# A versatile approach to oligostilbenoid natural products – synthesis of permethylated analogues of viniferifuran, malibatol A, and shoreaphenol†

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A highly practical route to oligostilbenoid natural products is described. A regioselective $Bi(OTf)_3$-catalyzed cyclodehydration provided ready access to 3-arylbenzofuran. Pd-catalyzed direct C–H activation of benzofuran and subsequent cross-coupling with aryl halide was successfully implemented for the introduction of aryl group at the C2 position of benzofuran. Further manipulation of the 2,3-diarylbenzofuran led to the efficient total synthesis of permethylated analogues of viniferifuran, malibatol A, and shoreaphenol.

## Introduction

Oligostilbenes[1] are a class of highly oxygenated natural products comprising more than two stilbene units. A number of oligostilbenoid natural products are known in the literature, with various modes of connection of stilbene units, oxidation levels, and the substitution patterns of aryl groups. These exhibit a wide variety of pharmacological activities including anti-inflammatory, antioxidant, antifungal, antibacterial, anti-HIV, and anticarcinogenic activities.[2] As shown in Fig. 1, highly substituted benzofurans are also within this family. The structure of viniferifuran was first identified from *Vitis vinifera* 'Kyohou' on the basis of the extensive NMR spectroscopic and chemical analysis by Niwa and coworkers.[3,4] Its congener, gnetuhainin B was isolated from the lianas of *Gnetum hainanense* by the Lin group.[5] In 1998, Boyd and coworkers at NCI disclosed the structures of two novel oligostilbenes, malibatols A and B, isolated from the organic extract of the leaves of *Hopea malibato*.[6] It was revealed that malibatols A and B exhibit cytotoxicity to the host cells (CEM SS) in an antiviral assay. Interestingly, an oxidized analogue of malibatol A, called shoreaphenol or hopeafuran, was isolated from the bark of *Shorea robusta* and the stem wood of *Hopea utilis*.[7] Despite their interesting biological activities as well as their unique carbon framework, few synthetic approaches towards these types of compounds have been reported.[8,9] Here we describe a direct approach towards these natural products.

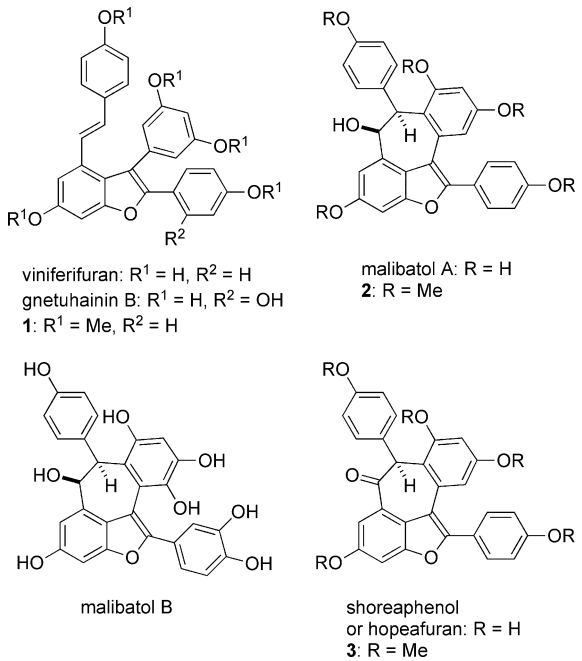


**Fig. 1** Some representative oligostilbenoid natural products.

## Results and discussion

At the outset, we hoped to design a synthetic strategy by which not only natural products but also synthetic analogues would be accessible. Considering the structural similarity and the easiness of handling, compounds **1**, **2**, and **3** were chosen as our synthetic targets to validate our approach.[10] A retrosynthetic route to these compounds is outlined in Scheme 1. We envisioned that aldehyde **4** could be a viable common intermediate for the synthesis of **1**, **2**, and **3**. In order to install the aromatic group at the C2 position of benzofuran **5**, a transition metal-catalyzed direct C–H activation of benzofuran **6** followed by intermolecular coupling with an appropriate aryl halide **7** was considered. The requisite benzofuran **6** was conceived to be easily available from the dehydrative cyclization of aryloxyketone **8**.

We commenced our synthesis with the preparation of aryloxyketone **8**, which was easily prepared from the reaction of the phenol **9**[11] with α-bromoketone **10**[12] in the presence of $K_2CO_3$ (Scheme 2). Initially, when this ketone **8** was exposed to $BCl_3$ as described in our previous communication,[13] the desired benzofuran **6** was obtained in 54–57% yield (entries 1 and 2, Table 1). Several parameters (concentration, temperatures, and equivalents of $BCl_3$)

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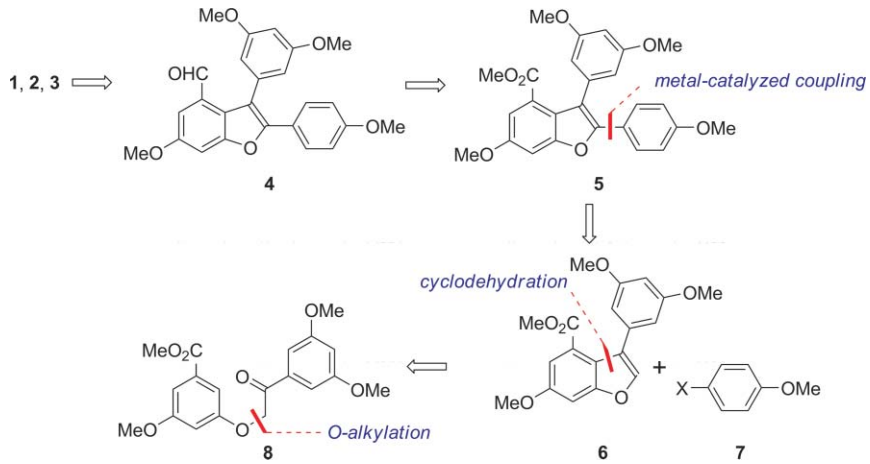
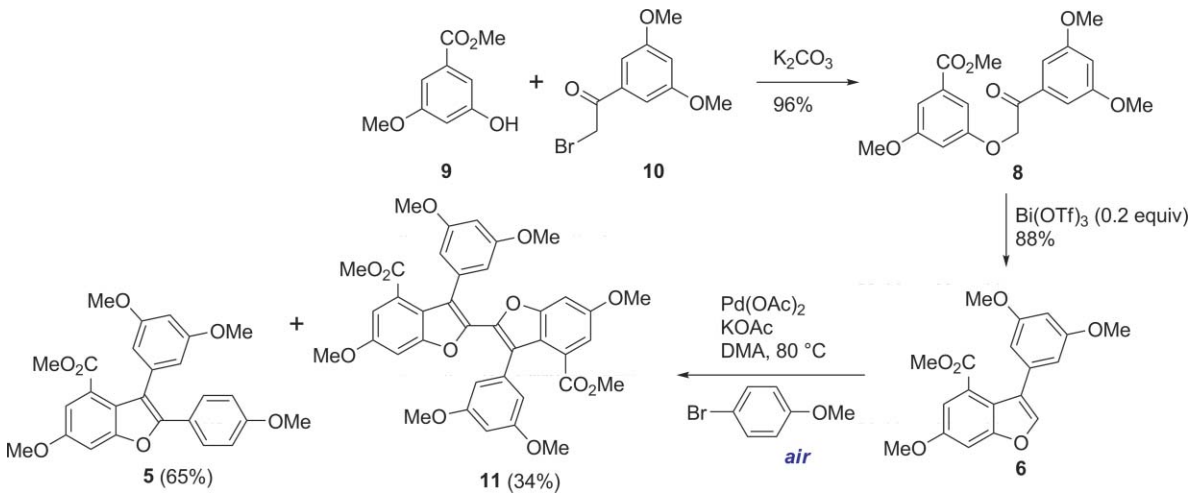
† Electronic supplementary information (ESI) available: Copies of $^1H$ and $^{13}C$ spectra of compounds **1–6**, **8** and **11–18**, and comparison of spectral data of **1–3** with those of the same compounds derived from the natural products; crystallographic details and CIF files for **5** and **11** (CCDC reference numbers 713936 and 713937, respectively). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901911a

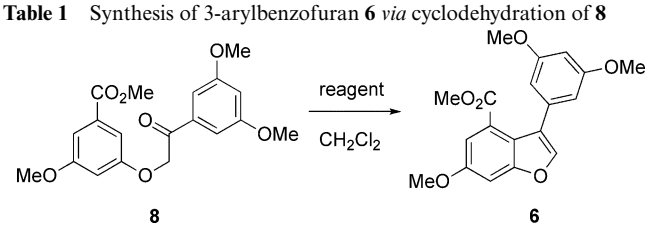



**Scheme 1** Retrosynthetic analysis.




**Scheme 2**

**Table 1** Synthesis of 3-arylbenzofuran **6** *via* cyclodehydration of **8**




| Entry | Reagent | Temperature | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $BCl_3$ (2 equiv) | −78 °C to rt | 2 | 54 |
| 2 | $BCl_3$ (1.2 equiv) | −78 °C to rt | 2 | 57 |
| 3 | $CF_3CO_2H$ (as solvent) | 80 °C | 8 | 76 |
| 4 | $InCl_3$ (0.2 equiv) | 60 °C | 16 | NR[a] |
| 5 | $FeCl_3$ (1 equiv) | rt | 3 | 59 |
| 6 | $FeCl_3$ (0.2 equiv) | 60 °C | 16 | 18[b] |
| 7 | $BiCl_3$ (0.2 equiv) | 60 °C | 18 | NR[a] |
| 8 | $Bi(OTf)_3$ (0.2 equiv) | 60 °C | 16 | 88 |

[a] No reaction. [b] Starting material was mainly recovered.

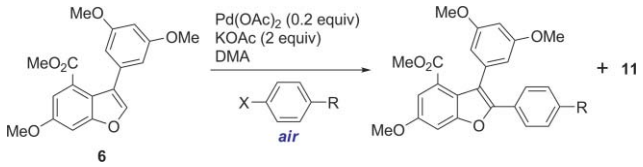
were changed to improve the efficiency, but no satisfactory result was obtained.[14]

At this point, other cyclodehydration conditions were examined. Subjection of **8** to refluxing trifluoroacetic acid resulted in a 76% yield of **6** (entry 3). While **8** was inert to both $InCl_3$ and $BiCl_3$, the desired cyclodehydration took place in the presence of stoichiometric amount of $FeCl_3$, albeit in modest yield (entries 4, 5, and 7). Use of a catalytic amount of $FeCl_3$ together with mild heating also allowed the formation of **6** but the starting material was mostly recovered after 16 h, indicating that the process is not catalytic (entry 6). Finally, we were pleased to find that exposure of **8** to $Bi(OTf)_3$ (0.2 equiv) in refluxing dichloromethane afforded the desired 3-arylbenzofuran in 88% yield (entry 8).[15]

Having established the efficient formation of **6**, we focused our attention to the incorporation of aryl group at the C2 site of benzofuran. Although preactivation of the C2 position of benzofuran by replacement of the C2 hydrogen with a halide[16] or a trialkyltin moiety[17] is a possible route for transition metal-catalyzed cross-coupling reactions, a more direct method was pursued. Since the pioneering work by Ohta,[18] direct C–H activation of (benzo)furans followed by coupling with aryl halides/triflates has been achieved by several groups.[19,20] Surprisingly, however, no examples of the direct activation of 3-arylbenzofuran and subsequent cross-coupling reaction have been reported to date.

When **6** was submitted to the conditions ($Pd(OAc)_2$ (0.2 equiv), KOAc (2 equiv), and 4-iodoanisole (2 equiv) in DMA, 120 °C),

**Table 2** Direct arylation at the C2 site of benzofuran **6**




| Entry | X | R | Temperature (°C) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | I | OMe | 120 | **5** | 43 |
| 2 | I | OMe | 80 | **5** | 60 |
| 3 | Br | OMe | 80 | **5** | 65 |
| 4 | $B(OH)_2$ | OMe | 80 | **5** | 15 |
| 5 | I | $NO_2$ | 80 | **12** | 59 |
| 6 | Br | F | 80 | **13** | 52 |
| 7 | Br | $CF_3$ | 80 | **14** | 57 |
| 8 | Br | CN | 80 | **15** | 65 |
| 9 | Br | $CO_2Et$ | 80 | **16** | 51 |

43% yield of arylated product **5** was isolated along with the dimerized product **11** (21%)[21] (entry 1, Table 2). It should be noted that the reaction was carried out open to the air.[22] The structures of **5** and **11** were unambiguously established by X-ray crystallographic analysis (Figs. 2 and 3).†

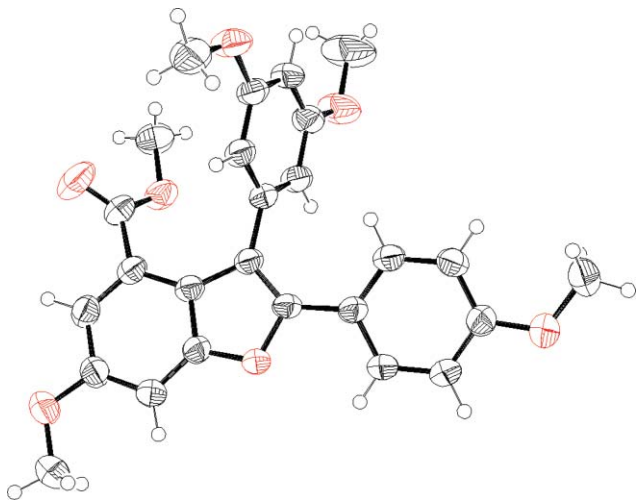


**Fig. 2** Crystal structure of **5**.

Lowering the reaction temperature to 80 °C increased the isolated yield of **5** and **11** but with a similar ratio (entry 2). Substitution of 4-iodoanisole by 4-bromoanisole also affected the yield in a positive manner (entry 3). When 4-methoxyphenylboronic acid was used as a coupling partner, **5** was obtained in a low yield (15%) along with the dimer **11** (70%) (entry 4). Despite the substantial increase in yield of **5**, however, we were not able to suppress the formation of dimer **11**.[23] Interestingly, when **6** was treated with $Pd(OAc)_2$ (0.2 equiv) and KOAc (2 equiv) in DMA at 80 °C in the absence of an aryl halide, the dimerized product **11** was isolated in 80% yield.[24] At this point, a variety of other aryl groups was introduced into **6** using the optimized conditions with a similar efficiency (entries 5–9).[25]

With gram quantities of the 2,3-diarylbenzofuran **5** in hand, the stage was set to incorporate the final aryl moiety to **5**. The ester group in **5** was converted to aldehyde *via* a two-step sequence (DIBAL reduction and Dess–Martin oxidation[26]) in

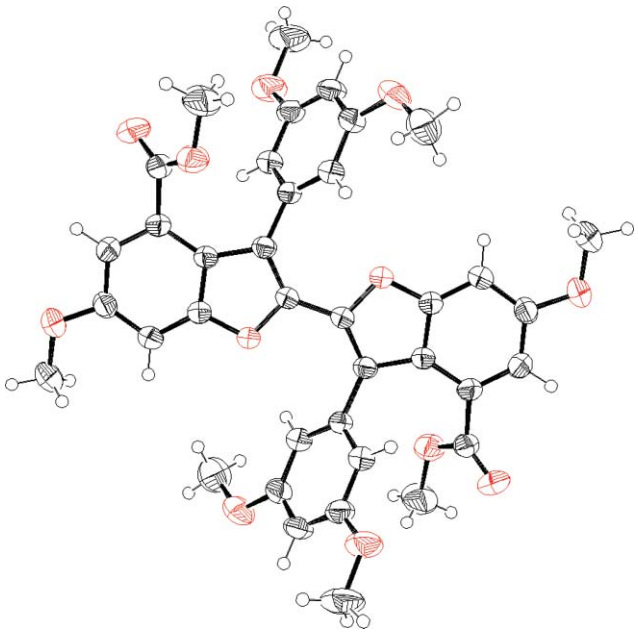
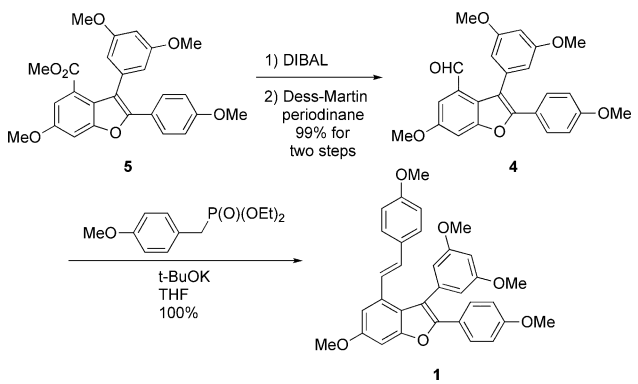


**Fig. 3** Crystal structure of **11**.

excellent overall yield (Scheme 3). Horner–Wadsworth–Emmons-type olefination of **4** with diethyl 4-methoxybenzylphosphonate provided **1** in quantitative yield. In order to construct the seven-membered ring embedded in **2** and **3**, a stereoselective epoxide ring opening *via* nucleophilic attack by the neighboring aromatic group was conceived based on the previous study.[8] Initial efforts to make epoxide **17** from olefin in **1** using mCPBA led to a complex mixture,[27] but this difficulty was circumvented by adopting the Corey–Chaykovsky protocol[28] for the synthesis of epoxide **17** (Scheme 4). As anticipated, the reaction of **4** with dimethyl(4-methoxybenzyl)sulfonium chloride[29] in the presence of NaH cleanly furnished *trans*-epoxide **17**, setting the stage for the stereoselective seven-membered ring formation.

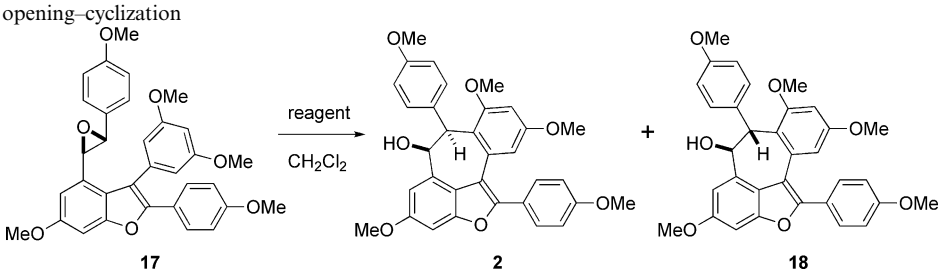



**Scheme 3**

Upon exposure of **17** to a catalytic amount of $SnCl_4$ at –78 °C, TLC revealed rapid formation of several products. Work-up and chromatography subsequently provided **2** (55%) and **18** (18%) (entry 1, Table 3). The relative stereochemistry of two stereogenic centers in **2** and **18** was easily assigned based on the *J* values (Fig. 4). In addition, the chemical shifts

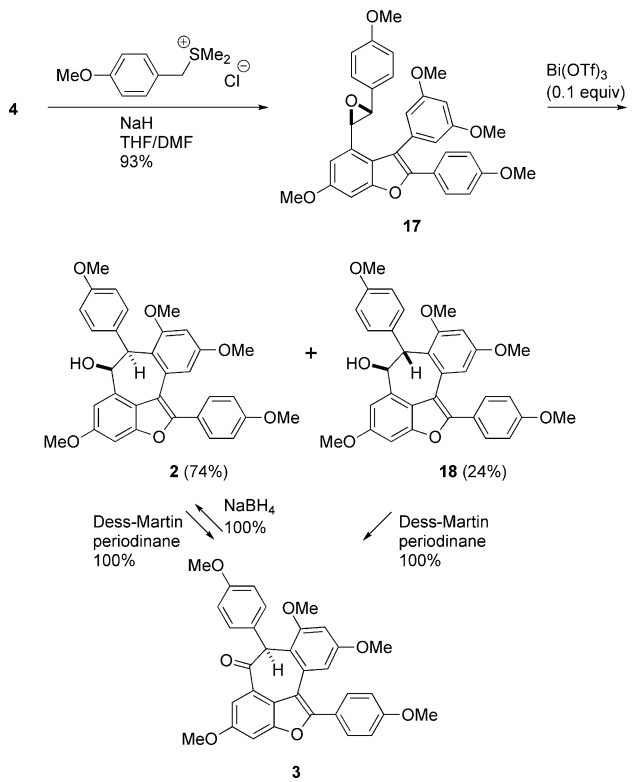
 

**Table 3** Epoxide ring opening–cyclization




| Entry | Reagent | Temperature | Time | Yield (%)[a] | Ratio (**2**:**18**)[b] |
|---|---|---|---|---|---|
| 1 | $SnCl_4$ (0.1 equiv) | −78 °C | 5 min | 55 | 3 : 1 |
| 2 | PTSA-$H_2O$ (0.1 equiv) | −78 °C to rt | 3 h | 33 | 1 : 1.7 |
| 3 | PPTS (0.1 equiv) | −78 °C to rt | 5 h | 31 | 1 : 2 |
| 4 | $InCl_3$ (0.1 equiv) | 0 °C to rt | 1 h | 34 | 1 : 1.6 |
| 5 | $CH_3CN$–$H_2O$, 1 : 1 (as solvent) | rt | 72 h | 25[c] | 1 : 2.2 |
| 6 | $Bi(OTf)_3$ (0.1 equiv) | −78 °C | 1 h | 74 | 3 : 1 |

[a] Isolated yield of **2**. [b] Determined by crude $^1$H NMR. [c] Starting material was recovered in 15% yield.




**Scheme 4**

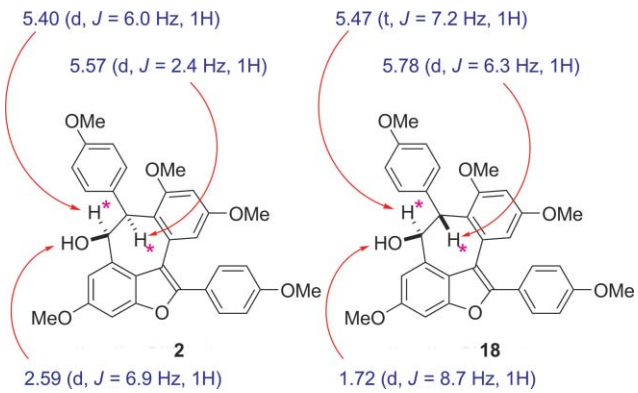



**Fig. 4**

of two adjacent protons (denoted by *) in **2** match those of the literature data of the compound derived from natural malibatol A.[31]

PTSA also effected ring opening but with a 1 : 1.7 ratio (entry 2). PPTS also gave a similar result (entry 3). $InCl_3$ induced seven-membered ring closure, slightly favoring **18** (entry 4). Notably, standing a solution of **17** in $CH_3CN$–$H_2O$ (1 : 1) without any catalyst also triggered the cyclization, affording a mixture of diastereomers in good overall yield (entry 5). When epoxide **17** was treated with $Bi(OTf)_3$ (0.1 equiv), **2** and its diastereomer **18** were formed in 3 : 1 ratio (entry 6).[31] It should be mentioned that the combined yield (**2** and **18**) were excellent in all cases examined except with $SnCl_4$.

Subsequent Dess–Martin oxidation of **2** proceeded straightforwardly, furnishing a quantitative yield of **3**.[32] Reduction of **3** with $NaBH_4$ only produced **2**, which can be explained by hydride delivery from the less hindered *re* face. This stereochemical outcome was further supported by the conversion of **18** to **2** *via* **3**.[33]

In summary, we have accomplished the total synthesis of permethylated analogues of viniferifuran, malibatol A, and shoreaphenol. For the construction of 2,3-diarylbenzofuran core, a $Bi(OTf)_3$-catalyzed cyclodehydration and a palladium-catalyzed direct arylation of benzofuran were employed. The efficient procedure for the synthesis of C2–C2′-linked benzofuran homodimers was also discovered during this study. The route described herein is very concise and practical, and should be useful for the synthesis of other oligostilbenoid natural products and their analogues given the fact that various (hetero)aromatic groups could be easily introduced at each aromatic ring position of these types of oligostilbenes. Currently, efforts are being made along these lines, and these will be reported in due course.

## Experimental section

### 2-Bromo-3′,5′-dimethoxyacetophenone (10)

**Method A.** To a stirred solution of 3′,5′-dimethoxyacetophenone (3.66 g, 20.3 mmol) in 60 mL of $Et_2O$–$CHCl_3$ (4 : 1) was added $Br_2$ (1.04 mL, 1.0 equiv) at 0 °C. After 1 h, the mixture was stirred at rt for an additional 2 h, and more $Br_2$ (0.4 mL, 0.4 equiv) was added at 0 °C. After being stirred at rt for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ at 0 °C. After the reaction mixture was concentrated under reduced pressure, the residue was diluted with ethyl acetate. The organic layer was washed with brine and the aqueous layer was extracted with ethyl acetate one more time. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The resulting residue was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 20 : 1 : 2) to afford α-bromoketone **10** (3.18 g, 60%).

**Method B.** To a solution of 3′,5′-dimethoxyacetophenone (3.19 g, 17.7 mmol) in 60 mL of $CHCl_3$–ethyl acetate (1 : 1) was added $CuBr_2$ (7.908 g, 2 equiv) at rt. After being refluxed for 16 h, the reaction mixture was cooled to rt. The mixture was filtered through Celite and washed with $CH_2Cl_2$. The filtrate was concentrated *in vacuo*. The residue was suspended in solvent (hexanes–ethyl acetate = 10 : 1), filtered, and rinsed with small amount of solvent (hexanes–ethyl acetate = 10:1). The solid **10** was dried under reduced pressure. The filtrate was concentrated and the resulting residue was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 20 : 1 : 2) to give **10** (total 3.44 g, 75%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.11 (d, $J$ = 2.1 Hz, 2H), 6.69 (d, $J$ = 2.1 Hz, 1H), 4.43 (s, 2H), 3.85 (s, 6H)

**Methyl 3-(2-(3,5-dimethoxyphenyl)-2-oxoethoxy)-5-methoxybenzoate (8).** To a solution of **9** (1.406 g, 7.72 mmol) and **10** (2 g, 7.72 mmol) in acetone (40 mL) was added $K_2CO_3$ (3.2 g, 3 equiv). The reaction mixture was heated to reflux for 2 h. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with $H_2O$ and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a crude residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 7 : 1 : 2 → 5 : 1 : 2) to afford **8** (2.67 g, 96%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.23 (d, $J$ = 1.2 Hz, 1H), 7.22 (d, $J$ = 1.2 Hz, 1H), 7.19 (dd, $J$ = 1.2, 2.1 Hz, 2H), 6.74 (dd, $J$ = 2.1, 2.4 Hz, 1H), 6.70 (dd, $J$ = 2.1, 2.4 Hz, 1H), 5.28 (s, 2H), 3.90 (s, 3H), 3.85 (s, 6H), 3.83 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 193.5, 166.8, 161.3, 160.9, 159.2, 136.4, 132.4, 108.6, 107.7, 106.9, 106.3, 106.0, 70.9, 55.9, 55.8, 52.5; **HRMS** (EI) calcd for $[C_{19}H_{20}O_7]^+$: $m/z$ 360.1209, found 360.1213.

**Methyl 3-(3,5-dimethoxyphenyl)-6-methoxybenzofuran-4-carboxylate (6).** To a solution of **8** (2 g, 5.556 mmol) in $CH_2Cl_2$ (56 mL) was added $Bi(OTf)_3$ (729 mg, 0.2 equiv) at rt. After being stirred at 60 °C for 16 h, the reaction mixture was cooled to rt. The mixture was filtered through a pad of Celite and the filtrate was evaporated *in vacuo* to give the residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2) to afford **6** (1.672 g, 88%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.33 (d, $J$ = 2.4 Hz, 1H), 7.21 (d, $J$ = 2.4 Hz, 1H), 6.50-6.46 (m, 3H), 3.90 (s, 3H), 3.81 (s, 6H), 3.32 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 168.1, 160.9, 157.7, 157.2, 143.1, 135.3, 125.8, 123.0, 118.7, 113.1, 106.5, 100.3, 99.9, 56.3, 55.6, 51.7; **HRMS** (EI) calcd for $[C_{19}H_{18}O_6]^+$: $m/z$ 342.1103, found 342.1108.

**Methyl 3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzofuran-4-carboxylate (5) and dimethyl 3,3′-bis(3,5-dimethoxyphenyl)-6,6′-dimethoxy-2,2′-bibenzofuran-4,4′-dicarboxylate (11).** To a solution of **6** (1 g, 2.92 mmol) in DMA (31 mL) was added 4-bromoanisole (0.73 mL, 2 equiv), $Pd(OAc)_2$ (131 mg, 0.2 equiv), and KOAc (573 mg, 2 equiv) at rt. After being stirred at 80 °C for 16 h, the reaction mixture was cooled to rt. The mixture was concentrated under reduced pressure to give the residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2 → 3 : 1 : 2) to afford **5** (851 mg, 65%) and **11** (339 mg, 34%). **5**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.49 (d, $J$ = 9.0 Hz, 2H), 7.24 (d, $J$ = 2.4 Hz, 1H), 7.21 (d, $J$ = 2.1 Hz, 1H), 6.82 (d, $J$ = 9.0 Hz, 2H), 6.50 (s, 3H) 3.90 (s, 3H), 3.80 (s, 3H), 3.77 (s, 6H), 3.23 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 168.2, 161.3, 159.9, 157.3, 155.5, 151.9, 136.8, 128.4, 125.5, 123.2, 121.9, 115.9, 114.1, 112.6, 107.7, 100.4, 99.8, 56.3, 55.7, 55.5, 51.7; **HRMS** (EI) calcd for $[C_{26}H_{24}O_7]^+$: $m/z$ 448.1522, found 448.1515. **11**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.23 (d, $J$ = 2.1 Hz, 2H), 7.18 (d, $J$ = 2.4 Hz, 2H), 6.28 (dd, $J$ = 2.1, 2.4 Hz, 2H), 6.08 (d, $J$ = 2.4 Hz, 4H), 3.90 (s, 6H), 3.65 (s, 12H), 3.16 (s, 6H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.8, 160.2, 158.2, 156.5, 142.8, 134.3, 126.4, 122.3, 119.3, 113.1, 106.6, 99.7, 99.3, 56.0, 55.2, 51.5; **HRMS** (EI) calcd for $[C_{38}H_{34}O_{12}]^+$: $m/z$ 682.2050, found 682.2055.

The compounds **12–16** (Table 2) were prepared under the optimized conditions above.

**Methyl 3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-nitrophenyl)-benzofuran-4-carboxylate (12).** **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.14 (d, $J$ = 9.0 Hz, 2H), 7.69 (d, $J$ = 8.7 Hz, 2H), 7.30 (d, $J$ = 2.1 Hz, 1H), 7.24 (d, $J$ = 2.4 Hz, 1H), 6.56 (dd, $J$ = 2.1, 2.4 Hz, 1H), 6.49 (d, $J$ = 2.1 Hz, 2H), 3.93 (s, 3H), 3.79 (s, 6H), 3.26 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.6, 161.7, 158.7, 156.1, 148.9, 147.0, 136.6, 135.6, 127.0, 126.7, 124.0, 121.3, 121.0, 114.0, 107.4, 100.6, 99.5, 56.3, 55.7, 51.8; **HRMS** (EI) calcd for $[C_{25}H_{21}NO_8]^+$: $m/z$ 463.1267, found 463.1265.

**Methyl 3-(3,5-dimethoxyphenyl)-2-(4-fluorophenyl)-6-methoxybenzofuran-4-carboxylate (13).** **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.54-7.50 (m, 2H), 7.26 (d, $J$ = 2.1 Hz, 1H), 7.21 (d, $J$ = 2.1 Hz, 1H), 7.01-6.95 (m, 2H), 6.53-6.48 (m, 3H), 3.90 (s, 3H), 3.77 (s, 6H), 3.25 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.8, 164.2, 161.2, 160.9, 157.4, 155.4, 150.6, 136.1, 128.7, 128.6, 126.5, 126.4, 125.6, 121.2, 116.9, 115.6, 115.3, 112.7, 107.3, 100.1, 99.5, 56.0, 55.5, 51.5; **HRMS** (EI) calcd for $[C_{25}H_{21}FO_6]^+$: $m/z$ 436.1322, found 436.1325.

**Methyl 3-(3,5-dimethoxyphenyl)-6-methoxy-2-(4-(trifluoromethyl)phenyl)benzofuran-4-carboxylate (14).** **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, $J$ = 8.1 Hz, 2H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 2.1 Hz, 1H), 7.24 (d, $J$ = 2.4 Hz, 1H), 6.53 (dd, $J$ = 2.1, 2.4 Hz, 1H), 6.49 (d, $J$ = 2.1 Hz, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 3.25 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.8, 161.5, 158.2, 155.8, 149.9, 136.0, 133.9, 130.2, 129.7, 126.9, 126.3, 126.0, 125.6, 125.56, 125.5, 125.46, 122.4, 121.2, 119.5, 113.5, 107.5, 100.5, 99.6, 56.3, 55.7, 51.8; **HRMS** (EI) calcd for $[C_{26}H_{21}F_3O_6]^+$: $m/z$ 486.1290, found 486.1293.

**Methyl 2-(4-cyanophenyl)-3-(3,5-dimethoxyphenyl)-6-methoxybenzofuran-4-carboxylate (15).** **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, $J$ = 8.4 Hz, 2H), 7.54 (d, $J$ = 8.7 Hz, 2H), 7.28 (d, $J$ = 2.4 Hz, 1H), 7.22 (d, $J$ = 2.4 Hz, 1H), 6.54 (d, $J$ = 2.1 Hz, 1H), 6.48 (d, $J$ = 2.1 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 6H), 3.25 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.7, 161.6, 158.5, 156.0, 149.2, 135.7, 134.7, 132.3, 126.9, 126.6, 121.1, 120.6, 119.0, 113.8, 111.4, 107.4, 100.6, 99.5, 56.3, 55.7, 51.8; **HRMS** (EI) calcd for $[C_{26}H_{21}NO_6]^+$: $m/z$ 443.1369, found 443.1362.

**Methyl 3-(3,5-dimethoxyphenyl)-2-(4-(ethoxycarbonyl)phenyl)-6-methoxybenzofuran-4-carboxylate (16).** **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, $J$ = 8.4 Hz, 2H), 7.60 (d, $J$ = 8.4 Hz, 2H), 7.27 (d, $J$ = 2.4 Hz, 1H), 7.23 (d, $J$ = 2.1 Hz, 1H), 6.53 (dd, $J$ = 2.1, 2.4 Hz, 1H), 6.50 (d, $J$ = 2.4 Hz, 2H), 4.36 (q, $J$ = 7.2 Hz, 2H), 3.91 (s, 3H), 3.78 (s, 6H), 3.25 (s, 3H), 1.38 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.9, 166.4, 161.5, 158.2, 155.9, 150.4, 136.1, 134.6, 130.0, 129.8, 126.5, 126.3, 121.3, 119.5, 113.4, 107.5, 100.6, 99.6, 61.2, 56.3, 55.7, 51.8, 14.5; **HRMS** (EI) calcd for $[C_{28}H_{26}O_8]^+$: $m/z$ 490.1628, found 490.1631.

**3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)benzofuran-4-carbaldehyde (4).** To a solution of **5** (664 mg, 1.482 mmol) in $CH_2Cl_2$ (17 mL) was added DIBAL (1 M solution in toluene, 5.9 mL, 4 equiv) at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was quenched with MeOH at −78 °C. After being stirred at rt for 30 min, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give the residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 5 : 1 : 2 → 3 : 1 : 2) to afford alcohol (623 mg, 100%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.45 (dd, $J$ = 2.1, 6.9 Hz, 2H), 7.00 (d, $J$ = 2.1 Hz, 1H), 6.89 (d, $J$ = 2.1 Hz, 1H), 6.79 (dd, $J$ = 2.1, 6.9 Hz, 2H), 6.60 (d, $J$ = 2.1 Hz, 2H), 6.55 (d, $J$ = 2.4 Hz, 1H), 4.45 (d, $J$ = 4.2 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 9H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 161.6, 159.5, 158.2, 154.9, 150.1, 136.8, 135.0, 127.6, 123.6, 121.5, 115.7, 114.1, 111.1, 108.3, 100.7, 95.3, 62.6, 56.0, 55.7, 55.5; **HRMS** (EI) calcd for $[C_{25}H_{24}O_6]^+$: $m/z$ 420.1573, found 420.1572.

To a solution of alcohol (147 mg, 0.35 mmol) in $CH_2Cl_2$ (3 mL) was added Dess–Martin periodinane (178 mg, 1.2 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give the residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2 → 7 : 1 : 2) to afford aldehyde **4** (145 mg, 99%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.53 (d, $J$ = 9.0 Hz, 2H), 7.46 (d, $J$ = 2.1 Hz, 1H), 7.33 (d, $J$ = 2.1 Hz, 1H), 6.84 (d, $J$ = 9.0 Hz, 2H), 6.61 (d, $J$ = 2.1 Hz, 2H), 6.56 (dd, $J$ = 2.1, 2.4 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.79 (s, 6H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 189.9, 162.1, 160.1, 157.7, 155.5, 152.4, 136.6, 129.6, 128.2, 127.0, 122.8, 115.1, 114.3, 108.1, 107.7, 103.4, 100.8, 56.3, 55.7, 55.5; **HRMS** (EI) calcd for $[C_{25}H_{22}O_6]^+$: $m/z$ 418.1416, found 418.1420.

**(*E*)-3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-(4-methoxystyryl)benzofuran (1).** To a stirred solution of diethyl 4-methoxybenzylphosphonate (0.031 mL, 1.5 equiv) in 1 mL of THF was added KOt-Bu (19 mg, 1.4 equiv) at 0 °C. After 5 min, a solution of **4** (50 mg, 0.12 mmol) in THF (1 + 1 mL for rinse) was added to this mixture at −78 °C. After being slowly warmed to rt for 16 h, the mixture was quenched with $H_2O$ at 0 °C and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a crude residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 15 : 1 : 2) to afford **1** (62 mg, 100%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.53 (d, $J$ = 9.0 Hz, 2H), 7.11 (d, $J$ = 2.1 Hz, 1H), 7.04 (s, 1H), 7.01 (s, 2H), 6.87 (s, 2H), 6.82 (d, $J$ = 8.7 Hz, 2H), 6.78 (d, $J$ = 8.7 Hz, 2H), 6.65 (s, 2H), 6.63 (t, $J$ = 2.1 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 6H);**$^1$H NMR** (700 MHz, $CDCl_3$) δ 7.52 (d, $J$ = 8.9 Hz, 2H), 7.10 (d, $J$ = 2.1 Hz, 1H), 7.01 (d, $J$ = 8.7 Hz, 2H), 6.99 (d, $J$ = 2.1 Hz, 1H), 6.87 (d, $J$ = 16.3 Hz, 1H), 6.84 (d, $J$ = 16.3 Hz, 1H), 6.81 (d, $J$ = 8.9 Hz, 2H), 6.77 (d, $J$ = 8.7 Hz, 2H), 6.65 (d, $J$ = 2.3 Hz, 2H), 6.63 (t, $J$ = 2.3 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74 (s, 6H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 161.7, 159.5, 159.4, 158.3, 155.2, 150.0, 137.2, 132.3, 130.5, 128.8, 127.9, 127.8, 123.8, 123.4, 122.3, 116.6, 114.2, 114.1, 108.8, 106.9, 100.7, 95.1, 56.1, 55.7, 55.5, 55.4; **HRMS** (EI) calcd for $[C_{33}H_{30}O_6]^+$: $m/z$ 522.2042, found 522.2045.

**3-(3,5-Dimethoxyphenyl)-6-methoxy-2-(4-methoxyphenyl)-4-((2*R*,3*R*)-3-(4-methoxyphenyl)oxiran-2-yl)benzofuran (17).** To a stirred suspension of **4** (370 mg, 0.88 mmol) and dimethyl(4-methoxybenzyl)sulfonium chloride (387 mg, 2 equiv) in 6 mL of THF/DMF (1/1) was added 60% NaH (141 mg, 4 equiv) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with $H_2O$ at 0 °C and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a crude residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 10 : 1 : 2 → 7 : 1 : 2) to afford **17** (443 mg, 93%). **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.46 (d, $J$ = 8.9 Hz, 2H), 7.03 (d, $J$ = 2.1 Hz, 1H), 6.91-6.86 (m, 3H), 6.80-6.76 (m, 4H), 6.53 (br s, 1H), 6.32 (br s, 1H), 6.18 (dd, $J$ = 2.1, 2.4 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (d, $J$ = 1.8 Hz, 1H), 3.75 (s, 3H), 3.74 (br s, 3H), 3.53 (d, $J$ = 1.8 Hz, 1H), 3.32 (br s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 161.3, 160.0, 159.5, 158.5, 154.6, 150.0, 136.3, 131.8, 128.8, 127.6, 127.2, 123.6, 122.8, 115.7, 114.1, 113.9, 108.1, 106.3, 100.1, 95.7, 63.4, 59.4, 56.1, 55.6, 55.5; **HRMS** (EI) calcd for $[C_{33}H_{30}O_7]^+$: $m/z$ 538.1992, found 538.1996.

**Pentamethyl ether of malibatol A (2) and its diastereomer 18.** To a stirred solution of **17** (38 mg, 0.071 mmol) in $CH_2Cl_2$ (3mL) was added $Bi(OTf)_3$ (5 mg, 0.1 equiv) at −78 °C. After being stirred at −78 °C for 1 h, the mixture was quenched with aqueous $NaHCO_3$ at −78 °C and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a crude residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 7 : 1 : 2 → 5 : 1 : 2) to afford **2** (28 mg, 74%) and **18** (9 mg, 24%). **2**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, $J$ = 9.0 Hz, 2H), 7.12-7.10 (m, 3H), 6.94 (d, $J$ = 9.0 Hz, 2H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.72 (d, $J$ = 2.4 Hz, 1H), 6.52 (d, $J$ = 9.0 Hz, 2H), 6.41 (d, $J$ = 2.7 Hz, 1H), 5.57 (d, $J$ = 2.4 Hz, 1H), 5.40 (d, $J$ = 6.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 3.46 (s, 3H), 2.59 (d, $J$ = 6.9 Hz, 1H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 160.2, 158.8, 158.5, 158.3, 157.7, 154.2, 151.1, 137.5, 134.4, 132.0, 130.5, 129.8, 124.6, 122.1, 118.2, 116.5, 114.2, 113.3, 108.4, 106.2, 98.3, 94.1, 73.8, 56.2, 55.9, 55.6, 55.2, 55.1, 47.9; **HRMS** (EI) calcd for $[C_{33}H_{30}O_7]^+$: $m/z$ 538.1992, found 538.1995. **18**: **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.67 (d, $J$ = 8.7 Hz, 2H), 6.97 (d, $J$ = 9.0 Hz, 2H), 6.95 (d, $J$ = 8.1 Hz, 2H), 6.88 (d, $J$ = 1.8 Hz, 1H), 6.84 (d, $J$ = 2.1 Hz, 1H), 6.78 (d, $J$ = 2.1 Hz,

1H), 6.53 (d, $J = 8.7$ Hz, 2H), 6.48 (d, $J = 2.4$ Hz, 1H), 5.78 (d, $J = 6.3$ Hz, 1H), 5.47 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.61 (s, 3H), 3.49 (s, 3H), 1.72 (d, $J = 8.7$ Hz, 1H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 161.1, 160.4, 158.9, 158.0, 157.5, 154.8, 151.9, 135.4, 135.2, 132.6, 130.5, 128.5, 124.4, 119.6, 117.7, 115.6, 114.3, 113.4, 113.1, 106.4, 98.5, 95.5, 74.6, 56.4, 56.0, 55.6, 55.2, 55.1, 44.4; **HRMS** (EI) calcd for $[C_{33}H_{30}O_7]^+$: $m/z$ 538.1992, found 538.1991.

**Pentamethyl ether of shoreaphenol (3) and alcohol 2 from 3.** To a solution of **2** (16 mg, 0.03 mmol) in $CH_2Cl_2$ (2 mL) was added Dess–Martin periodinane (15 mg, 1.2 equiv) at 0 °C. After being stirred at rt for 1 h, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to give the residue which was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 7 : 1 : 2) to afford ketone **3** (16 mg, 100%). Alcohol **18** was also converted to ketone **3** in a similar manner. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, $J =$ 9.0 Hz, 2H), 7.44 (d, $J = 2.1$ Hz, 1H), 7.06 (d, $J = 2.1$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.75 (d, $J =$ 2.1 Hz, 1H), 6.55 (d, $J = 8.7$ Hz, 2H), 6.50 (d, $J = 2.4$ Hz, 1H), 6.20 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.61(s, 3H), 3.52 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 196.3, 160.9, 159.9, 159.2, 158.0, 157.9, 154.2, 153.1, 134.3, 130.8, 130.4, 130.2, 127.8, 123.5, 122.7, 116.5, 116.1, 114.4, 113.5, 109.9, 105.8, 101.5, 98.8, 56.4, 56.3, 55.6, 55.3, 55.2; **HRMS** (EI) calcd for $[C_{33}H_{28}O_7]^+$: $m/z$ 536.1835, found 536.1833.

To a solution of **3** (15 mg, 0.028 mmol) in 3 mL of MeOH/THF (1/1) was added $NaBH_4$ (2.6 mg, 2.5 equiv) at 0 °C. After 30 min, the mixture was quenched with saturated $NH_4Cl$ at 0 °C. After the mixture was concentrated *in vacuo*, the residue was diluted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give **2** (15 mg, 100%). Characterisation data identical to that described earlier.

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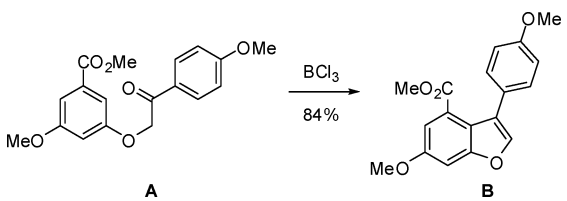


**A** **B**

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33 In addition, a crude mixture of diastereomers (**2** + **18**) resulting from treatment of **17** with $Bi(OTf)_3$ was directly subjected to Dess–Martin oxidation conditions, affording **3** in 98% two-step overall yield.