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ORIGINAL PAPER

General approach to neolignan-core of the boehmenan natural product family

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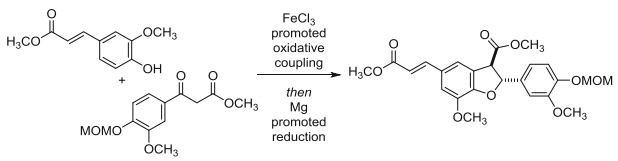
Abstract A novel approach to the neolignan-core skeletons of boehmenan natural products and to dehydrodiconiferyl alcohol glucosides based on the Fe(III)-promoted oxidative coupling has been achieved. Obtained common intermediates were further selectively modified to yield the basic molecular core possessing three orthogonally protected alkoxy functionalities available for further selective modifications.

Graphical abstract



Keywords Biomimetic synthesis · Natural products · Enzymes · Oxidative coupling

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Introduction

Neolignans belong to the phenylpropanoid-derived family of plant secondary metabolites that are obtained via the Shikimate biosynthetic pathway [1]. Phenylpropanoids, the direct secondary metabolites obtained from the Shikimate pathway, are further modified within plant cells to furnish structurally diverse biologically active natural products. In nature, basic phenylpropanoids are further dimerized or polymerized with the help of peroxidases, laccases, and enzyme-promoted phenol oxidative coupling [2, 3], furnishing various classes of natural products [4] (lignins, lignans, neolignans, etc.).

Our interest is to understand the oxidation processes [2, 3] related to the phenolic plant secondary metabolites on a molecular level and relate their effects on human health. Thus, we are focused on the investigation of plant produced phenolic compounds and their oxidative coupling products [5]. Unfortunately, the plant metabolome contains virtually thousands of various phenylpropanoid-related compounds. As a consequence, identification of compounds of interest is challenging. To face such problems, we have focused our synthetic efforts on the development of synthetic strategies that allows us to yield the majority of phenylpropanoid-based phytochemicals in a short end efficient manner.

The first step in this quest was establishing a short and efficient way to phenylpropanoid monomers and structurally related coumarins [6]. Next, we focused our attention to phenylpropanoid C-8, C-5 homocoupling products—8-5′-neolignans **2**—and their functional group derivatives containing the 2,3-dihydrobenzofuran motive **3** (Scheme 1).

In the literature, the synthesis of benzofurans is widely covered [7, 8] and many different approaches to

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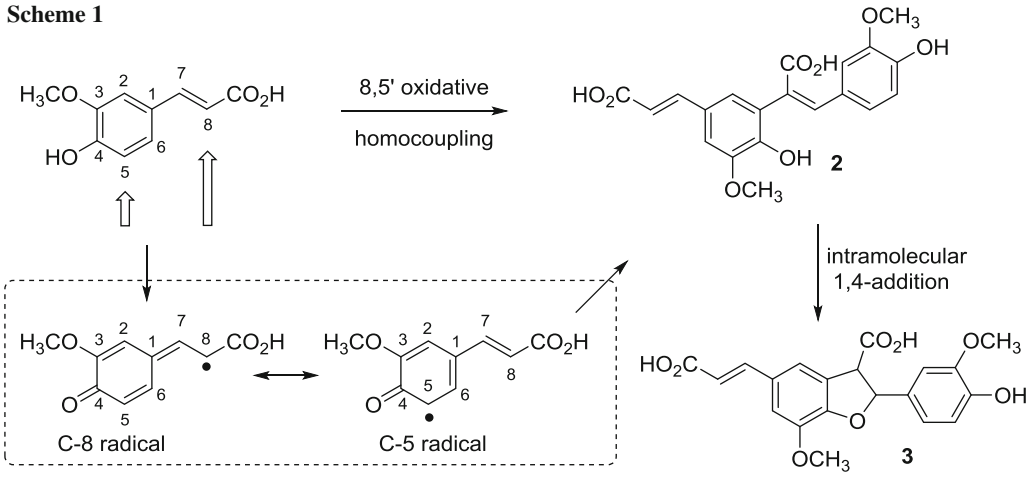
Scheme 1

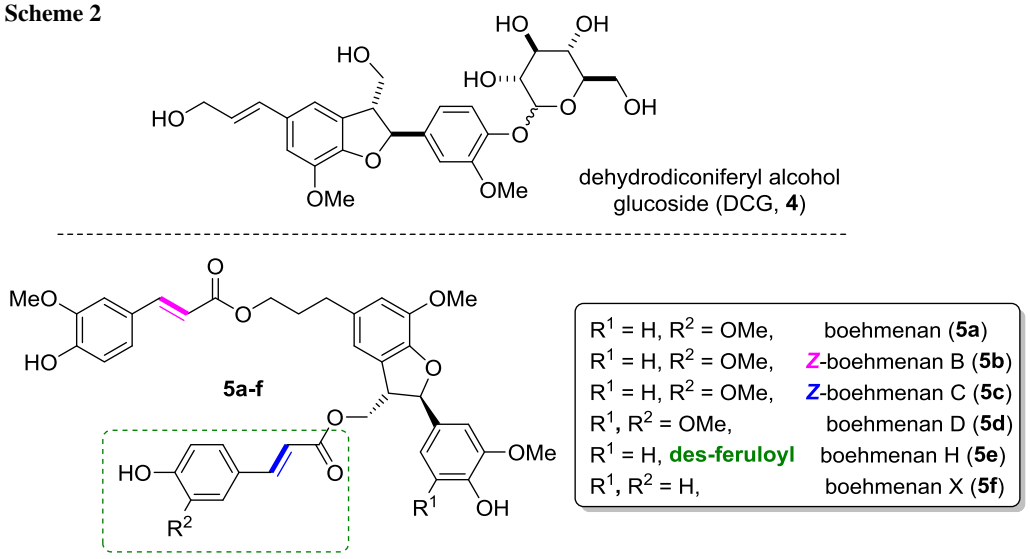


benzofuran-core structures have been developed. Most of these approaches are based either on the use of enzymes (peroxidases, laccases) [9], biomimicking radical homocouplings [10], or on the use of transition metal-mediated coupling reactions [11]. In our case, we wished to adopt a short, efficient and easy to scale-up approach to benzofuran skeletons included in boehmenan family natural products **4** and dehydrodiconiferyl glucose (DCG) derivatives **5** (Scheme 2). Our interest in these two targets arose from their biological activity. Some time ago, it was suggested that DCG **5** derivatives may act as cytokinins (phytohormones) within the plant signaling pathways [12]. On the other hand, boehmenans **5** were identified from extraction-driven biological tests of various plant extracts used in traditional Chinese medicine [13]. Based on the preliminary studies, boehmenan-type structures **5** regulate the Wnt/β-catenin signaling pathway important to treat, e.g. ,non-small cell lung cancer [14]. From a synthesis view point, DCG structure **4** [15] and boehmenan **5a** [16] have been already published. However, in our case, we wished to develop a short and efficient approach that would allow us to prepare not only targeted compounds but also their structural analogues.

Results and discussion

We planned to approach the synthesis of dihydrobenzofuran-core skeleton of **4** and **5** in a modular fashion where both aromatic rings of the core scaffold could be possibly

Scheme 2



modified prior to the dihydrofuran-ring assembly. Such approach, thus, excluded all homodimerization methods commonly based on the transition metal-promoted oxidative coupling reactions (e.g., starting from methyl ferulate and catalyzed by Fe^{III} [17] or Ag^{I} [18] salts). On the other hand, oxidative coupling reactions allow rapid, short and very convenient assembly of the targeted benzofuran molecular core of the neolignan natural products. Thus, we decided to base our approach on iron(III)-catalyzed oxidative coupling of β-ketoester **7** and phenol **6** [19, 20] followed by Mg-promoted *trans* reduction of the formed benzofurane adduct **8** [21] (Scheme 3).

The synthesis of targeted neolignans **4** and **5** core structure started with the preparation of the coupling partners methyl ferulate **6a** and β-ketoester **7a** (Scheme 4). In the case of ester **6a**, our recently developed microwave-assisted synthetic protocol was applied and the desired compound was prepared in 98% yield and > 95:1 *E/Z* selectivity starting from vanillin **10** [6]. β-Ketoester **7a** was prepared from vanillin (**10**) in three steps consisting of phenolic group MOM protection, followed by Fe-promoted Reformatsky-type condensation [22], and finished with PCC oxidation of β-hydroxy group. The desired product **7a** was prepared in 18% overall yield.

The Reformatsky reaction—transformation of aldehyde **11** to hydroxyester **12** in this sequence— is worth of mentioning. Surprisingly, we found that the Fe^{III} modification of the Reformatsky protocol gave in our hands superior yields over the "classical" Zn-promoted protocols (Table 1). Although, even in this case, the desired product **12** was formed in rather low yield of 25%. We speculate that the presence of electron-rich aromatic aldehyde might be a reason for the observed low yields.

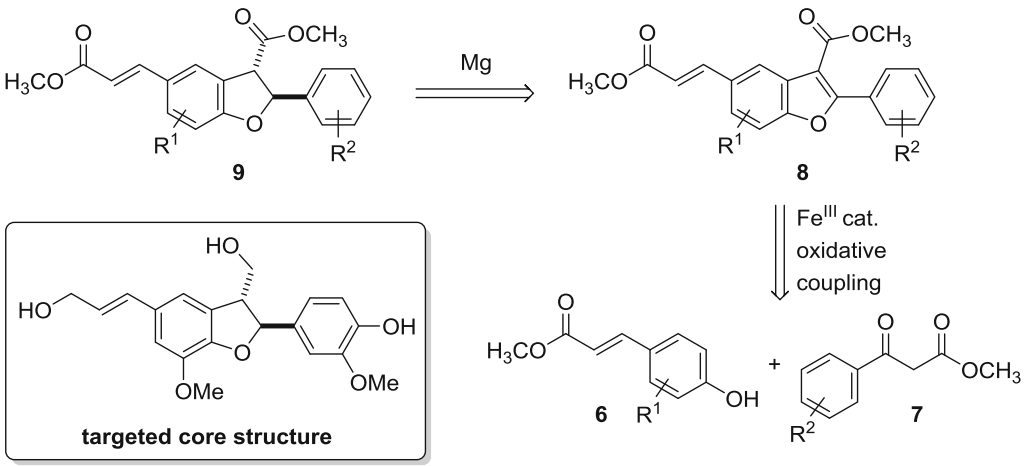
Having an access to the desired starting materials, the Fe^{III}-promoted oxidative coupling could then be attempted (Table 2). Upon screening of various reported oxidative coupling conditions [19, 20], we were delighted to observe the formation of the desired benzofuran **8a** albeit in moderate yield (Table 2, entry 3). Subsequent *trans* selective reduction [21] of the furan core **8a** to the dihydrofuran skeleton yielded the desired neolignan **9a** in 59% yield (Scheme 5).

Alternatively, we decided to prepare the same product **9a** via a homodimerization process. Thus, methyl fumarate **6a** was reacted under various literature protocols to yield the desired product **13** (Table 3). Both enzymatic as well as transition metal-catalyzed homocoupling conditions were attempted, and the desired product **13** was obtained in the best case in 28% yield and 91:9 *trans*/*cis* selectivity (Table 3, entry 2). The corresponding MOM-protected neolignan derivative **9a** was then prepared in 89% yield using the standard protecting group protocol (Scheme 6).

Finally having acquired the substantial amount of neolignan core **9a**, we could start the second aim of our project—selective modification of the ester groups. First, global DIBAL-H reduction of both methyl esters in **9a** to the corresponding alcohols was attempted. The reduction proceeded well and no product of undesired unsaturated olefin reduction was observed. Desired diol **14** was then per acetylated and the MOM-protected phenolic group was removed to yield DCG **4** core neolignan structure **16** in 3 steps (from intermediate **9a**) in 59% yield.

Next, selective monoreduction of the dihydrofuran ring-attached methyl ester group was attempted (Table 4). In our synthetic plans, it was important to distinguish both ester groups (respectively, generated primary alcohols) to

Scheme 3



Scheme 4

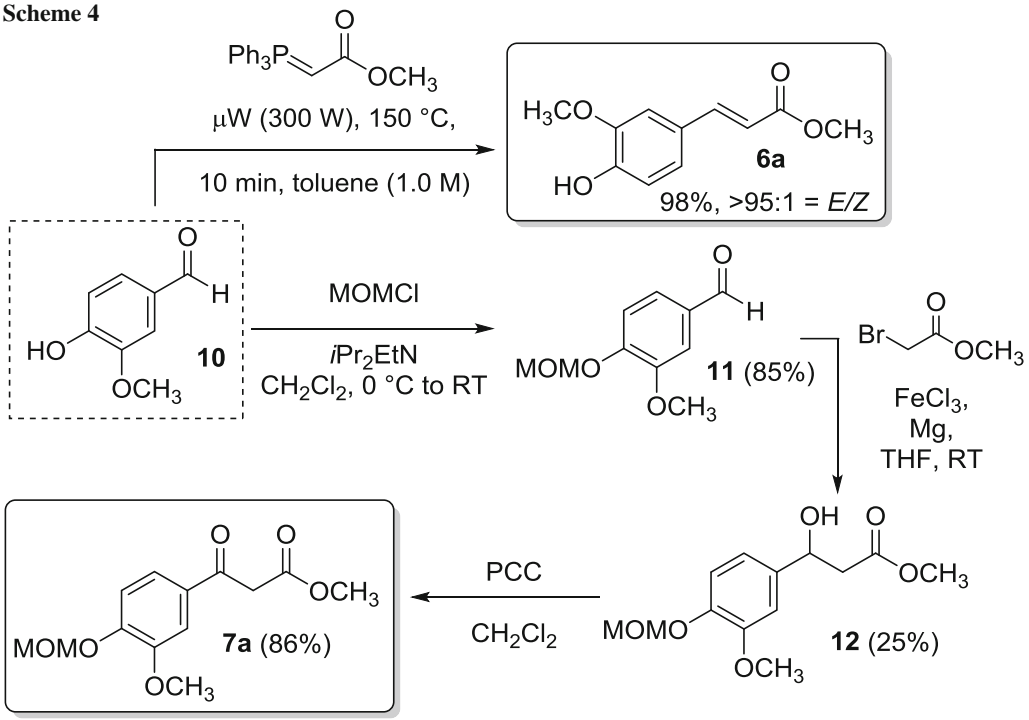
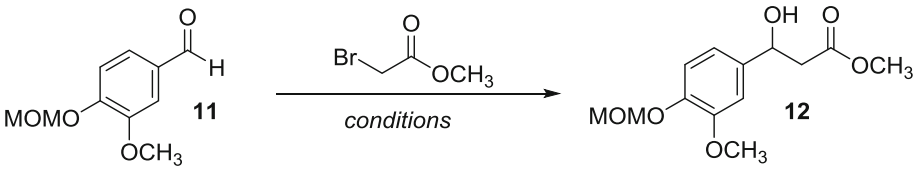


Table 1 Reformatsky reaction between aldehyde **11** and methyl α-bromo acetate—reaction conditions optimization



Entry	Conditions	**11**[a]/%	**12**[a]/%
1	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), toluene, 90 °C	65	4
2	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), THF, 60 °C	81	6
3[b]	Zn (10 equiv), $BrCH_2CO_2Me$ (5 equiv), THF, 60 °C	43	2
4	$FeCl_3$ (3 equiv), Mg (10 equiv), $BrCH_2CO_2Me$ (2 equiv), THF, 60 °C	73	5
5	$FeCl_3$ (3 equiv), Mg (10 equiv), $BrCH_2CO_2Me$ (2 equiv), THF, RT	29	25

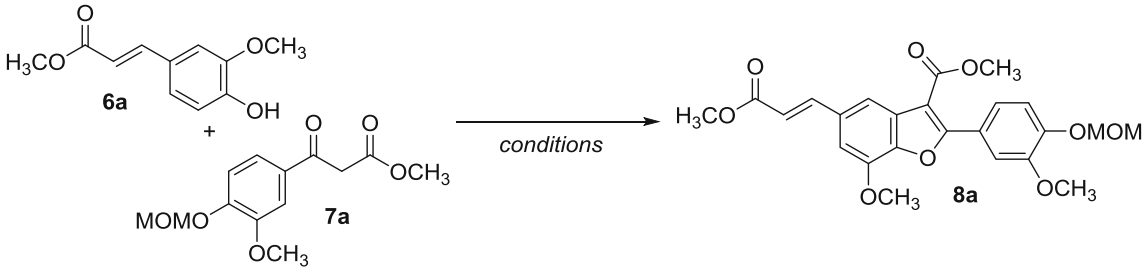
[a]Refers to pure isolated compounds

[b]$BrCH_2CO_2Me$ was slowly added as a THF solution

be able to later on selectively introduce various ester functionalities or other substituents to prepare all possible members of the boehmenan family (Scheme 1). First, the reduction of MOM-protected diester **9b** was attempted. Unfortunately, the desired alcohol product **18** was not obtained under any evaluated reaction conditions (Table 4, entries 1–8). In all cases, nonselective reduction of both ester functionalities and/or complex mixture of partially reduced products were/was obtained. It was speculated that the reason for this reaction mixture behaving this way is due to the stabilization of the mono-reduced DHF-ring placed ester functionality.

It was speculated that the presence of the MOM-protecting group might stabilize the monoreduced intermediate 20 (Scheme 7). To disrupt generated intermediate **20,** the reaction mixture must be warmed up and the competitive reduction of α,β-unsaturated ester group in the side chain occurs. To test our hypothesis, the phenol functionality in neolignan **13** was protected in the form of TBS ether and the reduction of the resulting TBS –

Table 2 Screening of oxidative radical coupling reaction conditions



Entry	Conditions	Yield[a]/%
1	$FeCl_3$ (10 mol%), 2,2′-dipyridine (5 mol%), DTBP (2.5 equiv), DCE, 70 °C	23
2	$FeCl_3$ (10 mol%), 2,2′-dipyridine (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	11
3	$FeCl_3$ (10 mol%), NHPI (5 mol%), DTBP (2.5 equiv), DCE, 70 °C	36
4	$FeCl_3$ (10 mol%), NHPI (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	12
5	$FeCl_3$ (10 mol%), DTBP (2.5 equiv), DCE, 70 °C	5
6	$FeCl_3$ (10 mol%), atmospheric air, DCE, 70 °C	14

DTBP diterbutylperoxide, *NHPI N*-hydroxyphthalimide

[a]Refer to pure isolated compound

Scheme 5

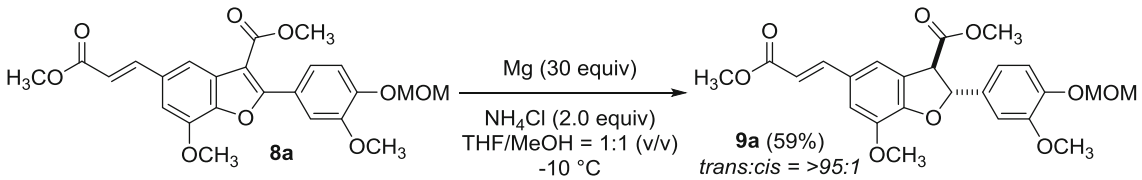
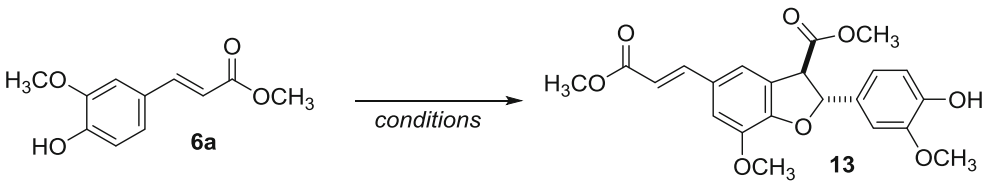


Table 3 Benzofuran **9a** synthesis: oxidative homocoupling reaction



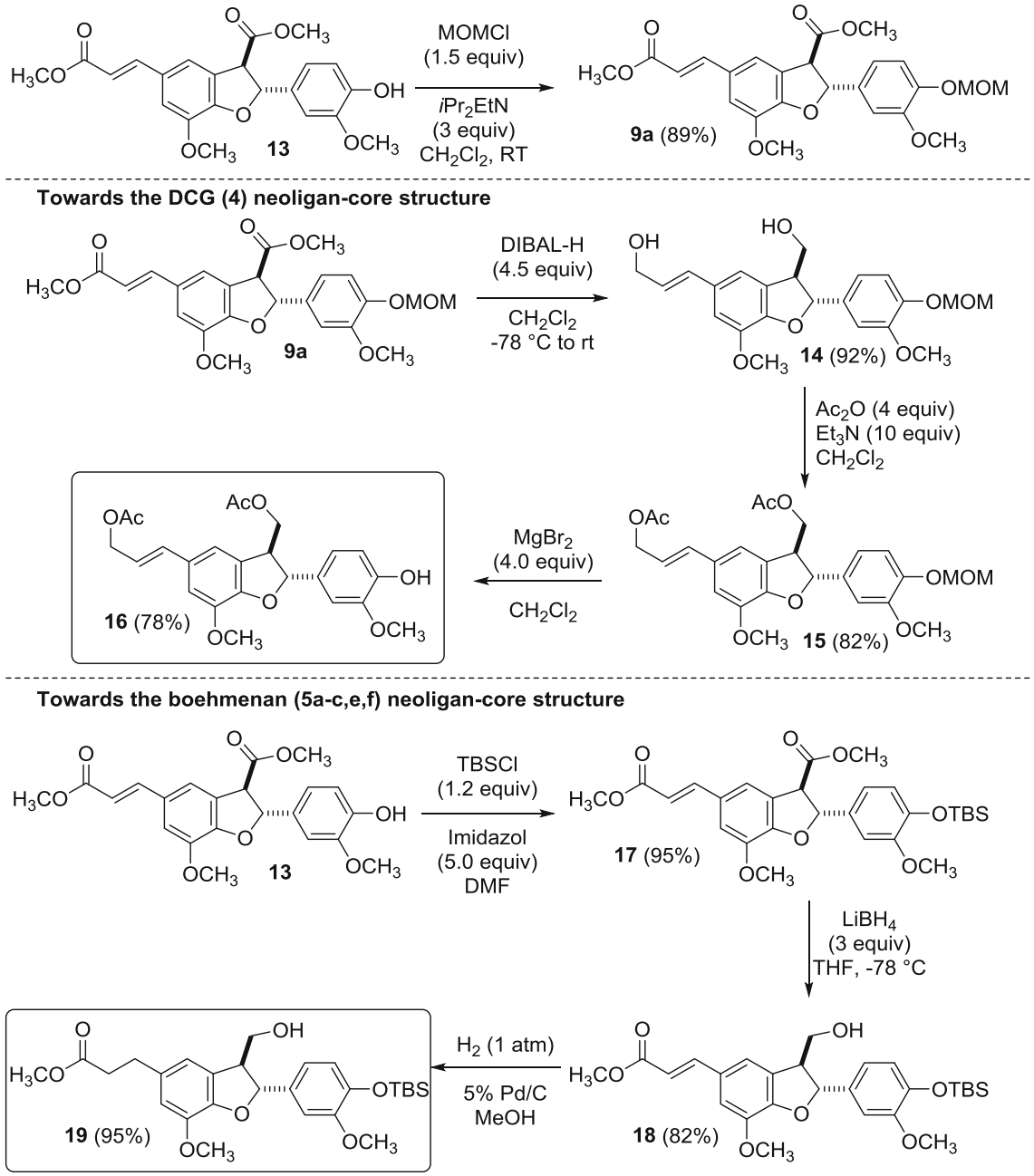
Entry	Conditions	Yield[a]/%	*trans/cis*[b]
1	$K_3[Fe(CN)_6]$ (2.1 equiv), $CH_2Cl_2/CHCl_3$ = 1:9 (V/V), RT	22	82:18
2	Ag_2O (2.1 equiv), acetone/benzene = 3:1, RT	28	91:9
3	Ag_2O (2.1 equiv), CH_2Cl_2, RT	7	89:11
4	Ag_2O (2.1 equiv), CH_2Cl_2/H_2O = 1:1 (v/v), RT	13	92:8
5	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 7.3	7	81:19
6	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 4.5	11	71:29
7	HRP[c], 1 M aq. H_2O_2 (10 equiv), phosphate buffer pH = 7.3 (dark)	10	89:11

[a]Refer to pure isolated compound

[b]Based on the ^1H NMR analysis

[c]25KU HRP used (1 mg per 1 mmol of **6a**)

Scheme 6



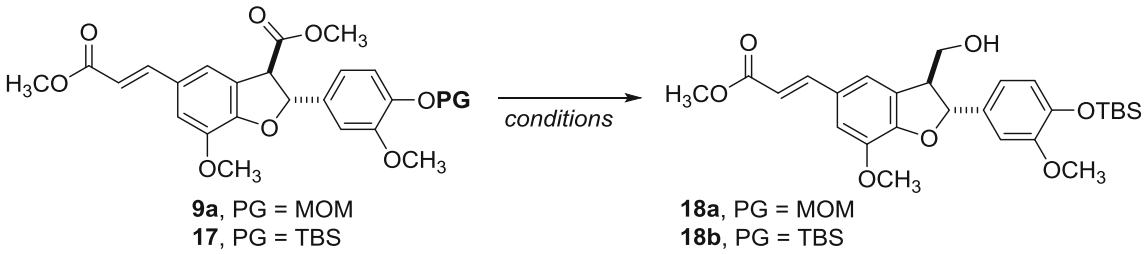
neolignan **17** was attempted. Gratifyingly, the desired alcohol **18b** was prepared selectively with use of $LiBH_4$ in 82% (Table 4, entry 12). No product of the second ester reduction was observed during the reaction.

Finally, selective hydrogenation of α,β-unsaturated olefin function in **18b** yielded the key intermediate **19**. The switch in the protecting group, thus, allowed us to achieve the synthesis of the boehmenan-core skeleton **19** that possesses three key oxygenated functional groups with orthogonal protecting groups—free hydroxy, TBS-protected phenol (to be removed with TBAF/AcOH system), and methyl ester group (transformed to the corresponding alcohol with TMSOK hydrolysis followed by a BH_3-reduction system).

Conclusion

We have developed a novel approach to the core skeleton of boehmenan (**5**) and DCG (**4**) natural products. Our approach allows the preparation of such neolignan-type skeletons via an oxidative coupling reaction. However, in

Table 4 Selective reduction of diester **9a** or **17** to alcohol **18**



9a, PG = MOM
17, PG = TBS

18a, PG = MOM
18b, PG = TBS

Entry	PG	Conditions	Yield[a]/%
1	MOM	DIBAL-H (2.1 equiv), CH_2Cl_2, − 78 °C	No reaction
2	MOM	DIBAL-H (2.1 equiv), CH_2Cl_2, − 50 °C	n.d.[b]
3	MOM	DIBAL-H (2.1 equiv), toluene, − 35 °C	No reaction
4	MOM	DIBAL-H (2.1 equiv), toluene, 0 °C	n.d.
5	MOM	DIBAL-H (2.1 equiv), THF, − 78 °C	No reaction
6	MOM	DIBAL-H (2.1 equiv), THF, − 20 °C	n.d.[b]
7	MOM	$LiBH_4$ (2.1 equiv), THF, − 78 °C	No reaction
8	MOM	$LiBH_4$ (2.1 equiv), THF, − 40 °C	n.d.[b]
9[c]	TBS	DIBAL-H (2.1 equiv), THF, − 78 °C	23%
10	TBS	DIBAL-H (2.1 equiv), THF, − 40 °C	n.d.[b]
11[d]	TBS	$LiBH_4$ (2.1 equiv), THF, − 78 °C	57%
12	TBS	$LiBH_4$ (3.0 equiv), THF, − 78 °C	82%

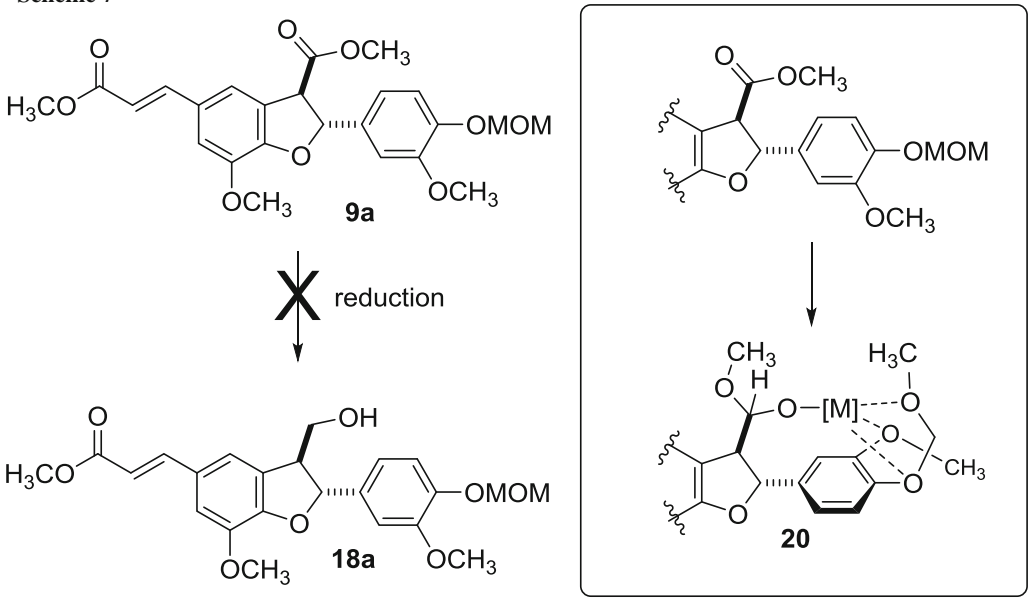
[a]Refer to pure isolated compound

[b]Complex mixture

[c]Reaction mixture also contained unreacted diester **17** (54%)

[d]Incomplete conversion of **17**

Scheme 7



comparison with the literature, our approach is versatile allowing the synthesis of products possessing a variety of substitution patterns on the presented aromatic rings. For the time being our approach suffers from the low yielding coupling step. We believe that systematic evaluation of the aromatic substitution influence of the phenolic coupling partner on the reactivity of the system will allow us to carry out the coupling reaction with better yields. On the other hand, our approach allows the preparation of the desired dihydrobenzofuran skeleton with superior *trans/cis* selectivity than that of any of the tested literature homocoupling reaction conditions could provide.

At this time, we are developing a new set of conditions that will hopefully allow the desired oxidative coupling reaction to occur in greater yields. The Mg-promoted selective *trans* reduction followed by the resulting stereoisomer separation should allow us to prepare targeted natural products as single enantiomers and to establish the absolute stereochemistry of the isolated boehmenan natural products.

Experimental

All reactions were performed in round-bottom flasks fitted with rubber septa using the standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (silica gel 60 F254, Merck). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in basic potassium permanganate solution or in ethanolic phosphomolybdic acid solution followed by brief heating. Flash-column chromatography was carried out on silica gel (60 Å, 230–400 mesh, Sigma-Aldrich) using Petroleum ether/EtOAc solvent mixtures.

All reagents and enzymes were obtained from commercial suppliers (Sigma-Aldrich or Acros Organics) and were used without further purification. Dry solvents were obtained using standard drying protocols: THF was distilled under argon from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2.

Nuclear magnetic resonance spectra were recorded using Bruker Avance II 300, JEOL 400ECS or JEOL 500ECA instruments at 25 °C. 1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ/ppm) ^1H NMR are reported in a standard fashion relative to the remaining $CHCl_3$ present in $CDCl_3$ ($\delta_H = 7.27$ ppm). ^{13}C NMR chemical shifts (δ/ppm) are reported relative to $CHCl_3$ ($\delta_C = 77.23$ ppm, central line of triplet). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), and multiplet (m), and coupling constants (J) are reported in Hz. HRMS data were obtained using quadrupole/ion trap mass analyzer. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY, and NOEdiff experiments.

All microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 cm^3 glass vials sealed with a Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

*Methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (***6a**)
A suspension of 0.76 g of vanillin **10** (5.00 mmol) and 1.84 g of stabilized Wittig ylide (5.5 mmol) in 5.0 cm^3 of toluene was placed in a microwave vial (35 cm^3) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed in a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 10 min (fixed time) at 150 °C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1) yielded 1.02 g of resulting ester **6a** (98%) in > 95:1 *E/Z* ratio. M.p.: 64–65 °C (Ref. [6], 63–65 °C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.60$ (d, $J = 16.0$ Hz, 1H), 7.03 (ddd, $J = 16.2$, 7.9, 1.9 Hz, 2H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.27 (d, $J = 15.9$ Hz, 1H), 6.15–5.98 (m, 1H), 3.89 (s, 3H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 167.92$, 148.10, 146.89, 145.11, 126.98, 123.13, 115.15, 114.87, 109.48, 56.00, 51.74 ppm; MS (ESI): $m/z = 209$ ($[M+H]^+$); HRMS (ESI): m/z calculated (for $C_{11}H_{13}O_4^+$) 209.0814, found 209.0815.

*3-Methoxy-4-(methoxymethoxy)benzaldehyde (***11**)
A solution of 10.0 g of vanillin (**10**, 65.7 mmol) in 66 cm^3 CH_2Cl_2 was cooled to 0 °C and 18.3 cm^3 of iPr$_2$EtN (105 mmol) was added. After 5 min, 40.7 cm^3 of MOM-Cl in toluene (85.4 mmol, 2.1 M solution in toluene) was added dropwise and the resulting mixture was stirred at RT for 24 h. Saturated aq. NH_4Cl (50 cm^3) was added and the resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3) and combined organic layers were washed with 50 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1) yielded 12.5 g of **11** (85%). M.p.: 40–41 °C (Ref. [23], 39–40 °C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H), 3.95 (s, 3H), 5.33 (s,

2H), 7.15–7.19 (m, 1H), 7.28 (dd, $J = 7.7$, 1.0 Hz, 1H), 7.44 (d, $J = 1.1$ Hz, 1H), 9.87 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 56.2$, 56.7, 95.2, 109.7, 114.8, 126.6, 131.2, 150.2, 152.2, 191.2 ppm; MS (ESI): *m/z* = 197 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{10}H_{13}O_4^+$) 197.0808, found 197.0808.

Methyl 3-hydroxy-3-[3-methoxy-4-(methoxymethoxy)-phenyl]propanoate (**12**, $C_{13}H_{18}O_6$)

A mixture of 1.0 g **11** (5.1 mmol), 0.96 cm^3 of methyl bromoacetate (10.2 mmol), and 2.48 g of $FeCl_3$ (15.3 mmol) in 51 cm^3 of dry THF was stirred at RT and 372 mg of Mg (124 mmol, fine powder) was added at once. The resulting mixture was stirred at RT for 24 h before it was diluted with 35 cm^3 H_2O and 65 cm^3 EtOAc. The resulting suspension was stirred for additional 15 min before it was filtered through Celite®. The whole mixture was diluted with 20 cm^3 2% HCl and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 cm^3). Combined organic layers were washed with 25 cm^3 water and 25 cm^3 brine, dried over Na_2SO_4, evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1– > 2:1– > 1:1) yielding 0.345 g of resulting hydroxy ester **12** (25%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.71$ (dd, $J = 16.4$, 3.6 Hz, 1H), 2.78 (dd, $J = 16.3$, 9.3 Hz, 1H), 3.52 (s, 3H), 3.74 (s, 3H), 3.90 (s, 3H), 5.10 (dd, $J = 9.2$, 3.6 Hz, 1H), 5.22 (s, 2H), 5.64 (broad s, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 2.0$ Hz, 1H), 7.12 (d, $J = 8.3$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 43.4$, 52.2, 56.1, 56.4, 70.3, 95.7, 109.4, 116.5, 137.1, 146.2, 150.1, 173.1 ppm; MS (ESI): *m/z* = 271 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{13}H_{19}O_6^+$) 271.1176, found 271.1179.

Methyl 3-[3-methoxy-4-(methoxymethoxy)phenyl]-3-oxo-propanoate (**7a**, $C_{13}H_{16}O_6$)

A solution of 0.11 g of **12** (0.4 mmol) in 4 cm^3 of dry CH_2Cl_2 was stirred at RT and 0.176 g of PCC (pyridinium chlorochromate, 0.8 mmol) was added. The resulting mixture was stirred at RT for 12 h before 0.3 g of Celite® was added in one portion. The whole mixture was stirred at RT for additional 10 min. The whole mixture was filtered through a plug of 2 g of Celite®. Filter cake was washed with CH_2Cl_2 (3 × 25 cm^3) and combined filtrates were dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1– > 2:1–> 1:1) and yielded 0.092 g of ketoester **7a** (86%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H), 3.76 (s, 3H), 3.95 (s, 3H), 3.98 (s, 2H), 5.33 (s, 2H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.51 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.57 (d, $J = 2.1$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 45.4$, 52.2, 56.0, 56.4, 95.9, 112.2, 116.6, 135.4, 142.8, 150.4, 151.7, 170.8, 193.8 ppm; MS (ESI): *m/z* = 269 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{13}H_{17}O_6^+$) 269.1020, found 269.1021.

Methyl (E)-7-methoxy-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2-[3-methoxy-4-(methoxymethoxy)phenyl]benzofuran-3-carboxylate (**8a**, $C_{24}H_{24}O_9$)

A solution of 0.366 g di-*tert*-butyl peroxide (2.5 mmol) in 1.0 cm^3 of 1,2-dichloroethane was added drop-wise into a stirred solution of 0.268 g of **7a** (1.0 mmol), 0.229 g of phenol **6a** (1.1 mmol), 0.09 g *N*-hydroxyphthalimide (0.05 mmol), and 0.16 g $FeCl_3$ (0.1 mmol) in 2 cm^3 of 1,2-dichloroethane under an argon atmosphere at room temperature. The reaction mixture was heated at 70 °C (external) for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1– > 2:1–> 1:1) and yielded 0.164 g of benzofuran **8a** (36%). M.p.: 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H), 3.94 (s, 3 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3H), 5.06 (s, 2 H), 6.41 (d, $J = 15.9$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 7.23 (d, $J = 2.1$ Hz, 1H), 7.44 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.56 (d, $J = 1.7$ Hz, 1H), 7.76 (d, $J = 15.8$ Hz, 1H), 7.80 (s, 1 H) ppm; ^{13}C NMR (100.1 MHz, $CDCl_3$): $\delta = 51.2$, 52.4, 54.2, 56.4, 58.9, 92.7, 110.0, 111.5, 111.6, 114.5, 115.6, 116.2, 121.2, 122.9, 128.1, 131.2, 143.3, 146.4, 146.6, 148.9, 149.9, 160.4, 167.5, 167.9 ppm; MS (ESI): *m/z* = 457 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{24}H_{25}O_9^+$) 457.1493, found 457.1490.

Methyl (2R,3R)-7-methoxy-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-3-carboxylate (**9a**, $C_{24}H_{26}O_9$)

Magnesium powder (0.08 g, 3.3 mmol) followed by 0.012 g of NH_4Cl (0.22 mmol) were added to a solution of 0.05 g of **8a** (0.11 mmol) in 4 cm^3 of THF/MeOH [1:1 (v/v)] mixture cooled to − 10 °C. The resulting mixture was vigorously stirred and then slowly allowed warm to RT over 4 h. The reaction was cooled to − 40 °C before being quenched by the addition of 20 cm^3 of saturated aqueous NH_4Cl. The mixture was allowed to warm to RT before being partitioned between 20 cm^3 of H_2O and 20 cm^3 of CH_2Cl_2. Resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 cm^3). The combined organic phases were dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1–> 2:1–> 1:1) and yielded 0.060 g of dihydrobenzofuran **9a** (59%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.50$ (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.35 (d, $J = 8.1$ Hz, 1H), 5.22 (s, 2H), 6.14 (d, $J = 8.1$ Hz, 1H), 6.33 (d, $J = 15.9$ Hz, 1H), 6.92 (dd, $J = 12.0$, 2.5 Hz, 1H), 6.95

(s, 2H), 7.03 (d, $J = 1.6$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 1.3$ Hz, 1H), 7.65 (d, $J = 16.0$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 51.9$, 53.1, 55.6, 56.2, 56.3, 56.4, 87.4, 95.6, 109.8, 112.3, 115.8, 116.5, 118.1, 118.9, 125.8, 128.8, 133.8, 144.9, 146.9, 150.1, 150.1, 167.8, 170.9 ppm; MS (ESI): *m/z* = 459 ($[M+H]^+$); HRMS (FAB): *m/z* calculated (for $C_{24}H_{26}NaO_9^+$) 481.1469, found 481.1470.

(E)-3-[(2R,3S)-3-(Hydroxymethyl)-7-methoxy-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-5-yl]prop-2-en-1-ol (**14**, $C_{22}H_{26}O_7$)

A solution of 0.436 g **9a** (0.95 mmol) in 10 cm^3 of CH_2Cl_2 was cooled to − 78 °C and 4.8 cm^3 of DIBAL-H (4.73 mmol, as 1 M solution in CH_2Cl_2) was added dropwise. The resulting solution was stirred at − 78 °C for 30 min and additional 2 h at RT. The resulting mixture was re-cooled to − 78 °C and 10 cm^3 of sat. aq. sol. of Rochel's salt was added. The whole mixture was allowed to stir at RT for 12 h. The resulting layers were separated and the aqueous layer was extracted with DCM (3 × 20 cm^3). Combined organic layers were washed with 20 cm^3 of brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.400 g of diol **14** (92%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J = 8.3$ Hz, 1H), 6.94 (d, $J = 1.8$ Hz, 1H), 6.89 (dd, $J = 8.3$, 2.1 Hz, 1H), 6.84 (d, $J = 3.1$ Hz, 2H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.19 (dt, $J = 15.6$, 5.8 Hz, 1H), 5.57 (d, $J = 6.7$ Hz, 1H), 5.18 (s, 2H), 4.24 (d, $J = 6.1$ Hz, 2H), 3.90 (dd, $J = 11.0$, 6.4 Hz, 1H), 3.87 (s, 3H), 3.84 (dd, $J = 10.7$, 5.8 Hz, 1H), 3.82 (s, 3H), 3.57 (dd, $J = 11.9$, 6.1 Hz, 1H), 3.47 (s, 3H), 2.79 (s, $J = 31.1$ Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 150.00$, 148.31, 146.43, 144.46, 135.50, 131.29, 131.02, 128.35, 126.53, 118.71, 116.39, 115.05, 110.56, 109.83, 95.54, 88.05, 77.23, 63.76, 60.60, 56.30, 56.11, 56.05, 53.66 ppm; MS (ESI): *m/z* = 403 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{22}H_{27}O_7^+$) 403.1751, found 403.1748.

(E)-3-[(2R,3S)-3-(Acetoxymethyl)-7-methoxy-2-[3-methoxy-4-(methoxymethoxy)phenyl]-2,3-dihydrobenzofuran-5-yl]allyl acetate (**15**, $C_{26}H_{30}O_9$)

A solution of 0.241 g of **14** (0.6 mmol) in 6 cm^3 of CH_2Cl_2 was cooled to 0 °C and 0.886 cm^3 of Et_3N (6.35 mmol) was added. The resulting mixture was stirred for 5 min and 0.213 cm^3 of acetyl chloride (3 mmol) was added. The resulting mixture was allowed to warm to RT and stirred for additional 36 h. Saturated aq. $NaHCO_3$ (20 cm^3) was added and resulting layers were separated. Aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic layers were washed with 10 cm^3 of brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 4:1– > 2:1) and yielded 0.239 g of diacetal **15** (82%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.05$ (s, 3H), 2.11 (s, 3H), 3.51 (s, 3H), 3.78 (td, $J = 7.2$, 5.3 Hz, 1H), 3.86 (s, 3H), 3.92 (s, 3H), 4.31 (dd, $J = 11.1$, 7.5 Hz, 1H), 4.44 (dd, $J = 11.2$, 5.4 Hz, 1H), 4.72 (dd, $J = 6.7$, 1.2 Hz, 2H), 5.22 (s, 2H), 5.51 (d, $J = 7.1$ Hz, 1H), 6.16 (dt, $J = 15.9$, 6.6 Hz, 1H), 6.61 (d, $J = 16.0$ Hz, 1H), 6.89 (s, 2H), 6.92 (dd, $J = 11.1$, 2.1 Hz, 2H), 7.12 (d, $J = 8.2$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.9$, 21.1, 50.4, 56.0, 56.1, 56.3, 65.3, 65.4, 88.5, 95.5, 109.6, 110.6, 115.4, 116.3, 118.8, 121.2, 127.7, 130.6, 134.5, 134.7, 144.5, 146.7, 148.3, 150.0, 170.9, 171.0 ppm; MS (ESI): *m/z* = 488 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{26}H_{31}O_9^+$) 487.1962, found 487.1966.

(E)-3-[(2R,3S)-3-(Acetoxymethyl)-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]allyl acetate (**16**, $C_{24}H_{26}O_8$)

A solution of 0.331 g of **15** (0.68 mmol) in 10 cm^3 of Et_2O was cooled to 0 °C and 0.525 g of $MgBr_2{\cdot}Et_2O$ (2.0 mmol) was added. The resulting mixture was allowed to warm to RT and stirred for 3 h. Water (15 cm^3) was added and the whole mixture was extracted with CH_2Cl_2 (3 × 20 cm^3). Combined organic layers were washed with 10 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.235 g of phenol **16** (78%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.06$ (s, 3H), 2.11 (s, 3H), 3.19–3.33 (m, 1H), 3.74 (s, 3H), 3.93 (s, 3H), 4.70 (s, 2H), 4.72 (dd, $J = 6.6$, 1.3 Hz, 2H), 5.64 (broad s, 1H), 6.16 (s, 1H), 6.19 (td, $J = 15.8$, 6.5 Hz, 1H), 6.58 (d, $J = 15.7$ Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 6.85 (dd, $J = 7.9$, 2.0 Hz, 1H), 6.90 (d, $J = 8.2$ Hz, 1H), 6.99 (dd, $J = 7.2$, 1.7 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 20.8$, 21.1, 55.8, 56.2, 64.1, 65.3, 77.4, 93.2, 110.3, 111.2, 114.3, 116.6, 119.0, 120.0, 122.4, 123.3, 126.3, 129.2, 132.0, 134.1, 144.6, 150.1, 170.8, 171.2 ppm; MS (ESI): *m/z* = 443 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{24}H_{27}O_8^+$) 443.1700, found 443.1702.

Methyl (2R,3R)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-7-methoxy-5-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate
(**17**, $C_{28}H_{36}O_8Si$)

A solution of 0.414 g of **13** (1.0 mmol) and 0.340 g of imidazole (5.0 mmol) in 10 cm^3 of dry DMF was cooled to 0 °C and 0.181 g of TBSCl was added in one portion. The resulting mixture was stirred at RT for 12 h before it was diluted with 25 cm^3 of sat. aq. $NaHCO_3$. The whole mixture was extracted with EtOAc (3 × 25 cm^3) and the organic layers were combined, washed with 10 cm^3 brine,

dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 20:1–> 10:1) and yielded 0.501 g of TBS-protected phenol **17** (95%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13 (s, 6H), 0.96 (s, 9H), 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 4.35 (d, J = 8.1 Hz, 1H), 6.14 (d, J = 8.1 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.92 (dd, J = 12.0, 2.5 Hz, 1H), 6.95 (s, 2H), 7.03 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 1.3 Hz, 1H), 7.65 (d, J = 16.0 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = − 4.5, 19.1, 25.8, 53.1, 55.6, 56.2, 56.3, 56.4, 87.4, 109.8, 112.3, 115.8, 116.5, 118.1, 118.9, 125.8, 128.8, 133.8, 144.9, 146.9, 150.1, 150.1, 167.8, 170.9 ppm; MS (ESI): *m/z* = 530 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{28}H_{37}O_8Si^+$) 529.2252, found 529.2250.

Methyl (E)-3-[(2R,3S)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]acrylate (**18**, $C_{27}H_{36}O_7Si$)

A solution of 0.264 g of **17** (0.5 mmol) in 10 cm^3 of THF was cooled to − 78 °C and 1.5 cm^3 of $LiBH_4$ (3.0 mmol, 1.0 M solution in THF) was added dropwise. Resulting mixture was stirred at − 78 °C for additional 30 min. The cooling bath was removed and the whole mixture was stirred at RT for additional 2 h. Saturated aqueous NH_4Cl (20 cm^3) was added and resulting layers were separated. Aqueous layer was extracted with EtOAc (3 × 25 cm^3) and combined organic layers were washed with 15 cm^3 brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2; petroleum ether:EtOAc = 2:1–> 1:1) and yielded 0.202 g of monoester **18** (82%, *trans/cis* = > 95:1). ^{1}H NMR (500 MHz, benzene-d_6): δ = 0.11 (s, 6H), 1.01 (s, 9H), 3.18 (s, 3H), 3.26 (p, J = 6.1 Hz, 1H), 3.29 (s, 3H), 3.34 (dd, J = 10.2, 6.5 Hz, 1H), 3.38 (dd, J = 10.7, 5.5 Hz, 1H), 3.49 (s, 3H), 5.55 (d, J = 6.5 Hz, 1H), 6.43 (d, J = 15.9 Hz, 1H), 6.69 (d, J = 1.4 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 6.82 (6.69 (d, J = 1.4 Hz, 1H), 6.86 (d, J = 1.1 Hz, 1H), 7.86 (d, J = 15.9 Hz, 1H) ppm; ^{13}C NMR (126 MHz, benzene-d_6): δ = − 4.7, 18.4, 25.7, 50.9, 53.5, 54.8, 55.4, 64.0, 88.2, 110.0, 112.6, 115.2, 117.5, 118.5, 120.9, 128.0, 128.4, 129.2, 135.1, 145.0, 145.1, 145.2, 151.3, 167.2 ppm; MS (ESI): *m/z* = 502 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{27}H_{37}O_7Si^+$) 501.2303, found 501.2304.

Methyl 3-[(2R,3S)-2-[4-[(tert-butyldimethylsilyl)oxy]-3-methoxyphenyl]-3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzofuran-5-yl]propanoate (**19**, $C_{27}H_{38}O_7Si$)

A solution of 0.05 g of olefin **18** (0.1 mmol) in 5 cm^3 of MeOH stirred at RT and 4 mg of 5 mol% Pd/C was added. Resulting mixture was placed under the atmosphere of H_2 (1.3 atm) and stirred at RT for 2 h. The resulting mixture was then filtered through a pad of Celite® and the filter cake was washed with EtOAc (3 × 20 cm^3). Combined organic layers were evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2; CH_2Cl_2:MeOH = 100:1–> 70:1) yielding 0.047 g of desired reduced product **19** (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.13 (s, 6H), 0.98 (s, 9H), 2.58 (dd, J = 8.4, 7.1 Hz, 1H), 2.64 (dd, J = 8.4, 7.1 Hz, 1H), 2.85 (t, J = 7.8 Hz, 1H), 2.88–2.99 (m, 1H), 3.46 (p, J = 7.2 Hz, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 3.98 (dd, J = 11.1, 5.8 Hz, 1H), 4.04 (dd, J = 12.6, 5.9 Hz, 1H), 5.54 (d, J = 7.4 Hz, 1H), 6.66–6.70 (m, 1H), 6.71 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.85 (dd, J = 8.2, 2.1 Hz, 1H), 6.91 (d, J = 2.1 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = − 4.5, − 4.4, 18.7, 25.6, 25.9, 31.1, 36.4, 51.9, 53.9, 55.6, 55.7, 64.1, 88.1, 110.4, 112.5, 116.1, 119.0, 121.0, 132.0, 134.2, 134.7, 142.4, 144.4, 147.1, 151.3, 173.7 ppm; MS (ESI): *m/z* = 504 ($[M+H]^+$); HRMS (ESI): *m/z* calculated (for $C_{27}H_{39}O_7Si^+$) 503.2460, found 503.2459.

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