Modular Synthesis of Polyphenolic Benzofurans, and Application in the Total Synthesis of Malibatol A and Shoreaphenol

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Abstract: A modular strategy for the synthesis of hexacyclic dimeric resveratrol polyphenolic benzofurans is reported. The developed synthetic technology was applied to the total synthesis of malibatol A, shoreaphenol, and other biologically relevant polyphenols.

Keywords: cascade reaction; polyphenol; resveratrol; Friedel-Crafts; natural product; total synthesis

1. Introduction

Polyphenolic secondary metabolites have attracted growing interest from the scientific community in recent years [1-6]. However, despite their fascinating molecular architectures and diverse biological properties, chemical syntheses of these natural products and/or designed analogues have been scarce [7,8]. With this in mind, and as a continuation of our chemical and biological investigations of polyphenolic natural products [9,10], we set out to develop a general strategy for the synthesis of dimeric, resveratrol-derived benzofurans represented by generic structure 1, as shown in Figure 1. We further demonstrated the developed technology in the total synthesis of malibatol A (2) and
shoreaphenol (3), two dimeric resveratrol polyphenolic benzofurans isolated from Hopea malibato and Shorea robusta, respectively [11-13].

**Figure 1.** Generic molecular structure of polyphenolic benzofuran 1 and structures of malibatol A (2) and shoreaphenol (3).

### 2. Results and Discussion

Recognizing the hexacyclic structure represented by 1 containing four substituted phenyl rings, we envisaged a modular approach where each one of the phenyl rings can be installed independently and sequentially. Therefore, as outlined in Scheme 1, the proposed synthesis begin with stilbene aldehyde 4, a building block with two aromatic domains brought together through a Horner-Wadswoth-Emmons (HWE) olefination reaction [14] and a subsequent Vilsmeier formylation [15]. Introduction of a third aromatic domain through the addition of an organometallic aryl species 5 to aldehyde 4, followed by subsequent oxidation (IBX) should give ketone 6. The intermediate benzylic alcohol obtained prior to IBX oxidation has previously been demonstrated by Snyder and co-workers as a versatile intermediate to access a number of resveratrol derived natural products [7,8]. Carbonyl-directed selective demethylation of 6 should lead to phenol 7, setting the stage for the attachment of the final aromatic moiety through an alkylation with benzyl halide 8 or a Mitsunobu reaction [16] with benzyl alcohol 9. With benzyl ether 10 in hand, the formation of the benzofuran ring is anticipated through its initial benzylic deprotonation (LiTMP), followed by an intramolecular cyclization (11 to 12) and subsequent dehydration (12 to 13, *p*-TsOH·H₂O), to deliver pentacyclic benzofuran 13 [17]. Finally, the olefinic functionality in stilbene 13 should serve as a versatile handle for either direct seven-membered ring formation, or further transformation (14, e.g. epoxidation) leading to functionalized hexacycles 1 upon ring closure.

With this general strategy in mind, its realization to generate a library of benzofuran polyphenols is illustrated in Tables 1–3. As shown in Table 1, aryl ketones 16 and benzyl ethers 17 were efficiently prepared in 85–90% yield (over the two steps from 15) and 71–95% yield (over the two steps from 16), respectively. Next, benzofuran formation from keto benzyl ethers 17 under the two-step procedure generally proceeded in good yields (71–85% yield, Table 2), apart from the failure of *p*-bromo substrate to participate in the cyclization (entry 3, Table 2) and the less satisfactory dehydration for the acid sensitive furanyl substrate (entry 5, Table 2).
Scheme 1. General, modular strategy for the construction of hexacyclic benzofuran 1
Table 1. Preparation of ketone 16 and benzyl ether 17.

| Entry | R   | Ar¹ | Ar² | 16 Yield (%)<sup>b</sup> | 17 Yield (%)<sup>b</sup> |
|-------|-----|-----|-----|--------------------------|--------------------------|
| 1(a)  | H   | C₆H₅| C₆H₅| 85%                      | 89%                      |
| 2(b)  | A   | 3,5-(MeO)₂C₆H₃| C₆H₅| 88%                      | 95%                      |
| 3(c)  | A   | 3,5-(MeO)₂C₆H₃| 4-(Br)C₆H₄| 88%                    | 92%                      |
| 4(d)  | A   | 3,5-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 88%                    | 90%                      |
| 5(e)<sup>a</sup> | A   | 3,5-(MeO)₂C₆H₃| 2-furyl| 88%                    | 71%                      |
| 6(f)  | A   | C₆H₅| 4-(MeO)C₆H₄| 85%                      | 91%                      |
| 7(g)  | A   | 3,4,5-(MeO)₃C₆H₂| 4-(MeO)C₆H₄| 90%                    | 95%                      |
| 8(h)  | A   | 3,4-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 87%                      | 90%                      |
| 9(i)  | B   | 3,5-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 86%                      | 87%                      |

Reagents and conditions: (a) Ar'MgBr (1.5 equiv), THF, 0 °C, 0.5 h; (b) IBX (2.0 equiv), DMSO, 23 °C, 2 h; (c) BCl₃ (1.0 M in CH₂Cl₂, 1.5 equiv), CH₂Cl₂, 0 °C, 1 h; (d) NaH (2.0 equiv), Ar²CH₂X (entry 1, X = Br; entry 4, 6, X = Cl; 1.4 equiv), DMF, 0 °C. <sup>a</sup>furyl alcohol (3.0 equiv), PPh₃ (3.0 equiv), DEAD (3.0 equiv), THF, 0 → 23 °C, 12 h. <sup>b</sup>Yields refer to chromatographically and spectroscopically homogeneous material. DMF = N,N'-dimethylformamide, IBX = o-iodoxybenzoic acid; DEAD = diethyl azodicarboxylate.

Table 2. Preparation of benzofuran 19.

| Entry | R   | Ar¹ | Ar² | 19 Yield (%)<sup>a</sup> |
|-------|-----|-----|-----|--------------------------|
| 1(a)  | H   | C₆H₅| C₆H₅| 83                      |
| 2(b)  | A   | 3,5-(MeO)₂C₆H₃| C₆H₅| 71                      |
| 3(c)  | A   | 3,5-(MeO)₂C₆H₃| 4-(Br)C₆H₄| 0                       |
| 4(d)  | A   | 3,5-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 87                      |
| 5(e)  | A   | 3,5-(MeO)₂C₆H₃| 2-furyl| 38                      |
| 6(f)  | A   | C₆H₅| 4-(MeO)C₆H₄| 80                      |
| 7(g)  | A   | 3,4,5-(MeO)₃C₆H₂| 4-(MeO)C₆H₄| 85                      |
| 8(h)  | A   | 3,4-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 81                      |
| 9(i)  | B   | 3,5-(MeO)₂C₆H₃| 4-(MeO)C₆H₄| 85                      |

Reagents and conditions: (a) LiTMP (0.5 M in THF, 5 equiv), THF, 0 °C, 2 h; (b) p-TsOH•H₂O (1.0 equiv), CH₂Cl₂, 23 °C, 1 h. <sup>a</sup>Yields refer to chromatographically and spectroscopically homogeneous material. LiTMP = Lithium 2,2,6,6-tetramethylpiperidide; p-TsOH = toluenesulfonic acid.
Finally, closure of the seven-membered ring was carried out under acidic conditions ($p$-TsOH•H$_2$O) to give cyclized compound 20 in high yields (90–95% yield, entries 1, 2, 5–7, Table 3). The incompatibility of the furanyl functionality under the acidic conditions was once again observed (entry 3, Table 3), and the electronically less favoured substrate 19d failed to participate in the Friedel–Crafts type cyclization (entry 4, Table 3).

Table 3. Friedel–Crafts type cyclization of benzofurans 20

| Entry | R  | $R^1$ | $Ar^2$ | Yield (%)$^a$ |
|-------|----|-------|--------|---------------|
| 1(a)  | A  | 3,5-(MeO)$_2$ | C$_6$H$_5$ | 95            |
| 2(b)  | A  | 3,5-(MeO)$_2$ | 4-(MeO)C$_6$H$_4$ | 90            |
| 3(c)  | A  | 3,5-(MeO)$_2$ | 2-furyl | 0             |
| 4(d)  | A  | H     | 4-(MeO)C$_6$H$_4$ | 0             |
| 5(e)  | A  | 3,4,5-(MeO)$_3$ | 4-(MeO)C$_6$H$_4$ | 92            |
| 6(f)  | A  | 3,4-(MeO)$_2$ | 4-(MeO)C$_6$H$_4$ | 90            |
| 7(g)  | B  | 3,4-(MeO)$_2$ | 4-(MeO)C$_6$H$_4$ | 95            |

Reagents and conditions: (a) $p$-TsOH•H$_2$O (3.0 equiv), CH$_2$Cl$_2$, 40 °C, 8 h. $^a$Yields refer to chromatographically and spectroscopically homogeneous material.

In addition, we demonstrated a one-pot procedure to prepare hexacyclic benzofuran 20b directly from keto benzyl ether stilbene 17d (Scheme 2). This highly efficient, cascade process involving deprotonation-cyclization (LiTMP), dehydration and Friedel–Crafts ring-closure ($p$-TsOH) illustrated the utility of the developed methodology in the synthesis of highly functionalized, polycyclic polyphenols, a useful structural class for both chemical and biological investigations.

Scheme 2. One-pot preparation of hexacyclic benzofuran 20b.

Reagents and conditions: (a) LiTMP (5.0 equiv), THF, 0 °C, 0.5 h; (b) $p$-TsOH•H$_2$O (3.0 equiv), CH$_2$Cl$_2$, 23 → 45 °C, 8 h, 80% for the two steps.
Next, the developed methodology was applied to the total synthesis of malibatol A (2) [18] and shoreaphenol (3), as shown in Scheme 3 [19]. In this instance, with pentacyclic benzofuran 19d in hand, construction of the oxygen-substituted, seven-membered ring in the malibatol A (2) and shoreaphenol (3) framework called for an intramolecular Friedel–Crafts type epoxide-opening process. Thus, epoxidation of stilbene 19d under the bromohydrin protocol (NBS, NaOH), followed by treatment of the resulting epoxide (21) with BBr₃ resulted the concomitant cyclization and global demethylation as a one-pot process, presumably through the intermediacy of 22, giving racemic malibatol A (2) as a single diastereoisomer in 20% yield. Oxidation of malibatol A (2) in the presence of PDC then afforded shoreaphenol (3), despite the modest yield of 46%. Both malibatol A (2) and shoreaphenol (3) exhibited spectroscopic data (¹H- and ¹³C-NMR) and mass spectrometry data matching those reported for the natural substances [11-13].

**Scheme 3.** Total synthesis of malibatol A (2) and shoreaphenol (3).

\[ \text{Reagents and conditions: (a) NBS (1.1 equiv), DMSO/H}_{2}\text{O (5:1), 0 °C, 0.5 h; then NaOH (4.0 M aq.), PhEt₃NCl (1.0 equiv), Et}_2\text{O, 23 °C, 2 h, 75%; (b) BBr₃ (1.0 M in CH}_2\text{Cl}_2, 12 equiv), CH}_2\text{Cl}_2, -78 \rightarrow 23 °C, 2 h, 20%; (c) PDC (1.2 equiv), THF, 0 \rightarrow 23 °C, 1 h, 46%. NBS = N-bromosuccinimide, DMSO = dimethylsulfoxide, PDC = pyridinium dichromate.} \]

3. Experimental

3.1. General

All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) and methylene chloride
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(CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Methanol (MeOH), N,N'-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and benzene were purchased in anhydrous form and used without further purification. Acetone, water, ethyl acetate (EtOAc), diethyl ether (Et₂O), methylene chloride (CH₂Cl₂), and hexanes were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H-NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate and anisaldehyde and heat as developing agents. E. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. ¹H and ¹³C-NMR spectra were recorded at 600 and 150 MHz, respectively, on a Bruker AV-600 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. Melting points (m.p.) are uncorrected and were recorded on a Buchi B-540 melting point apparatus. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage.

3.2. General procedure A (Preparation of diaryl ketones 16, Table 1)

To a solution of aldehyde 15 (2.0 mmol) in THF (20 mL) at 0 °C was added the appropriate Grignard reagent (0.5 M in THF, 3.0 mmol). The resulting mixture was stirred for 0.5 h before it was quenched with NH₄Cl (5 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo to afford the crude benzyl alcohol, which was used directly without further purification. To the solution of crude benzyl alcohol (obtained as above) in DMSO (5 mL) at 23 °C was added IBX (1.15 g, 4.1 mmol) in one portion. The resulting mixture was stirred for 2 h before it was quenched with Na₂S₂O₃ (5 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel) afforded diaryl ketone 16. Using this general procedure the following compounds were prepared:

(2,4-Dimethoxyphenyl)(phenyl)methanone (16a). From 2,4-dimethoxybenzaldehyde and phenylmagnesium bromide. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded ketone 16a (412 mg, 85%) as a pale yellow foam. All physical properties of this compound were identical to those reported in literature [20].

(E)-(2,4-Dimethoxy-6-(4-methoxystyryl)phenyl)(3,5-dimethoxyphenyl)methanone (16b). From (E)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde and 3,5-dimethoxyphenylmagnesium bromide. Flash
column chromatography (silica gel, hexanes-EtOAc 2:1) afforded ketone 16b (764 mg, 88%) as a pale yellow foam. All physical properties of this compound were identical to those reported in literature [8].

**(E)-(2,4-Dimethoxy-6-(4-methoxystyryl)phenyl)(phenyl)methanone (16f).** From (E)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde and phenylmagnesium bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded ketone 16f (636 mg, 85%) as a pale yellow foam. 16f: Rf = 0.45 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2938, 1661, 1595, 1510, 1253, 1161, 1078, 920, 830, 721 cm−1; 1H-NMR (CD3CN): δ = 7.80–7.78 (m, 2 H), 7.58–7.55 (m, 1 H), 7.46–7.43 (m, 2 H), 7.25 (d, J = 9.0 Hz, 2 H), 7.13 (d, J = 16.2 Hz, 1 H), 6.97 (d, J = 1.8 Hz, 1 H), 6.81 (d, J = 9.0 Hz, 2 H), 6.70 (d, J = 16.2 Hz, 1 H), 6.56 (d, J = 1.8 Hz, 1 H), 3.89 (s, 3 H), 3.74 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 197.2, 161.6, 159.7, 158.3, 138.3, 137.4, 133.5, 131.2, 129.4, 129.1, 128.7, 127.9, 122.4, 121.0, 114.1, 101.4, 97.7, 55.5, 55.3, 54.9 ppm; HRMS (ESI): calcd for C24H22O4Na+ [M + Na+] 397.1410, found 397.1406.

**(E)-(2,4-Dimethoxy-6-(4-methoxystyryl)phenyl)(3,4,5-trimethoxyphenyl)methanone (16g).** From (E)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde and 3,4,5-trimethoxyphenylmagnesium bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded ketone 16g (836 mg, 90%) as a pale yellow foam. 16g: Rf = 0.25 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2938, 1661, 1578, 1511, 1413, 1327, 1156, 1126, 834 cm−1; 1H-NMR (CD3CN): δ = 7.28 (d, J = 8.4 Hz, 2 H), 7.13 (d, J = 16.2 Hz, 1 H), 7.08 (s, 2 H), 6.95 (d, J = 2.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 16.2 Hz, 1 H), 6.56 (d, J = 2.4 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 6 H), 3.74 (s, 3 H), 3.68 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 195.8, 161.5, 159.7, 158.2, 153.3, 142.7, 137.5, 133.6, 131.1, 129.4, 127.9, 122.6, 120.8, 114.1, 106.6, 101.4, 97.7, 60.0, 55.7, 55.5, 55.3, 54.9 ppm; HRMS (ESI): calcd for C27H28O7Na+ [M + Na+] 487.1727, found 487.1712.

**(E)-(2,4-Dimethoxy-6-(4-methoxystyryl)phenyl)(3,4-dimethoxyphenyl)methanone (16h).** From (E)-2,4-dimethoxy-6-(4-methoxystyryl)benzaldehyde and 3,4-dimethoxyphenylmagnesium bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded ketone 16h (755 mg, 87%) as a pale yellow foam. 16h: Rf = 0.20 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2937, 1739, 1653, 1595, 1511, 1267, 1158, 835 cm−1; 1H-NMR (CD3CN): δ = 7.50 (d, J = 1.8 Hz, 1 H), 7.26 (d, J = 9.0 Hz, 2 H), 7.20 (dd, J = 8.4, 2.4 Hz, 1 H), 7.13 (d, J = 16.2 Hz, 1 H), 6.94 (d, J = 2.4 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 16.2 Hz, 1 H), 6.56 (d, J = 2.4 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.74 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 195.5, 161.3, 159.7, 158.0, 153.8, 149.2, 137.1, 131.3, 130.9, 129.4, 127.8, 125.1, 122.5, 121.3, 114.1, 110.5, 110.1, 101.1, 97.7, 55.5, 55.3, 55.2, 54.9 ppm; HRMS (ESI): calcd for C26H26O6Na+ [M + Na+] 457.1621, found 457.1610.

**(2,4-Dimethoxy-6-((4-methoxyphenyl)ethynyl)phenyl)(3,5-dimethoxyphenyl)methanone (16i).** From 2,4-dimethoxy-6-[(4-methoxyphenyl)ethynyl]benzaldehyde and 3,5-dimethoxyphenylmagnesium bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded ketone 16i (743 mg, 86%) as a pale yellow foam. 16i: Rf = 0.28 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2938, 1671, 1590, 1569, 1510, 1247, 1153, 1065, 832 cm−1; 1H-NMR (CD3CN): δ = 7.10 (d, J = 9.0 Hz, 2 H), 6.92
(d, J = 2.4 Hz, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 6.73 (d, J = 2.4 Hz, 1 H), 6.72 (t, J = 2.4 Hz, 1 H), 6.66 (d, J = 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.77 (s, 6 H), 3.75 (s, 3 H), 3.72 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 195.7, 162.3, 162.0, 161.0, 158.8, 140.7, 133.6, 125.0, 123.2, 115.0, 114.8, 108.6, 107.7, 106.1, 100.3, 94.2, 86.4, 56.5, 56.3, 56.2, 55.9 ppm; HRMS (ESI): calcd for C26H24O6Na+ [M + Na+] 455.1465, found 455.1467.

3.3. General procedure B (Preparation of benzyl ethers 17, Table 1)

To a solution of diaryl ketone 16 (1.0 mmol) in CH2Cl2 (10 mL) at 0 °C was added BCl3 (1.0 M in CH2Cl2, 1.5 mL, 1.5 mmol) dropwise. The resulting mixture was stirred for 1 h before it was quenched with NH4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na2SO4) and concentrated in vacuo to afford the crude phenol, which was used directly without further purification. To a solution of the crude phenol (obtained as above) in DMF (5 mL) at 0 °C was added NaH (80 mg, 60% wt/wt in mineral oil, 2.0 mmol). The resulting mixture was stirred for 0.5 h before benzyl bromide (or chloride) (1.4 mmol) was added. The reaction mixture was warmed to 23 °C and the progress was monitored by TLC analysis. Upon completion of the reaction (<4 h for most cases), the reaction mixture was quenched with NH4Cl (20 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with Et2O (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na2SO4) and concentrated in vacuo. Flash column chromatography (silica gel) afforded the desired benzyl ether 17. Using the described general procedure the following substances were prepared:

(2-(Benzyloxy)-4-methoxyphenyl)(phenyl)methanone (17a). From ketone 16a and benzyl bromide. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzyl ether 17a (283 mg, 89%) as a yellow foam. 17a: Rf = 0.35 (silica gel, hexanes-EtOAc 4:1); IR (film) νmax 1651, 1601, 1579, 1501, 1446, 1272, 1166, 1120, 737, 697 cm⁻¹; 1H-NMR (CD3CN): δ = 7.73–7.72 (m, 2 H), 7.57–7.55 (m, 1 H), 7.46–7.41 (m, 3 H), 7.21–7.16 (m, 3 H), 6.93–6.92 (m, 2 H), 6.69 (d, J = 2.4 Hz, 1 H), 6.64 (dd, J = 8.4, 2.4 Hz, 1 H), 4.97 (s, 2 H), 3.84 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 195.6, 163.4, 158.3, 139.2, 136.5, 132.5, 131.6, 129.2, 128.3, 128.2, 127.6, 126.9, 121.7, 105.6, 99.7, 69.8, 55.4 ppm; HRMS (ESI): calcd for C21H18O3Na+ [M + Na+] 341.1148, found 341.1156.

(E)-(2-(Benzyloxy)-4-methoxy-6-(4-methoxystyryl)phenyl)(3,5-dimethoxyphenyl)methanone (17b). From ketone 16b and benzyl bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzyl ether 17b (485 mg, 95%) as a yellow foam. 17b: Rf = 0.45 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 1667, 1594, 1511, 1301, 1204, 1156, 1065, 829 cm⁻¹; 1H-NMR (CD3CN): δ = 7.31 (d, J = 9.0 Hz, 2 H), 7.24–7.23 (m, 3 H), 7.14 (d, J = 16.2 Hz, 1 H), 7.04–7.02 (m, 2 H), 6.96 (d, J = 2.4 Hz, 1 H), 6.88 (d, J = 2.4 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.73–6.70 (m, 2 H), 6.59 (d, J = 1.8 Hz, 1 H), 4.99 (s, 2 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.75 ppm (s, 6 H); 13C-NMR (CD3CN): δ = 196.8, 161.5, 161.1, 159.8, 157.2, 140.8, 137.7, 136.6, 131.3, 129.4, 128.3, 127.9, 127.8, 127.2, 122.4, 121.3, 114.1, 106.7, 105.1, 101.7, 99.0, 70.0, 55.3, 55.3, 54.9 ppm; HRMS (ESI): calcd for C32H30O6Na+ [M + Na+] 533.1934, found 533.1951.
(E)-(2-((4-Bromobenzyl)oxy)-4-methoxy-6-(4-methoxystyryl)phenyl)(3,5-dimethoxyphenyl)methanone (17c). From ketone 16b and 4-bromobenzyl bromide. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzyl ether 17c (542 mg, 92%) as a yellow foam. 17c: Rf = 0.41 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2837, 1666, 1593, 1510, 1300, 1156, 1066, 806 cm⁻¹; ¹H-NMR (CD3CN): δ = 7.37 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 9.0 Hz, 2 H), 7.15 (d, J = 16.2 Hz, 1 H), 6.97 (d, J = 2.4 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.84 (s, 2 H), 6.72 (d, J = 16.2 Hz, 1 H), 6.70 (t, J = 2.4 Hz, 1 H), 6.58 (d, J = 2.4 Hz, 1 H), 4.95 (s, 2 H), 3.88 (s, 3 H), 3.75 (s, 3 H), 3.74 ppm (s, 6 H); ¹³C-NMR (CD3CN): δ = 196.8, 161.5, 161.1, 159.8, 157.1, 140.9, 137.9, 135.9, 131.3, 131.3, 129.4, 129.1, 127.9, 122.3, 121.3, 121.1, 114.1, 106.6, 105.1, 105.1, 99.0, 69.3, 55.3, 55.3, 54.9 ppm; HRMS (ESI): calcd for C₃₂H₂₉BrO₆Na⁺ [M + Na⁺] 611.1039, found 611.1033.

(E)-(3,5-Dimethoxyphenyl)(4-methoxy-2-((4-methoxybenzyl)oxy)-6-(4-methoxystyryl)phenyl)methanone (17d). From ketone 16b and 4-methoxybenzyl chloride. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzyl ether 17d (486 mg, 90%) as a pale yellow solid. 17d: Rf = 0.40 (silica gel, hexanes-EtOAc 2:1); m.p. = 118–119 °C (hexanes-EtOAc); IR (film) νmax 2970, 1738, 1594, 1512, 1352, 1302, 1249, 1204, 1156, 834 cm⁻¹; ¹H-NMR (CDCl₃): δ = 7.31 (d, J = 9.0 Hz, 2 H), 7.03 (d, J = 15.0 Hz, 1 H), 6.98 (d, J = 2.4 Hz, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 6.86 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 14.4 Hz, 1 H), 6.82 (d, J = 9.0 Hz, 2 H), 6.74 (d, J = 9.0 Hz, 2 H), 6.66 (t, J = 2.4 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 4.88 (s, 2 H), 3.87 (s, 3 H), 3.77 (s, 6 H), 3.76 (s, 3 H), 3.75 ppm (s, 3 H); ¹³C-NMR (CDCl₃): δ = 197.3, 162.2, 161.9, 160.6, 159.3, 158.9, 157.3, 140.9, 137.8, 130.8, 129.4, 128.4, 128.2, 127.9, 122.8, 121.6, 113.8, 113.4, 106.9, 105.3, 101.2, 98.9, 69.8, 55.4, 55.3, 55.1, 55.0 ppm; HRMS (ESI): calcd for C₃₃H₃₂O₇Na⁺ [M + Na⁺] 563.2040, found 563.2037.

(E)-(3,5-Dimethoxyphenyl)(2-(furan-2-ylmethoxy)-4-methoxy-6-(4-methoxystyryl)phenyl)methanone (17e). To a solution of phenol 16b (420 mg, 1.0 mmol) in THF (10 mL) at 23 °C was added PPh₃ (786 mg, 3.0 mmol). The resulting mixture was cooled to 0 °C before a solution of DEAD (522 mg, 3.0 mmol) and furfuryl alcohol (294 mg, 3.0 mmol) in THF (2 mL) were added. The resulting mixture was warmed to 23 °C and stirred for 12 h before it was quenched with NH₄Cl (5 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded furanyl ether 17e (355 mg, 71%) as a yellow oil. 17e: Rf = 0.72 (silica gel, benzene-EtOAc 8:1); IR (film) νmax 2937, 1667, 1592, 1510, 1456, 1300, 1155, 1063, 819 cm⁻¹; ¹H-NMR (CD3CN): δ = 7.38 (d, J = 1.2 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 2 H), 7.13 (d, J = 16.2 Hz, 1 H), 6.97 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 2 H), 6.82 (d, J = 2.4 Hz, 2 H), 6.69 (t, J = 2.4 Hz, 1 H), 6.68 (d, J = 2.4 Hz, 1 H), 6.65 (t, J = 16.2 Hz, 1 H), 6.33–6.32 (m, 1 H), 6.28 (d, J = 3.6 Hz, 1 H), 4.95 (s, 2 H), 3.90 (s, 3 H), 3.75 (s, 3 H), 3.74 ppm (s, 6 H); ¹³C-NMR (CD3CN): δ = 197.4, 162.2, 161.9, 160.6, 157.6, 150.7, 144.2, 141.3, 138.5, 132.2, 130.2, 128.8, 123.1, 122.3, 115.0, 111.3, 111.1, 107.6, 106.0, 103.0, 100.1, 63.5, 56.2, 56.1, 55.8 ppm; HRMS (ESI): calcd for C₃₀H₂₇O₇Na⁺ [M + Na⁺] 563.2040, found 563.2037.

(E)-(4-Methoxy-2-((4-methoxybenzyl)oxy)-6-(4-methoxystyryl)phenyl)(phenyl)methanone (17f). From ketone 16f and 4-methoxybenzyl chloride. Flash column chromatography (silica gel, hexanes-EtOAc
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2:1 afforded benzyl ether 17f (437 mg, 91%) as a yellow foam. 17f: Rf = 0.50 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 1661, 1595, 1511, 1249, 1163, 1033, 721 cm⁻¹; ¹H-NMR (CD3CN): δ = 7.77–7.75 (m, 2 H), 7.62–7.59 (m, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 16.2 Hz, 1 H), 6.97 (d, J = 1.8 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.72 (d, J = 16.2 Hz, 1 H), 6.61 (d, J = 1.8 Hz, 1 H), 4.89 (s, 2 H), 3.89 (s, 3 H), 3.74 ppm (s, 3 H); ¹³C-NMR (CD3CN): δ = 198.5, 162.8, 161.0, 160.6, 158.7, 139.9, 139.0, 134.7, 132.5, 130.7, 130.4, 130.3, 130.0, 129.7, 129.2, 123.7, 122.8, 115.4, 114.9, 103.0, 100.4, 71.2, 56.6, 56.2, 56.1 ppm; HRMS (ESI): calcd for C₃₁H₂₈O₅Na⁺ [M + Na⁺] 503.1829, found 503.1817.

(E)-(4-Methoxy-2-((4-methoxybenzyl)oxy)-6-(4-methoxystyryl)phenyl)(3,4,5-trimethoxyphenyl)methanone (17g). From ketone 16g and 4-methoxybenzyl chloride. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzyl ether 17g (542 mg, 95%) as a yellow foam. 17g: Rf = 0.30 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 1655, 1595, 1512, 1413, 1327, 1249, 1157, 1126, 832 cm⁻¹; ¹H-NMR (d₆-acetone): δ = 7.35 (d, J = 9.0 Hz, 2 H), 7.22 (d, J = 15.6 Hz, 1 H), 7.08 (s, 2 H), 7.05 (d, J = 2.4 Hz, 1 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 15.6 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 2.4 Hz, 1 H), 4.99 (s, 2 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.77 (s, 9 H), 3.74 ppm (s, 3 H); ¹³C-NMR (d₆-acetone): δ = 195.3, 161.4, 159.8, 159.3, 157.5, 153.4, 142.8, 137.7, 134.4, 130.8, 129.6, 128.7, 128.6, 127.9, 122.7, 121.6, 114.0, 113.4, 106.6, 101.4, 99.0, 69.4, 59.8, 55.6, 54.9, 54.6, 54.5 ppm; HRMS (ESI): calcd for C₃₄H₃₄O₈Na⁺ [M + Na⁺] 593.2145, found 593.2137.

(E)-(3,4-Dimethoxyphenyl)(4-methoxy-2-((4-methoxybenzyl)oxy)-6-(4-methoxystyryl)phenyl)methanone (17h). From ketone 16h and 4-methoxybenzyl chloride. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzyl ether 17h (486 mg, 90%) as a yellow foam. 17h: Rf = 0.25 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 1652, 1594, 1511, 1265, 1249, 1157, 1126, 832 cm⁻¹; ¹H-NMR (CD3CN): δ = 7.45 (d, J = 1.8 Hz, 1 H), 7.27 (d, J = 9.0 Hz, 2 H), 7.22 (d, J = 15.6 Hz, 1 H), 7.08 (s, 2 H), 7.05 (d, J = 2.4 Hz, 1 H), 6.97 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 15.6 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 2 H), 6.68 (d, J = 2.4 Hz, 1 H), 4.99 (s, 2 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.77 (s, 9 H), 3.74 ppm (s, 3 H); ¹³C-NMR (CD3CN): δ = 195.7, 161.2, 159.7, 159.3, 157.1, 153.8, 149.2, 137.3, 131.6, 130.9, 129.4, 129.0, 128.5, 127.8, 124.9, 122.5, 121.9, 114.1, 113.6, 110.5, 110.2, 101.4, 99.2, 69.9, 55.6, 55.3, 55.3, 54.9, 54.8 ppm; HRMS (ESI): calcd for C₃₃H₃₂O₇Na⁺ [M + Na⁺] 563.2145, found 593.2137.

(3,5-Dimethoxyphenyl)(4-methoxy-2-((4-methoxybenzyl)oxy)-6-((4-methoxyphenyl)ethynyl)phenyl)methanone (17i). From ketone 16i and 4-methoxybenzyl chloride. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzyl ether 17i (468 mg, 87%) as a yellow foam. 17i: Rf = 0.27 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 2937, 1671, 1591, 1511, 1300, 1248, 1155, 1063, 832 cm⁻¹; ¹H-NMR (CD3CN): δ = 7.12 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 9.0 Hz, 2 H), 6.88 (d, J = 2.4 Hz, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 6.74 (d, J = 2.4 Hz, 1 H), 6.72 (t, J = 2.4 Hz, 1 H), 6.71 (d, J = 2.4 Hz, 1 H), 4.97 (s, 2 H), 3.85 (s, 3 H), 3.77 (s, 6 H), 3.76 (s, 3 H), 3.74 ppm (s, 3 H); ¹³C-NMR (CD3CN): δ = 195.8, 162.2, 162.0, 161.0, 160.3, 157.8, 140.9, 133.6, 130.0,
129.1, 125.5, 123.4, 115.0, 114.8, 114.5, 108.9, 107.6, 106.0, 101.8, 94.1, 86.4, 70.9, 56.3, 56.2, 55.9, 55.7 ppm; HRMS (ESI): calcd for C_{33}H_{30}O_{7}Na^{+} [M + Na^{+}] 561.1883, found 561.1883.

3.4. General procedure C (Preparation of benzofurans 19, Table 2)

To a solution of benzyl ether 17 (0.2 mmol) in THF (2 mL) at 0 °C was added LiTMP (0.5 M in THF, 2 mL, 1.0 mmol). The resulting mixture was stirred at 0 °C and the progress was monitored by TLC analysis. Upon completion of the reaction (~ 2 h for most cases), the reaction mixture was quenched with NH_{4}Cl (5 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_{2}SO_{4}) and concentrated in vacuo to afford crude tertiary alcohol 18, which was used directly without further purification. To a solution of the crude tertiary alcohol 18 (obtained as above) in CH_{2}Cl_{2} (3 mL) at 23 °C was added p-TsOH•H_{2}O (38 mg, 0.2 mmol). The resulting mixture was stirred for 1 h before it was quenched with NaHCO_{3} (3 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH_{2}Cl_{2} (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_{2}SO_{4}) and concentrated in vacuo. Flash column chromatography (silica gel) afforded the desired benzofuran 19. Using this general procedure the following compounds were prepared:

6-Methoxy-2,3-diphenylbenzofuran (19a). From benzyl ether 17a. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzofuran 19a (50 mg, 83%) as a pale yellow oil. All physical properties of this compound were identical to those reported in literature [21].

(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-4-(4-methoxystyryl)-2-phenylbenzofuran (19b). From benzyl ether 17b. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzofuran 19b (70 mg, 71%) as a yellow oil. 19b: R_{f} = 0.42 (silica gel, hexanes-EtOAc 2:1); IR (film) ν_{max} 1601, 1510, 1420, 1249, 1204, 1143, 1064, 1033, 808, 693 cm^{-1}; ^{1}H-NMR (CD_{3}CN): δ = 7.58–7.57 (m, 2 H), 7.32–7.25 (m, 3 H), 7.15 (d, J = 2.4 Hz, 1 H), 7.06 (d, J = 2.4 Hz, 1 H), 7.01 (d, J = 16.2 Hz, 1 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.79 (d, J = 16.2 Hz, 1 H), 6.72 (t, J = 2.4 Hz, 1 H), 6.65 (d, J = 2.4 Hz, 2 H), 3.88 (s, 3 H), 3.77 (s, 3H), 3.74 ppm (s, 6 H); ^{13}C-NMR (CD_{3}CN): δ = 163.1, 160.8, 159.9, 156.3, 150.6, 138.0, 133.6, 131.9, 131.2, 130.1, 129.8, 129.3, 128.8, 127.1, 123.4, 122.8, 119.3, 115.3, 109.9, 108.0, 101.0, 96.1, 56.8, 56.6, 56.3 ppm; HRMS (ESI): calcd for C_{32}H_{28}O_{5}Na^{+} [M + Na^{+}] 515.1829, found 515.1837.

(E)-2-(4-Bromophenyl)-3-(3,5-dimethoxyphenyl)-6-methoxy-4-(4-methoxystyryl)benzofuran (19c). From benzyl ether 17c. The desired benzofuran 19c was not obtained in this reaction.

(E)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)benzofuran (19d). From benzyl ether 17d. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzofuran 19d (91 mg, 87%) as a yellow solid. 19d: R_{f} = 0.52 (silica gel, hexanes-EtOAc 2:1); m.p. = 61–62 °C (hexanes-EtOAc); IR (film) ν_{max} 2936, 1603, 1509, 1250, 1153, 1143, 1033, 833, 808 cm^{-1}; ^{1}H-NMR (CD_{3}CN): δ = 7.43 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 2.4 Hz, 1 H), 6.95–6.89 (m, 4 H), 6.79–6.70 (m, 3 H), 6.39–6.30 (m, 3 H), 3.82 (s, 3 H), 3.71 (s, 3H), 3.68 ppm (s, 6 H); ^{13}C-NMR (CD_{3}CN): δ = 163.1, 160.8, 159.9, 156.3, 150.6, 138.0, 133.6, 131.9, 131.2, 130.1, 129.8, 129.3, 128.8, 127.1, 123.4, 122.8, 119.3, 115.3, 109.9, 108.0, 101.0, 96.1, 56.8, 56.6, 56.3 ppm; HRMS (ESI): calcd for C_{32}H_{28}O_{5}Na^{+} [M + Na^{+}] 515.1829, found 515.1837.
6.78–6.75 (m, 5 H), 6.68 (t, J = 2.4 Hz, 1 H), 6.59 (d, J = 2.4 Hz, 2 H), 3.82 (s, 3 H), 3.73 (s, 3 H), 3.70 (s, 6 H), 3.69 ppm (s, 3 H); 13C-NMR (CD3CN): δ = 161.6, 159.4, 159.3, 158.1, 154.8, 149.4, 137.0, 131.8, 130.0, 128.4, 127.4, 127.3, 123.1, 122.4, 121.7, 116.2, 113.9, 113.8, 108.7, 106.4, 99.5, 94.7, 55.3, 55.2, 54.9, 54.8 ppm; HRMS (ESI): calcd for C33H30O6Na+ [M + Na+] 545.1934, found 545.1951.

(E)-3-(3,5-Dimethoxyphenyl)-2-(furan-2-yl)-6-methoxy-4-(4-methoxystyryl)benzofuran (19e). From furanyl ether 17e. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzofuran 19e (36 mg, 38%) as a yellow oil. 19e: Rf = 0.40 (silica gel, hexane s-EtOAc 2:1); IR (film) νmax 2936, 1600, 1510, 1421, 1250, 1152, 1064, 819 cm⁻¹; 1H-NMR (CD3CN): δ = 7.50 (d, J = 1.2 Hz, 1 H), 7.16 (d, J = 2.4 Hz, 1 H), 7.06 (d, J = 2.4 Hz, 1 H), 7.02 (d, J = 15.6 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 2 H), 6.84–6.82 (m, 3 H), 6.70 (t, J = 2.4 Hz, 1 H), 6.62 (d, J = 2.4 Hz, 2 H), 6.46 (q, J = 1.8 Hz, 1 H), 6.38 (d, J = 3.0 Hz, 1 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.76 ppm (s, 6 H); 13C-NMR (CD3CN): δ = 162.2, 160.4, 159.5, 156.1, 146.2, 143.9, 143.4, 136.3, 133.1, 130.7, 129.8, 128.3, 123.0, 121.5, 114.9, 112.5, 109.4, 107.7, 100.6, 95.8, 56.4, 56.1, 55.8 ppm; HRMS (ESI): calcd for C30H26O6Na+ [M + Na+] 505.1621, found 505.1603.

(E)-6-Methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)-3-phenylbenzofuran (19f). According to General Procedure C using benzyl ether 17f. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzofuran 19f (74 mg, 80%) as a yellow oil. 19f: Rf = 0.60 (silica gel, hexanes-EtOAc 2:1); IR (film) νmax 1605, 1511, 1251, 1175, 1144, 1033, 833, 702 cm⁻¹; 1H-NMR (d6-acetone): δ = 7.62–7.59 (m, 3 H), 7.52–7.50 (m, 2 H), 7.45 (d, J = 9.0 Hz, 2 H), 7.18 (d, J = 2.4 Hz, 1 H), 7.09 (d, J = 2.4 Hz, 1 H), 7.03 (d, J = 16.2 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.73 (d, J = 16.2 Hz, 1 H), 3.91 (s, 3 H), 3.77 ppm (s, 6 H); 13C-NMR (d6-acetone): δ = 159.5, 159.5, 158.4, 155.0, 149.7, 135.1, 131.9, 130.7, 129.9, 129.3, 128.6, 128.0, 127.6, 127.3, 123.2, 121.9, 121.8, 116.4, 113.8, 113.8, 110.6, 106.5, 94.7, 55.2, 54.7, 54.6 ppm; HRMS (ESI): calcd for C31H26O4Na+ [M + Na+] 485.1723, found 485.1713.

(E)-6-Methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)-3-(3,4,5-trimethoxyphenyl)benzofuran (19g). According to General Procedure C using benzyl ether 17g. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded benzofuran 19g (94 mg, 85%) as a yellow oil. 19g: Rf = 0.34 (silica gel, hexanes:EtOAc 2:1); IR (film) νmax 2936, 1604, 1511, 1409, 1250, 1126, 1033, 838 cm⁻¹; 1H-NMR (CD3CN): δ = 7.50 (d, J = 9.0 Hz, 2 H), 7.14 (d, J = 1.8 Hz, 1 H), 7.05–6.99 (m, 4 H), 6.86 (d, J = 9.0 Hz, 2 H), 6.81 (d, J = 16.2 Hz, 1 H), 6.78 (d, J = 9.0 Hz, 2 H), 6.75 (s, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.68 ppm (s, 6 H); 13C-NMR (CD3CN): δ = 159.5, 159.4, 158.2, 154.8, 154.0, 149.7, 137.9, 132.0, 130.1, 130.0, 128.8, 127.4, 127.3, 123.2, 122.3, 121.7, 116.4, 114.0, 113.9, 107.9, 106.6, 94.8, 60.3, 55.9, 55.4, 54.9, 54.9 ppm; HRMS (ESI): calcd for C34H25O7Na+ [M + Na+] 575.2040, found 575.2048.

(E)-3-(3,4-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)benzofuran (19h). From benzyl ether 17h. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded benzofuran 19h (85 mg, 81%) as a yellow oil. 19h: Rf = 0.35 (silica gel, hexanes-EtOAc 2:1); IR (film)
$\nu_{\text{max}}$ 2923, 1604, 1509, 1128, 1026, 833, 734 cm$^{-1}$; $^1$H-NMR (CD$_3$CN): $\delta$ = 7.49 (d, $J$ = 9.0 Hz, 2 H), 7.12 (d, $J$ = 1.8 Hz, 1 H), 7.08 (d, $J$ = 8.4 Hz, 1 H), 7.03 (d, $J$ = 2.4 Hz, 1 H), 7.02 (d, $J$ = 2.4 Hz, 1 H), 6.99–6.96 (m, 4 H), 6.85 (d, $J$ = 9.0 Hz, 2 H), 6.79 (d, $J$ = 9.0 Hz, 2 H), 6.73 (d, $J$ = 16.2 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.67 ppm (s, 3 H); $^{13}$C-NMR (CD$_3$CN): $\delta$ = 159.4, 159.4, 158.2, 154.8, 149.9, 149.8, 149.3, 132.0, 130.0, 128.5, 127.5, 127.3, 126.9, 123.3, 122.9, 122.3, 122.0, 116.3, 114.2, 113.9, 112.2, 106.4, 94.8, 55.6, 55.5, 55.4, 54.9 ppm; HRMS (ESI): calcd for C$_{33}$H$_{30}$O$_6$Na$^+$ [M + Na$^+$] 545.1934, found 545.1946.

3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-((4-methoxyphenyl)ethynyl)benzofuran (19i). From benzyl ether 17i. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded benzofuran 19i (88 mg, 85%) as a yellow oil. 19i: $R_f$ = 0.70 (silica gel, hexanes-EtOAc 2:1); IR (film) $\nu_{\text{max}}$ 2935, 1604, 1510, 1485, 1248, 1152, 1035, 831 cm$^{-1}$; $^1$H-NMR (CD$_3$CN): $\delta$ = 7.47 (d, $J$ = 9.0 Hz, 2 H), 7.16 (d, $J$ = 2.4 Hz, 1 H), 7.02 (d, $J$ = 8.4 Hz, 2 H), 6.99 (d, $J$ = 2.4 Hz, 1 H), 6.87 (d, $J$ = 9.0 Hz, 2 H), 6.64 (d, $J$ = 2.4 Hz, 2 H), 6.56 (t, $J$ = 2.4 Hz, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.70 ppm (s, 6 H); $^{13}$C-NMR (CD$_3$CN): $\delta$ = 161.8, 160.7, 160.6, 158.5, 155.4, 151.5, 135.8, 128.6, 123.9, 123.7, 117.3, 116.4, 116.0, 115.5, 114.8, 114.7, 109.9, 100.4, 97.6, 94.6, 86.1, 56.5, 55.9, 55.8 ppm; HRMS (ESI): calcd for C$_{33}$H$_{28}$O$_6$Na$^+$ [M + Na$^+$] 543.1778, found 543.1773.

3.5. General procedure D (Preparation of hexacyclic benzofurans 20, Table 3)

To a solution of benzofuran 19 (0.04 mmol) in CH$_2$Cl$_2$ (6 mL) at 23 °C was added $p$-TsOH•H$_2$O (22.8 mg, 0.12 mmol). The resulting mixture was heated to 40 °C and stirred for 8 hours before it was quenched with NaHCO$_3$ (3 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash column chromatography (silica gel) afforded the desired hexacyclic benzofuran 20. The following compounds were prepared via this general procedure:

1,3,8-Trimethoxy-11-(4-methoxyphenyl)-5-phenyl-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20a). From benzofuran 19b. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded hexacyclic benzofuran 20a (18.7 mg, 95%) as a yellow oil. 20a: $R_f$ = 0.57 (silica gel, hexanes-EtOAc 2:1); IR (film) $\nu_{\text{max}}$ 2933, 1598, 1509, 1461, 1248, 1144, 1065, 853, 696 cm$^{-1}$; $^1$H-NMR (CD$_3$CN): $\delta$ = 7.66–7.64 (m, 2 H), 7.47–7.41 (m, 3 H), 7.01 (d, $J$ = 8.4 Hz, 2 H), 6.78 (d, $J$ = 1.8 Hz, 1 H), 6.71 (d, $J$ = 1.8 Hz, 1 H), 6.59 (d, $J$ = 8.4 Hz, 2 H), 6.58 (d, $J$ = 2.4 Hz, 1 H), 6.53 (d, $J$ = 2.4 Hz, 1 H), 5.44 (d, $J$ = 5.4 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.72 (dd, $J$ = 16.2, 5.4 Hz, 1 H), 3.58 (s, 3 H), 3.44 (s, 3 H), 3.37 ppm (d, $J$ = 16.2 Hz, 1 H); $^{13}$C-NMR (CD$_3$CN): $\delta$ = 158.6, 158.3, 158.1, 157.2, 154.2, 150.6, 135.4, 134.1, 133.9, 131.7, 128.9, 128.7, 128.3, 123.9, 119.8, 112.9, 112.6, 107.2, 97.8, 92.7, 55.8, 55.2, 54.5, 54.4, 36.7, 36.6 ppm; HRMS (ESI): calcd for C$_{32}$H$_{28}$O$_5$Na$^+$ [M + Na$^+$] 515.1829, found 515.1835.

1,3,8-Trimethoxy-5,11-bis(4-methoxyphenyl)-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20b). From benzofuran 19d. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded
hexacyclic benzofuran 20b (18.8 mg, 90%) as a yellow oil. 20b: \( R_f = 0.49 \) (silica gel, hexanes-EtOAc 2:1); IR (film) \( \nu_{\text{max}} \) 2933, 1599, 1508, 1460, 1248, 1143, 1067, 1032, 834 cm\(^{-1}\); \(^1\)H-NMR (CD\(_3\)CN): \( \delta = 7.57 \) (d, \( J = 9.0 \) Hz, 2 H), 7.00–6.98 (m, 4 H), 6.75 (d, \( J = 1.8 \) Hz, 1 H), 6.69 (d, \( J = 1.8 \) Hz, 1 H), 6.61 (d, \( J = 2.4 \) Hz, 1 H), 6.58 (d, \( J = 9.0 \) Hz, 2 H), 6.51 (d, \( J = 2.4 \) Hz, 1 H), 5.43 (d, \( J = 6.0 \) Hz, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.69 (dd, \( J = 16.2, 6.0 \) Hz, 1 H), 3.57 (s, 3 H), 3.47 (s, 3 H), 3.35 ppm (d, \( J = 16.2 \) Hz, 1 H); \(^{13}\)C-NMR (CD\(_3\)CN): \( \delta = 160.2, 158.6, 158.3, 157.8, 157.2, 154.0, 150.7, 135.2, 134.2, 134.1, 130.2, 128.3, 123.9, 123.8, 119.9, 116.1, 114.1, 112.9, 112.3, 106.9, 97.6, 92.6, 55.8, 55.2, 55.1, 54.5, 54.4, 36.7, 36.6 ppm; HRMS (ESI): calcd for C\(_{33}\)H\(_{30}\)O\(_6\)Na\(^+\) [M + Na\(^+\)] 545.1934, found 545.1948.

5-(Furan-2-yl)-1,3,8-trimethoxy-11-(4-methoxyphenyl)-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20c). From benzofuran 19e. The desired product 20c was not obtained in this reaction.

8-Methoxy-5,11-bis(4-methoxyphenyl)-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20d). From benzofuran 19f. The desired product 20d was not obtained in this reaction.

1,2,3,8-Tetramethoxy-5,11-bis(4-methoxyphenyl)-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20e). From benzofuran 19g. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded hexacyclic benzofuran 20e (20.3 mg, 92%) as a yellow oil. 20e: \( R_f = 0.48 \) (silica gel, hexanes-EtOAc 2:1); IR (film) \( \nu_{\text{max}} \) 2933, 1611, 1508, 1316, 1248, 1143, 1037, 835 cm\(^{-1}\); \(^1\)H-NMR (CD\(_3\)CN): \( \delta = 7.60 \) (d, \( J = 8.4 \) Hz, 2 H), 7.02–7.00 (m, 4 H), 6.89 (s, 1 H), 6.75 (s, 1 H), 6.69 (s, 1 H), 6.58 (d, \( J = 8.4 \) Hz, 2 H), 5.31 (d, \( J = 5.4 \) Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.74 (dd, \( J = 16.2, 5.4 \) Hz, 1 H), 3.71 (s, 3 H), 3.49 (d, \( J = 16.2 \) Hz, 1 H), 3.39 ppm (s, 3 H); \(^{13}\)C-NMR (CD\(_3\)CN): \( \delta = 160.2, 157.9, 157.2, 154.0, 152.2, 151.2, 150.1, 141.4, 134.9, 134.1, 130.1, 129.4, 128.3, 128.0, 123.9, 119.9, 115.8, 114.1, 112.9, 112.4, 110.2, 92.7, 61.2, 60.2, 55.2, 55.1, 54.8, 54.5, 38.0, 36.8 ppm; HRMS (ESI): calcd for C\(_{33}H_{30}O_6Na^+\) [M + Na\(^+\)] 545.1934, found 545.1948.

2,3,8-Trimethoxy-5,11-bis(4-methoxyphenyl)-10,11-dihydrobenzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20f). From benzofuran 19h. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded hexacyclic benzofuran 20f (18.8 mg, 90%) as a yellow oil. 20f: \( R_f = 0.35 \) (silica gel, hexanes-EtOAc 2:1); IR (film) \( \nu_{\text{max}} \) 2934, 1611, 1508, 1316, 1248, 1143, 1037, 835 cm\(^{-1}\); \(^1\)H-NMR (CD\(_3\)CN): \( \delta = 8.07 \) (d, \( J = 9.0 \) Hz, 2 H), 7.23 (s, 1 H), 7.08 (d, \( J = 9.0 \) Hz, 2 H), 6.86 (d, \( J = 8.4 \) Hz, 2 H), 6.69 (d, \( J = 8.4 \) Hz, 2 H), 6.58 (d, \( J = 2.4 \) Hz, 1 H), 6.21 (d, \( J = 2.4 \) Hz, 1 H), 4.63 (dd, \( J = 6.6, 2.4 \) Hz, 1 H), 3.90 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.62 (dd, \( J = 14.4, 2.4 \) Hz, 1 H), 3.15 ppm (dd, \( J = 14.4, 6.6 \) Hz, 1 H); \(^{13}\)C-NMR (CD\(_3\)CN): \( \delta = 193.6, 165.3, 165.0, 162.1, 158.8, 153.5, 150.5, 148.4, 139.9, 139.6, 136.3, 132.9, 131.8, 130.4, 127.8, 122.6, 114.9, 114.6, 114.1, 113.4, 112.7, 107.6, 56.3, 56.3, 56.2, 56.1, 55.6, 49.7, 41.4 ppm; HRMS (ESI): calcd for C\(_{33}H_{30}O_6Na^+\) [M + Na\(^+\)] 545.1934, found 545.1943.

1,3,8-Trimethoxy-5,11-bis(4-methoxyphenyl)benzo[6,7]cyclohepta[1,2,3-cd]benzofuran (20g). From benzofuran 19i. Flash column chromatography (silica gel, hexanes-EtOAc 4:1) afforded hexacyclic benzofuran 20g (19.8 mg, 95%) as a yellow oil. 20g: \( R_f = 0.70 \) (silica gel, hexanes-EtOAc 2:1); IR
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(film) $\nu_{\max}$ 2919, 1738, 1606, 1505, 1462, 1365, 1247, 1199, 833 cm$^{-1}$; $^1$H-NMR (CD$_3$CN): $\delta$ = 7.82 (d, $J$ = 9.0 Hz, 2 H), 7.21 (d, $J$ = 9.0 Hz, 2 H), 7.08 (d, $J$ = 9.0 Hz, 2 H), 6.86 (d, $J$ = 9.0 Hz, 2 H), 6.78 (d, $J$ = 1.8 Hz, 1 H), 6.64 (d, $J$ = 1.8 Hz, 1 H), 6.62 (d, $J$ = 2.4 Hz, 1 H), 6.59 (s, 1 H), 6.29 (d, $J$ = 2.4 Hz, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.43 (s, 3 H), 3.17 ppm (s, 3 H); $^{13}$C-NMR (CD$_3$CN): $\delta$ = 161.4, 161.4, 161.3, 159.8, 158.8, 155.0, 151.9, 141.9, 141.7, 138.2, 133.8, 132.4, 131.0, 127.4, 127.1, 125.0, 116.4, 115.1, 114.1, 111.9, 106.2, 100.3, 94.6, 56.2, 56.0, 56.0, 55.7, 55.3 ppm; HRMS (ESI): calcd for C$_{33}$H$_{30}$O$_{6}$Na$^+$ [M + Na$^+$] 543.1784, found 543.1745.

3.6. One-pot preparation of hexacyclic benzofuran 20b

To a solution of benzyl ketone 17d (100 mg, 0.185 mmol) in THF (3 mL) at 0 °C was added LiTMP (0.5 M in THF, 1.9 mL, 0.93 mmol). The resulting mixture was stirred at 0 °C for 30 min before it was quenched with NH$_4$Cl (5 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to afford crude alcohol, which was used directly without further purification. To a solution of the crude alcohol (obtained as above) in CH$_2$Cl$_2$ (3 mL) at 23 °C was added p-TsOH•H$_2$O (105 mg, 0.56 mmol). The resulting mixture was heated to 45 °C and stirred for 8 h before it was quenched with NaHCO$_3$ (3 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded the desired hexacyclic benzofuran 20b (77 mg, 80%) as a yellow oil.

(E)-(3,5-Dimethoxyphenyl)(2-hydroxy-4-methoxy-6-(4-methoxystyryl)phenyl)methanone (16b'). To a solution of ketone 16b (13.0 g, 30 mmol) in CH$_2$Cl$_2$ (100 mL) at 0 °C was added BCl$_3$ (1 M in CH$_2$Cl$_2$, 45 mL, 45 mmol) dropwise. The resulting mixture was stirred for 1 h before it was quenched with NaHCO$_3$ (50 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash column chromatography (silica gel, hexanes-EtOAc 4:1:1) afforded phenol 16b' (12 g, 95%) as a yellow solid. 16b': R$_f$ = 0.45 (silica gel, hexanes-EtOAc 2:1); m.p. = 139–140 °C (hexanes-EtOAc); IR (film) $\nu_{\max}$ 2939, 1600, 1511, 1457, 1254, 1204, 1157, 1064, 840, 808 cm$^{-1}$; $^1$H-NMR (CDCl$_3$): $\delta$ = 11.5 (br s, 1 H), 6.89 (d, $J$ = 8.4 Hz, 2 H), 6.74 (d, $J$ = 8.4 Hz, 2 H), 6.72 (d, $J$ = 2.4 Hz, 2 H), 6.67 (d, $J$ = 2.4 Hz, 1 H), 6.65 (d, $J$ = 16.2 Hz, 1 H), 6.48 (t, $J$ = 2.4 Hz, 1 H), 6.47 (d, $J$ = 2.4 Hz, 1 H), 6.46 (d, $J$ = 15.6 Hz, 1 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.68 ppm (s, 6 H); $^{13}$C-NMR (CDCl$_3$): $\delta$ = 200.1, 164.7, 164.6, 160.6, 159.4, 142.7, 142.7, 130.0, 129.5, 127.7, 126.9, 113.8, 113.3, 106.9, 106.3, 104.4, 99.9, 55.6, 55.2 ppm; HRMS (ESI): calcd for C$_{25}$H$_{24}$O$_6$Na$^+$ [M + Na$^+$] 443.1465, found 443.1454.

3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(3-(4-methoxyphenyl)oxiran-2-yl)benzofuran (21). To a solution of benzofuran 19d (4.20 g, 8.04 mmol) in DMSO (50 mL) and water (10 mL) at 0 °C was added NBS (1.57 g, 8.84 mmol) in one portion. The resulting mixture was stirred for 0.5 h before it was quenching with Na$_2$S$_2$O$_3$ (50 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with Et$_2$O (3 × 100 mL). The combined organic layers were washed with brine.
(100 mL), dried (Na₂SO₄) and concentrated in vacuo to afford the crude bromohydrin, which was use directly without further purification. To a solution of crude bromohydrin (obtained as above) in Et₂O (100 mL) at 23 °C were added NaOH (4 M, aq., 30 mL) and PhEt₃NCl (1.83 g, 8.04 mmol). The resulting mixture was stirred for 2 h before the layers were separated, and the aqueous layer was extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, hexanes-EtOAc 2:1) afforded epoxide 21 (3.25 g, 75%, over the two steps) as a yellow solid. 21: Rf = 0.55 (silica gel, hexanes-EtOAc 2:1); m.p. = 147–148 °C (hexanes/CH₂Cl₂); IR (film) νmax 2939, 1738, 1611, 1587, 1512, 1204, 1154, 1033, 832 cm⁻¹; ¹H-NMR (CDCl₃): δ = 7.47 (d, J = 9.0 Hz, 2 H), 7.02 (d, J = 1.8 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 1.8 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.79 (d, J = 9.0 Hz, 2 H), 6.54 (br, 1 H), 6.31 (br, 1 H), 6.18 (t, J = 1.8 Hz, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 3.79 (d, J = 2.4 Hz, 1 H), 3.77 (s, 3 H), 3.74 (br, 3 H), 3.53 (d, J = 2.4 Hz, 1 H), 3.30 ppm (br, 3 H); ¹³C-NMR (CDCl₃): δ = 161.0, 159.7, 159.2, 158.2, 154.2, 149.7, 136.0, 131.5, 128.5, 126.9, 123.2, 115.4, 113.8, 113.6, 107.7 (br), 105.9, 99.7, 95.3, 63.1, 59.1, 55.8, 55.3, 55.2, 54.7 (br) ppm; HRMS (ESI): calcd for C₃₃H₃₀O₇Na⁺ [M + Na⁺] 561.1883, found 561.1898.

Malibatol A (2): To a solution of epoxide 21 (100 mg, 0.19 mmol) in CH₂Cl₂ (30 mL) at −78 °C was added BBr₃ (1.0 M in CH₂Cl₂, 2.28 mL, 2.28 mmol). The resulting mixture was warmed to 23 °C and stirred for 2 h before it was quenched with NaHCO₃ (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, CH₂Cl₂-MeOH 9:1) afforded malibatol (2, 17.8 mg, 20%) as a tan oil. Compound 2: Rf = 0.23 (silica gel, CH₂Cl₂-MeOH 9:1); IR (film) νmax 3323, 2918, 1612, 1510, 1433, 1366, 1231, 1139, 833 cm⁻¹; ¹H-NMR (CD₃OD): δ = 7.45 (d, J = 8.6 Hz, 2 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.01 (d, J = 2.4 Hz, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 6.87 (dd, J = 2.4, 1.2 Hz, 1 H), 6.51 (d, J = 2.4 Hz, 1 H), 6.33 (d, J = 9.0 Hz, 2 H), 6.30 (d, J = 2.4 Hz, 1 H), 5.46 (brs, 1 H), 5.28 ppm (m, 1 H); ¹³C-NMR (CD₃OD): δ = 159.1, 157.4, 156.7, 156.2, 155.3, 155.1, 151.2, 139.6, 135.8, 133.4, 130.9, 130.6, 124.6, 121.2, 119.0, 117.3, 116.4, 114.7, 109.9, 109.7, 102.1, 95.9, 74.8, 48.9 ppm; HRMS (ESI): calcd for C₂₈H₂₀O₇Na⁺ [M + Na⁺] 491.1101, found 491.1092.

Shoreaphenol (3): To a solution of malibatol A (2) (5 mg, 10.7 µmol) in THF (1 mL) at 23 °C was added PDC (4.8 mg, 12.8 µmol). The resulting mixture was stirred for 1 h before it was quenched with Na₂S₂O₃ (1 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 mL), dried (Na₂SO₄) and concentrated in vacuo. Flash column chromatography (silica gel, CH₂Cl₂-MeOH 5:1) afforded shoreaphenol (3, 2.3 mg, 46%) as a yellow oil. Compound 3: Rf = 0.26 (silica gel, CH₂Cl₂-MeOH 9:1); IR (film) νmax 3339, 1738, 1612, 1366, 1216, 829 cm⁻¹; ¹H-NMR (d₆-acetone): δ = 7.70 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 2.4 Hz, 1 H), 7.04 (d, J = 1.8 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 2 H), 6.85 (d, J = 7.8 Hz, 2 H), 6.70 (d, J = 2.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 6.55 (d, J = 8.4 Hz, 2 H), 6.12 (brs, 1 H), 5.28 ppm (m, 1 H); ¹³C-NMR (d₆-acetone): δ = 196.3, 159.5, 158.3, 157.7, 156.4, 156.1, 154.9, 153.3, 135.2, 131.1, 131.0, 130.6, 128.5, 123.1, 122.4, 116.6, 116.4, 115.6, 114.0, 112.0, 109.0, 103.0, 102.4, 56.1 ppm; HRMS (ESI): calcd for C₂₈H₁₈O₇Na⁺ [M + Na⁺] 489.0950, found 489.0955.
4. Conclusions

In conclusion, a modular and efficient entry to the dimeric resveratrol derived polyphenolic benzofurans has been developed, and applied to the total synthesis of malibatol A (2) and shoreaphenol (3). In view of the largely untapped potential of the polyphenolic secondary metabolites, the synthetic methodology described herein should find wide application in the chemical and biological investigations of this fascinating class of compounds.

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