash column chromatography (silica gel, PE–EtOAc, 3:1); this gave **5aa**.

White solid; yield: 1.00 g (78%); mp 162.3–164.0 °C.

IR (KBr): 3041, 1598, 1478, 1269, 1141, 1061 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 16.4 Hz, 1 H), 7.17 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.16 (s, 1 H), 7.12 (m, 1 H), 7.07 (dd, *J* = 8.3, 1.8 Hz, 1 H), 6.83–6.87 (m, 2 H), 6.76 (dd, *J* = 8.0, 1.2 Hz, 1 H), 5.96 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 148.9, 146.7, 143.3, 131.1, 129.3, 124.0, 121.1, 119.9, 119.5, 118.7, 111.3, 109.2, 109.0, 56.1, 56.0, 55.9.

MS (EI): *m*/*z* (%) = 286 (100) [M$^+$], 284 (50), 271 (40), 211 (10).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 70.98; H, 6.36.

2-[4-(Benzyloxy)-3-methoxystyryl]-4-bromo-6-methoxyphenol (5bb)

White solid; mp 138.2–139.0 °C.

IR (KBr): 3419, 1595, 1513, 1462, 1266 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 2 H), 7.35–7.39 (m, 2 H), 7.30–7.32 (m, 2 H), 7.17–7.21 (m, 1 H), 7.04–7.10 (m, 2 H), 6.99–7.01 (m, 1 H), 6.85–6.87 (m, 2 H), 5.85 (s, 1 H), 5.18 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 148.2, 147.3, 142.3, 137.1, 131.0, 130.2, 128.6, 127.8, 127.2, 125.4, 121.1, 120.0, 119.8, 114.0, 112.3, 111.7, 109.5, 71.0, 56.4, 56.0.

MS (EI): *m*/*z* (%) = 440 (20) [M$^+$], 349 (100), 241 (25), 96 (100).

Anal. Calcd for $C_{23}H_{21}BrO_4$: C, 62.60; H, 4.80. Found: C, 62.38; H, 4.52.

2-(3,4-Methylenedioxystyryl)-4-bromo-6-methoxyphenol (5ba)
White solid; mp 173.5–175.1 °C.

IR (KBr): 3485, 1604, 1502, 1445, 1251 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 13.4 Hz, 1 H), 7.19 (d, *J* = 16.4 Hz, 1 H), 6.81–7.12 (m, 5 H), 6.00 (s, 2 H), 5.88 (s, 1 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 147.3, 142.3, 131.9, 130.1, 125.3, 121.8, 121.0, 119.8, 112.4, 111.7, 108.4, 105.7, 101.2, 56.4.

MS (EI): *m*/*z* (%) = 348 (85) [M^+], 254 (45), 152 (60), 139 (60).

Anal. Calcd for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75. Found: C, 55.21; H, 3.49.

2-(3,4-Dimethoxystyryl)-4-bromo-6-methoxyphenol (5bc)
White solid; mp 157.0–158.5 °C.

IR (KBr): 3407, 1597, 1513, 1427, 1264 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (s, 1 H), 7.13 (d, *J* = 16.4 Hz, 1 H), 6.99–7.03 (m, 3 H), 6.79 (d, *J* = 6.2 Hz, 2 H), 5.78 (s, 1 H), 3.87 (s, 3 H), 3.83 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 147.3, 142.3, 130.5, 130.3, 125.5, 121.1, 120.2, 119.6, 112.3, 111.7, 111.3, 109.0, 56.4, 55.94, 55.91.

MS (EI): *m*/*z* (%) = 364 (20) [M^+], 366 (21), 225 (20), 138 (100), 63 (95).

Anal. Calcd for $C_{17}H_{17}BrO_4$: C, 55.91; H, 4.69. Found: C, 56.03; H, 4.47.

2-(3,4-Methylenedioxystyryl)-4-bromophenol (5ca)
White solid; mp 173.0–174.0 °C.

IR (KBr): 1603, 1501, 1485, 1444, 1257, 1039 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 2.2 Hz, 1 H), 7.00–7.23 (m, 4 H), 6.96 (d, *J* = 7.99 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 5.95 (s, 2 H), 5.32 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 147.6, 130.8, 130.7, 129.3, 121.8, 119.8, 117.5, 108.4, 105.6, 101.2, 44.9.

MS (EI): *m*/*z* (%) = 318 (86) [M^+], 181 (56), 152 (69).

Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.21; H, 3.20.

2-[4-(Benzyloxy)-3-methoxyphenyl]-5-bromo-7-methoxybenzofuran (6bb); Typical Procedure for the Synthesis of 5-Bromobenzofurans 6 by Oxidative Cyclization
Anhyd K_2CO_3 (1.53 g, 11.1 mmol) was added to a soln of **5bb** (0.88 g, 2 mmol) in THF (20 mL), and subsequently the mixture was stirred for 10 min. I_2 (2.82 g, 11.1 mmol) was added, and the mixture was stirred at r.t. until *o*-vinylphenol **5bb** was consumed. The mixture was poured into sat. aq $NaHCO_3$ (30 mL) and treated with sat. aq $NaHSO_3$ (25 mL) to remove the nonreacted I_2. The mixture was extracted with EtOAc (3 × 50 mL) and the organic layer was dried (Na_2SO_4) and then concentrated. The crude material was purified by column chromatography (silica gel, PE–EtOAc, 4:1); this gave **6bb**.

White solid; yield: 0.82 g (94%); mp 154.0–155.6 °C.

IR (KBr): 1613, 1513, 1476, 1208 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.47 (m, 6 H), 7.30 (d, *J* = 1.7 Hz, 2 H), 6.93–6.95 (m, 1 H), 6.90 (d, *J* = 1.7 Hz, 1 H), 6.82 (s, 1 H), 5.22 (s, 2 H), 4.03 (s, 3 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 149.8, 149.0, 145.4, 142.8, 136.8, 132.3, 128.6, 128.0, 127.3, 123.3, 118.2, 115.9, 115.7, 113.9, 109.8, 108.7, 99.8, 71.0, 56.3, 56.2.

MS (EI): *m*/*z* (%) = 438 (15) [M^+], 346 (60), 240 (45), 91 (100).

Anal. Calcd for $C_{23}H_{19}BrO_2$: C, 62.88; H, 4.36. Found: C, 63.10; H, 4.59.

2-(3,4-Methylenedioxyphenyl)-5-bromo-7-methoxybenzofuran (6ba)
White solid; mp 167.4–168.4 °C.

IR (KBr): 1621, 1501, 1474, 1260 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 1.7, 8.2 Hz, 1 H), 7.30 (dd, *J* = 1.7, 9.4 Hz, 2 H), 6.89 (m, 2 H), 6.79 (s, 1 H), 6.02 (s, 2 H), 4.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 148.4, 148.1, 145.5, 142.8, 132.2, 124.1, 119.5, 115.9, 115.7, 110.0, 108.7, 105.6, 101.4, 99.8, 56.4.

MS (EI): *m*/*z* (%) = 346 (40) [M^+], 268 (100), 152 (75), 84 (35).

Anal. Calcd for $C_{16}H_{11}BrO_4$: C, 55.36; H, 3.19. Found: C, 55.59; H, 3.38.

2-(3,4-Dimethoxyphenyl)-5-bromo-7-methoxybenzofuran (6bc)
White solid; mp 204.5–205.8 °C.

IR (KBr): 3007, 1614, 1510, 1470.0, 1254 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.35 (d, *J* = 2.0 Hz, 1 H), 7.22 (d, *J* = 1.7 Hz, 1 H), 7.02 (m, 1 H), 6.95 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 1.7 Hz, 1 H), 3.93 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 149.8, 149.0, 145.2, 142.0, 132.0, 121.9, 117.7, 115.5, 115.2, 112.0, 109.8, 108.3, 100.3, 56.2, 55.6, 55.5.

MS (EI): *m*/*z* = 364 (50) [M^+], 362 (50), 149 (53), 81 (69), 69 (100).

Anal. Calcd for $C_{17}H_{15}BrO_4$: C, 56.22; H, 4.16. Found: C, 56.32; H, 4.42.

2-(3,4-Methylenedioxyphenyl)-5-bromobenzofuran (6ca)
White solid; mp 156.6–158.0 °C.

IR (KBr): 1605, 1572, 1483, 1172, 1110 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.35–7.40 (m, 3 H), 7.31 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.82 (s, 1 H), 6.05 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 135.3, 133.7, 128.8, 128.6, 128.0, 127.6, 126.1, 125.8, 125.7, 123.8, 123.6, 121.5, 116.0, 41.8.

MS (EI): *m*/*z* (%) = 316 (100) [M^+], 179 (35), 150 (51), 75 (24).

Anal. Calcd for $C_{15}H_9BrO_3$: C, 56.81; H, 2.86. Found: C, 57.06; H, 2.58.

5-(3-Acetoxyprop-1-ynyl)-2-[4-(benzyloxy)-3-methoxyphenyl]-7-methoxybenzofuran (7bb); Typical Procedure for the Synthesis of 5-(3-Acetoxypropynyl)benzofurans 7 by Sonogashira Coupling
A mixture of **6bb** (660 mg, 1.5 mmol), [$PdCl_2(NCPh)_2$] (58 mg, 0.15 mmol), [*t*-Bu_3PH]BF_4 (170 mg, 0.60 mmol), CuI (61 mg, 0.32 mmol), propargyl acetate (1 mL), Et_3N (1 mL), and DMF (5 mL) was introduced into a three-necked flask. After being degassed, the mixture was stirred and heated at 90 °C for 20 h. The reaction was quenched with 10% aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with 10% aq NH_4OH until the purple color disappeared and then washed with distilled H_2O to neutral. After being dried (Na_2SO_4), the organic layer was concentrated. The crude material was purified by column chromatography (silica gel, PE–EtOAc, 3:1); this gave **7bb**.

White solid; yield: 488 mg (71%); mp 147–148.8 °C (Lit.[3a] 149–151 °C).

IR (KBr): 2952, 2131, 1741, 1457, 1377, 1221 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.2 Hz, 2 H), 7.24–7.32 (m, 5 H), 7.21 (s, 1 H), 6.81–6.88 (m, 2 H), 6.73 (s, 1 H), 5.13 (s, 2 H), 4.61 (s, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.04 (s, 3 H).

5-(3-Acetoxyprop-1-ynyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (7ba)

White solid; mp 131.0–132.8 °C.

IR (KBr): 2952, 2130, 1747, 1454, 1378, 1225 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.26–7.31 (m, 2 H), 6.87–6.89 (m, 2 H), 6.78 (s, 1 H), 6.01 (s, 2 H), 4.68 (s, 2 H), 4.02 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 167.8, 157.0, 148.4, 148.2, 145.4, 132.2, 124.0, 119.5, 115.9, 115.7, 110.1, 108.6, 105.6, 101.3, 99.8, 97.0, 88.7, 56.3, 51.9, 20.6.

MS (EI): *m*/*z* (%) = 364 (25) [M^+], 306 (30), 170 (80), 151 (90).

Anal. Calcd for $C_{21}H_{16}O_6$: C, 69.23; H, 4.43. Found: C, 69.46; H, 4.70.

5-(3-Acetoxyprop-1-ynyl)-2-(3,4-dimethoxyphenyl)-7-methoxybenzofuran (7bc)

White solid; mp 196.0–197.6 °C.

IR (KBr): 2953, 2131, 1750, 1457, 1377 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.47 (m, 3 H), 7.06–7.09 (m, 3 H), 4.67 (s, 2 H), 3.99 (s, 3 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 156.6, 149.9, 149.1, 145.3, 142.0, 132.1, 121.9, 117.8, 115.5, 115.3, 112.1, 109.8, 108.4, 100.3, 96.9, 89.7, 56.2, 55.7, 55.6, 51.5, 20.3.

MS (EI): *m*/*z* (%) = 380 (30) [M^+], 365 (45), 337 (90), 139 (55).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.65; H, 5.52.

5-(3-Acetoxyprop-1-ynyl)-2-(3,4-methylenedioxyphenyl)benzofuran (7ca)

White solid; mp 122.5–124.0 °C.

IR (KBr): 2924, 2130, 1747, 1439, 1378, 1229, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (s, 1 H), 7.19–7.32 (m, 4 H), 6.81–6.83 (d, *J* = 8.1 Hz, 1 H), 6.74 (s, 1 H), 5.96 (s, 2 H), 4.69 (s, 2 H), 2.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 157.1, 153.4, 148.4, 148.2, 131.3, 126.7, 124.1, 123.2, 119.4, 115.9, 112.4, 108.8, 105.5, 101.4, 99.5, 95.6, 90.1, 52.0, 20.7.

MS (EI): *m*/*z* (%) = 334 (35) [M^+], 291 (95), 197 (40), 168 (60).

Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.61; H, 4.49.

5-(3-Acetoxypropyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxybenzofuran (10); Typical Procedure for the Synthesis of 5-(3-Acetoxypropyl)benzofurans 10 and 11 by Catalytic Hydrogenation

Benzofuran **7bb** (700 mg, 1.5 mmol) was dissolved in MeOH (15 mL). Pd/C (10%, 0.13 g) was added and the reaction mixture was stirred under H_2 (1 atm) at r.t. After compound **7bb** had been consumed (as monitored by TLC), the reaction mixture was filtered and then evaporated to dryness. The residue was purified by column chromatography (silica gel, PE–EtOAc, 3:1); this gave **10**.

White solid; yield: 470 mg (85%); mp 76–78 °C (Lit.[3a] 80–80.5 °C).

IR (KBr): 3400, 2932, 1744, 1604, 1467, 1376, 1241, 1146 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.3 Hz, 2 H), 7.29 (s, 1 H), 6.89–6.96 (m, 2 H), 6.82 (s, 1 H), 5.44 (s, 1 H), 4.39 (t, *J* = 6.7 Hz, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 2.71 (t, *J* = 7.9 Hz, 2 H), 2.16 (s, 3 H), 1.65–1.69 (m, 2 H).

5-(3-Acetoxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (11ba)

White solid; mp 94.5–96.0 °C (Lit.[6c] 94–95 °C).

IR (KBr): 1746, 1462, 1373, 1237 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.41 (dd, *J* = 10.2, 2.1 Hz, 1 H), 7.27–7.32 (m, 2 H), 6.90 (s, 1 H), 6.88 (d, *J* = 10.0 Hz, 1 H), 6.79 (s, 1 H), 6.02 (s, 2 H), 4.27 (t, *J* = 6.7 Hz, 2 H), 4.03 (s, 3 H), 2.67 (t, *J* = 7.9 Hz, 2 H), 2.16 (s, 3 H), 1.49–1.55 (m, 2 H).

5-(3-Acetoxypropyl)-2-(3,4-dimethoxyphenyl)-7-methoxybenzofuran (11bc)

White solid; mp 91–92 °C (Lit.[7] 90–91 °C).

IR (KBr): 2925, 1747, 1462, 1376, 1237 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.39 (dd, *J* = 6.4, 2.0 Hz, 1 H), 7.28 (d, *J* = 2.0 Hz, 1 H), 7.19 (s, 1 H), 6.82–6.89 (m, 2 H), 6.27 (s, 1 H), 4.26 (t, *J* = 6.9 Hz, 2 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 2.70 (t, *J* = 7.9 Hz, 2 H), 2.17 (s, 3 H), 1.48–1.56 (m, 2 H).

5-(3-Acetoxypropyl)-2-(3,4-methylenedioxyphenyl)benzofuran (11ca)

White solid; mp 95.5–97 °C (Lit.[8b] 97.8 °C).

IR (KBr): 1746, 1462, 1373, 1237cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1 H), 7.25–7.39 (m, 4 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 6.80 (s, 1 H), 6.02 (s, 2 H), 4.27 (t, *J* = 6.7 Hz, 2 H), 2.67 (t, *J* = 7.9 Hz, 2 H), 2.16 (s, 3 H), 1.49–1.55 (m, 2 H).

5-(3-Hydroxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (Egonol, 2a); Typical Procedure for the Synthesis of 5-(3-Hydroxypropyl)benzofurans 2a–c by Hydrolysis

5-(3-Acetoxypropyl)benzofuran **11ba** (180 mg, 0.5 mmol) was added to a soln of NaOH (100 mg, 2.5 mmol) in MeOH (15 mL). The mixture was refluxed until the hydrolysis was completed (as monitored by TLC) and was evaporated to dryness. The residue was dissolved in distilled H_2O (30 mL), and the soln was neutralized with 3% aq HCl and extracted with EtOAc (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 3:1); this gave egonol (**2a**).

White solid; yield: 150 mg (92%); mp 117–119 °C (Lit.[7] 115–116 °C).

IR (KBr): 3338, 2924, 1459, 1378, 1234, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.41 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.27–7.32 (m, 2 H), 6.87–6.90 (m, 2 H), 6.79 (s, 1 H), 6.02 (s, 2 H), 4.03 (s, 3 H), 3.62 (t, *J* = 6.8 Hz, 2 H), 3.06 (s, 1 H), 2.65 (t, *J* = 7.9 Hz, 2 H), 1.51–1.56 (m, 2 H).

2-(3,4-Dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran (Homoegonol, 2b)

White solid; mp 118–119 °C (Lit.[7] 120–122 °C).

IR (KBr): 3329, 2924, 1460, 1377, 1307, 1254, 1224 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.40 (dd, *J* = 6.4, 2.0 Hz, 1 H), 7.28 (d, *J* = 1.9 Hz, 1 H), 7.22 (d, *J* = 1.7 Hz, 1 H), 6.82–6.87 (m, 2 H), 6.76 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.42 (t, *J* = 6.7 Hz, 2 H), 3.04 (s, 1 H), 2.69 (t, *J* = 7.9 Hz, 2 H), 1.48–1.57 (m, 2 H).

5-(3-Hydroxypropyl)-2-(3,4-methylenedioxyphenyl)benzofuran (Demethoxyegonol, 2c)

White solid; mp 116–118 °C (Lit.[8b] 118–119 °C).

IR (KBr): 3338, 2924, 1459, 1378, 1234, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1 H), 7.34–7.39 (m, 3 H), 7.29 (d, *J* = 1.6 Hz, 1 H), 6.89–6.90 (d, *J* = 8.2 Hz, 1 H), 6.78 (s, 1 H), 6.02 (s, 2 H), 3.51 (t, *J* = 6.8 Hz, 2 H), 3.06 (s, 1 H), 2.65 (t, *J* = 7.9 Hz, 2 H), 1.49–1.55 (m, 2 H).

Ailanthoidol (1)

5-(3-Acetoxyprop-1-ynyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxybenzofuran (8)

$TiCl_4$ (0.09 mL, 0.8 mmol) was added dropwise by a syringe to a soln of **7bb** (320 mg, 0.7 mmol) in CH_2Cl_2 (25 mL) at r.t. The mixture was stirred until completion of the reaction (as monitored by TLC). The reaction mixture was quenched by the slow addition of distilled H_2O (1 mL) and treated with activated carbon. After the resulting mixture had been filtered and concentrated, the residue was subjected to flash column chromatography (silica gel, PE–EtOAc, 3:1); this gave **8**.

White solid; yield: 230 mg (88%); mp 141–142.6 °C.

IR (KBr): 3315, 2952, 2132, 1759, 1457, 1377 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.47 (m, 2 H), 7.29 (d, *J* = 1.7 Hz, 1 H), 6.89–6.96 (m, 2 H), 6.82 (s, 1 H), 5.09 (s, 1 H), 4.57 (s, 2 H), 4.03 (s, 3 H), 4.00 (s, 3 H), 2.16 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 157.6, 149.8, 149.1, 145.5, 136.8, 132.3, 123.3, 118.3, 115.9, 115.7, 114.0, 109.9, 108.6, 99.8, 96.3, 89.8, 56.3, 56.2, 52.0, 20.8.

MS (EI): *m*/*z* (%) = 366 (45) [M^+], 336 (85), 294 (90), 165 (60).

Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.59; H, 4.68.

2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxyprop-1-ynyl)-7-methoxybenzofuran (9)

Compound **8** (220 mg, 0.6 mmol) was hydrolyzed by a typical hydrolysis procedure[25] to afford **9**.

White solid; yield: 180 mg (93%); mp 136–138 °C.

IR (KBr): 3314, 2928, 2126, 1597, 1460, 1377, 1227, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 1 H), 6.45 (s, 1 H), 7.30 (d, *J* = 1.7 Hz, 1 H), 6.93–6.96 (m, 1 H), 6.90 (d, *J* = 1.7 Hz, 1 H), 6.82 (s, 1 H), 5.21 (s, 2 H), 4.51 (s, 2 H), 4.03 (s, 3 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 150.1, 148.9, 145.5, 136.8, 132.3, 123.3, 118.3, 115.9, 115.7, 114.0, 109.9, 108.6, 99.8, 96.3, 89.8, 56.3, 56.2, 50.9.

MS (EI): *m*/*z* (%) = 324 (35) [M^+], 294 (85), 181 (100).

Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.13; H, 4.68.

(*E*)-2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxyprop-1-enyl)-7-methoxybenzofuran (Ailanthoidol, 1)

A soln of **9** (150 mg, 0.5 mmol) in THF (10 mL) was added dropwise to a suspension of LAH (38 mg, 1.0 mmol) in THF (15 mL) while the temperature was kept at <0 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with distilled H_2O (15 mL). The pH of the resulting mash was adjusted to 3–4 with 5% aq HCl, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2); this gave ailanthoidol (**1**).

White solid; yield: 130 mg (82%); mp 195–196 °C (Lit.[3a] 199–201 °C).

IR (KBr): 3326, 3170, 2925, 1604, 1463, 1377, 1148 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.2 Hz, 1 H), 6.45 (s, 1 H), 7.30 (s, 1 H), 6.93–6.96 (m, 1 H), 6.89 (d, *J* = 1.7 Hz, 1 H), 6.82 (s, 1 H), 6.59 (d, *J* = 16.3 Hz, 1 H), 5.72 (d, *J* = 16.3 Hz, 1 H), 4.21 (s, 2 H), 4.00 (s, 3 H), 4.04 (s, 3 H), 3.42 (s, 1 H).

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