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Total Synthesis of Boletopsin 11 Enabled by Directed *ortho*-C(sp^2)−H Arylation

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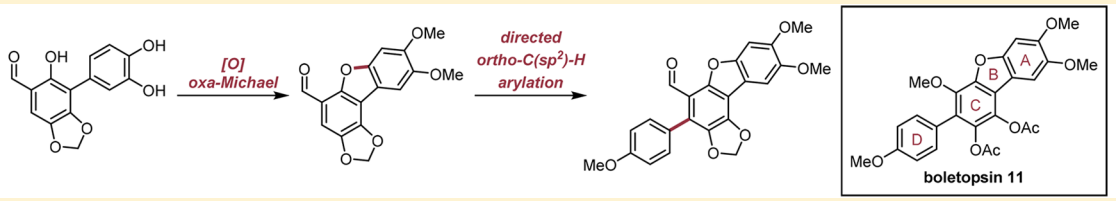
Supporting Information



ABSTRACT: A nine-step synthesis of boletopsin 11 (**1**), a bioactive fungal natural product, is disclosed. Key features include a one-pot [O]-oxa-Michael cascade to establish the polyoxygenated dibenzofuran core followed by a Pd-catalyzed directed *ortho*-C(sp^2)−H arylation to complete the fully functionalized carbon skeleton. Exploration of the latter transformation led to the discovery of an unexpected tandem *ortho*-C(sp^2)−H arylation event, and the scope of the directed *ortho*-C(sp^2)−H reaction was further investigated with coupling partners varying in stereoelectronic properties.

Boletopsins 1−14, isolated from the *Boletopsis sp.* of mushrooms, are a family of natural products containing a *p*-terphenyl carbon skeleton and a highly functionalized 3-phenyldibenzofuran core.[1] A significant proportion of the boletopsin family exhibit antibiotic properties,[2] and several boletopsins are identified as active ingredients in the fungi utilized in Papua New Guinean medicine possessing *in vitro* activity against a panel of human pathogenic bacteria.[1b]

Given their medicinal properties and their intriguing structures, the boletopsins (and related natural products)[2,3] have attracted ongoing interest from synthetic chemists (Scheme 1).[4] The highly oxygenated nature of the boletopsins and their fully substituted aromatic C ring renders their synthesis a challenge. Several dibenzofuran *p*-terphenyl natural products have been prepared previously by our group[5] and that of Takahashi,[6] including the syntheses of boletopsins 7, 11 (**1**), 12 (**2**), and vialinin B (**3**), which were completed in either 13 or 14 steps. The *p*-terphenyl carbon scaffolds were constructed via sequential Suzuki−Miyaura cross-coupling reactions, and the dibenzofuran core was forged through Baeyer−Villiger oxidation and intramolecular Ullmann coupling. Both synthetic routes required the use of unstable intermediates, and boronic acid cross-coupling partners that were not commercially available, which hindered material throughput.

As part of our ongoing interest in the development of new methods for the preparation of dibenzofuran natural products, we sought to formulate a new modular approach to the boletopsin scaffold that was more efficient and would mitigate undesired decomposition pathways, which primarily stem from the oxidation prone, electron-rich C ring. Herein we disclose a successful realization of this goal that culminated in a nine-step synthesis of boletopsin 11 (**1**). Our plan centered on the strategic replacement of the C-4 methoxy group with a formyl group that we anticipated would slow undesired oxidative decomposition of the central C ring and serve as an enabling group for the direct attachment of the D ring via a Pd-catalyzed directed *ortho*-C(sp^2)−H arylation, inspired by recent publications from the Yu laboratory[7] and others.[8] In this fashion, the D ring of the boletopsin carbon framework was disconnected from the rest of the molecule to reveal benzaldehyde **4**.

Based on related studies published from within our group,[9] we anticipated benzaldehyde **4** could be disconnected back to catechol **5** via an [O]-oxa-Michael transform.[10] We presumed catechol **5** would be easily accessible through Suzuki−Miyaura cross-coupling of known bromide **6** and commercially available 3,4-dimethoxyphenyl boronic acid followed by chemoselective demethylation.

Our synthesis of boletopsin 11 began with the preparation of aryl bromide **6** in two steps from sesamol.[5,11] Suzuki−Miyaura cross-coupling[4c] of aryl bromide **6** with commercially available 3,4-dimethoxyphenyl boronic acid using catalytic $Pd(OAc)_2$ and triphenylphosphine furnished biphenyl **7** in 89% yield (Scheme 2). The selective cleavage of the methyl ethers of **7**, in preference over the methylenedioxy moiety, was successfully realized with boron tribromide in DCM. Initial subjection of catechol **5** to sodium periodate in a biphasic DCM/water reaction medium[12] resulted in a successful [O]-oxa-Michael reaction; however, the isolated yield was poor due to the instability of the dibenzofuran catechol product **8**. This problem was ultimately circumvented by switching the oxidant to iodobenzene diacetate and using a mixed solvent system of DCM/MeOH, followed by *in situ* protection of the catechol

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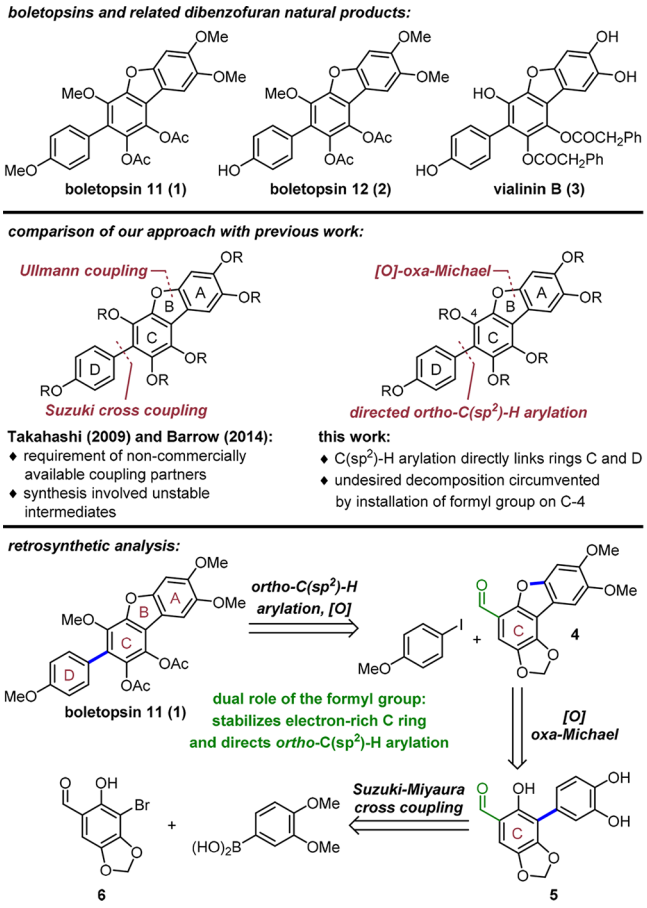
Scheme 1. *p*-Terphenyl Natural Products and Retrosynthetic Analysis



functionality. Thus, upon completion of the [O]-oxa-Michael process, the byproducts including the solvent could be easily removed under vacuum and the intermediary dibenzofuran catechol subjected to dimethylation conditions using methyl iodide and potassium carbonate, delivering benzaldehyde **4** in two steps from biphenyl **7**.

With benzaldehyde **4** in hand, the stage was set to complete the boletopsin carbon skeleton and install the D ring via directed *ortho*-C(sp^2)−H arylation. We were delighted to find that subjection of benzaldehyde **4** and *p*-iodoanisole to the protocol developed by Yu and co-workers,[7a] using amino acid **9** as the transient directing group (DG), led to the isolation of the desired product **10** in 51% yield, along with 26% of recovered benzaldehyde **4**. Attempts to push the reaction to completion using a higher catalyst loading, prolonged reaction time, or additional equivalents of silver trifluoroacetate proved unsuccessful and resulted in diminished overall yield.[13] It was surmised that this process was hampered by the steric encumbrance of both the transient DG **9** and the heavily substituted benzaldehyde **4**, impeding formation of the intermediary five-membered palladacycle and subsequent reaction with *p*-iodoanisole. To the best of our knowledge, this is the first example of a 2,3,4,5-tetrasubstituted benzaldehyde engaging in a Pd-catalyzed directed *ortho*-C(sp^2)−H arylation. Furthermore, during our attempts to optimize this transformation by employing a large excess of *p*-iodoanisole, a secondary directed C(sp^2)−H arylation event was discovered on the newly appended *p*-methoxyphenyl ring, leading to triaryl **11** in 3% yield. Presumably formed through the transient seven-membered palladacycle,[8g] this tandem Pd-catalyzed directed *ortho*-C(sp^2)−H arylation sequence is currently under further investigation in our laboratory and could have great potential for the rapid synthesis of exotic helical triaryls.[14]

At this stage, our attention turned to the removal of the methylenedioxy moiety of **10** and acetylation of the resulting catechol functionality. Previous syntheses of the boletopsins and related structures were compelled to undertake multiple concession steps at this point to realize this goal. Anticipating that the aldehyde functionality at C-5 would stabilize the electron-rich catechol C ring upon deprotection, treatment of **10** with phosphorus pentachloride followed by hydrolysis successfully cleaved the methylenedioxy group, and although the intermediary catechol was isolable, we found it convenient to simply acetylate the crude reaction mixture with acetic anhydride and triethylamine, which furnished diacetate **12** in 83% yield over two steps from **10**.

To complete the total synthesis of boletopsin 11, diacetate **12** was submitted to Baeyer−Villiger oxidation with *m*-CPBA and sodium bicarbonate. Subsequent *in situ* formate hydrolysis followed by treatment with excess potassium carbonate and methyl iodide successfully effected methylation to deliver boletopsin 11 (**1**), in a single-pot operation.

We were particularly intrigued by the versatility of the Pd-catalyzed *ortho*-C(sp^2)−H arylation reaction that enabled the direct functionalization of a sterically encumbered benzaldehyde **4**. In efforts to further evaluate the breadth of this transformation, a brief substrate screen was conducted with aryl iodides differing in electronics and substitution patterns to examine the effects of electronic and steric properties of the aryl iodide on the reaction outcome.

As shown in Scheme 3, the directed *ortho*-C(sp^2)−H arylation was performed on five additional examples. Both electron-rich and -deficient *ortho*-substituted aryl iodides performed poorly, presumably owing to steric effects (**13** and **14**), while reaction with 4-iodotoluene and 3-bromoiodobenzene exhibited modest reactivity (**15** and **16**).[15] The best result was obtained with 4-iodobenzoate, affording the adduct **17** in 72% isolated yield.

In summary, the total synthesis of boletopsin 11 (**1**) has been completed in nine steps from sesamol. In comparison to the previous route (13 steps),[5] our synthesis is not only shorter but also more robust, employing bench stable synthetic intermediates and commercially available cross-coupling partners that provide a more scalable route to the natural product. The pivotal steps include a one-pot [O]-oxa-Michael addition reaction to forge the dibenzofuran scaffold, followed by a sterically challenging directed *ortho*-C(sp^2)−H arylation reaction that appends the D ring to complete the carbon framework. The latter, to the best of our knowledge, is the first application of this methodology in natural product synthesis.[16] The key feature of our synthetic plan was the strategic placement of the C-5 formyl group on the C ring, which served as a stabilizing group as well as the synthetic handle to enact the directed *ortho*-C(sp^2)−H arylation. During the course of this study, a secondary *ortho*-C(sp^2)−H arylation reaction was discovered, with the isolation of triaryl **11**. Further explorations into this tandem directed *ortho*-C(sp^2)−H arylation reaction focusing on induction of axial chirality employing chiral directing groups[8c,17] are currently ongoing in our laboratory.

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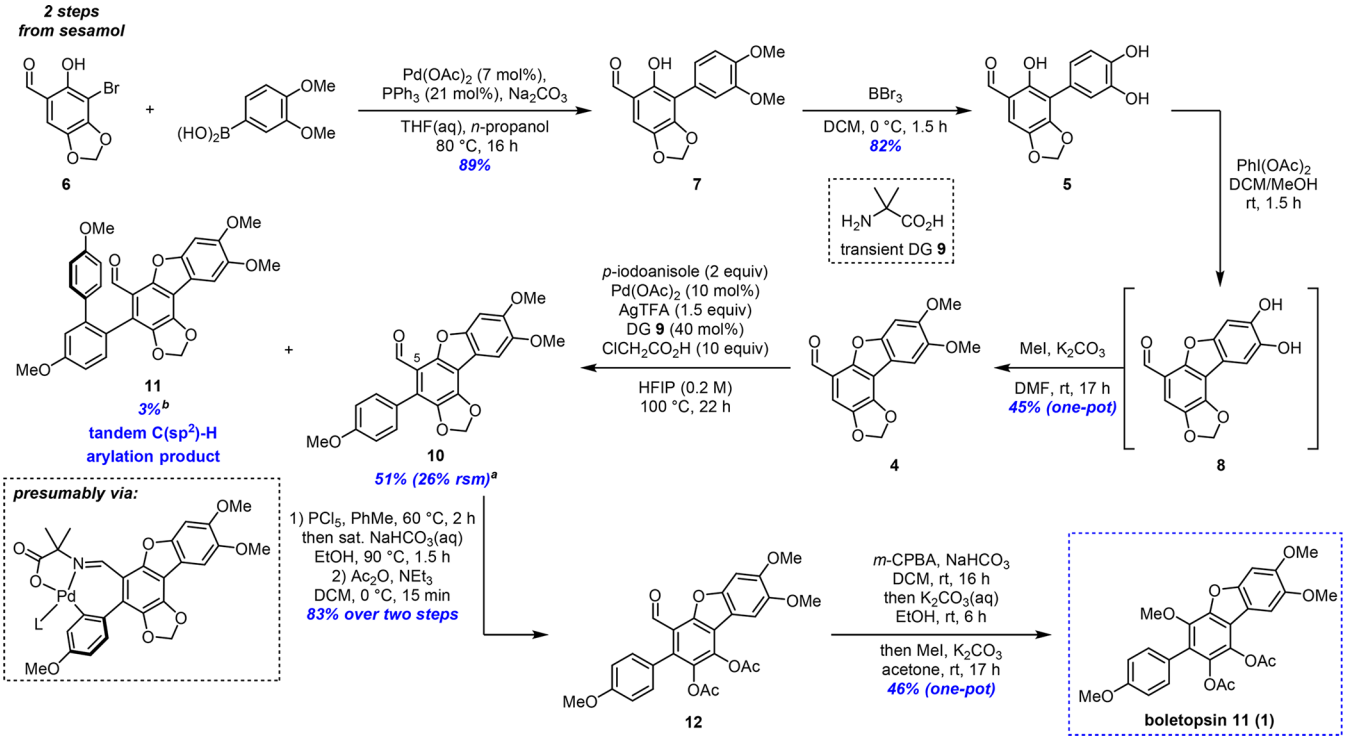
Scheme 2. Total Synthesis of Boletopsin 11 (1)



[a]Isolated yield (rsm (recovered starting material) yield of **4**). [b]Yield was determined by ^{1}H NMR spectroscopy using dibromomethane as the internal standard. The NMR yield of the tandem *ortho*-C(sp^2)−H product **11** could be improved to 10% with reaction conditions: $Pd(OAc)_2$ (10 mol %), DG **9** (40 mol %), AgTFA (2 equiv), $ClCH_2CO_2H$ (10 equiv), *p*-iodoanisole (7 equiv), HFIP (0.2 M), 110 °C, 36 h.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were recorded at 298 K, 400 MHz for ^{1}H, 100 MHz for ^{13}C, on an Avance 400 instrument. Chemical shifts are reported in ppm (δ). NMR experiments were run in $CDCl_3$ or $(CD_3)_2CO$ as indicated. ^{1}H NMR spectra are referenced to the resonance from residual $CHCl_3$ at 7.26 ppm and CHD_2COCD_3 at 2.05 ppm. ^{13}C NMR spectra are referenced to the central peak in the signal from $CDCl_3$ at 77.0 ppm and $(CD_3)_2CO$ at 29.8 ppm. The multiplicities of ^{1}H NMR resonances are expressed by abbreviations: br (broad), s (singlet), d (doublet), t (triplet), quartet (q), m (multiplet), and combinations thereof for highly coupled systems. ^{13}C NMR spectra were run as proton decoupled experiments. EI-MS were recorded on an Agilent HP 6890 series gas GC/MS with a 7683 series injector. HREI-MS data were recorded on a Waters AutoSpec Premier spectrometer magnetic sector instrument, operating at 70 eV. ESI-MS data were recorded on a ZMD Micromass spectrometer with a Waters Alliance 2690 HPLC. HRESI-MS were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer and a Thermo Fisher Scientific Velos Pro Orbitrap mass spectrometer. Mass spectra are displayed as mass/charge ratios (m/z) and relative abundance (% of base peak intensity). Thin layer chromatography (TLC) was run on Merck silica gel 60 F_{254} aluminum backed plates, and details of the eluents are described in each procedure. Plates were observed under UV light (254 nm) and/or developed in a ceric phosphomolybdic acid dip followed by heating. Flash column chromatography was run on silica gel (230−400 mesh) using the eluent system detailed for each procedure. Anhydrous solvents were obtained from commercial sources unless otherwise noted. The petroleum ether (pet.) fraction used was 60−80 °C unless otherwise stated. IR spectra were recorded on the Alpha Bruker Optics FT-IR spectrometer or the PerkinElmer Spectrum Two FT-IR spectrometer (neat), and all data were reported in wavenumbers. Peak intensities are described by s (strong), m (medium), w (weak), and br (broad). 6-Hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde[5] and 7-bromo-6-hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde (**6**)[11] were prepared according to literature procedures.

7-(3,4-Dimethoxyphenyl)-6-hydroxybenzo[d][1,3]dioxole-5-carbaldehyde (7). In a two-neck flask fitted with a condenser, aryl bromide **6** (1.00 g, 4.08 mmol, 1.0 equiv), 3,4-dimethoxyphenyl boronic acid (1.49 g, 8.19 mmol, 2.0 equiv), $Pd(OAc)_2$ (64 mg, 0.285 mmol, 7 mol %), and triphenylphosphine (225 mg, 0.859 mmol, 21 mol %) were degassed and refilled with nitrogen. A 30 mL aliquot of solvent (THF/*n*-propanol = 1:1, degassed by bubbling nitrogen) was added to the solids and stirred for 10 min at which time 6 mL of degassed 2 M Na_2CO_3 solution were added and the reaction was heated to 80 °C in an oil bath for 17 h. The mixture was cooled to room temperature and diluted with EtOAc and brine. The mixture was extracted with EtOAc, washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was subjected to flash column chromatography on silica, using a gradient elution of EtOAc/pet. = 1:3 to 1:2 to afford the title compound as a yellow solid (1.10 g, 3.63 mmol, 89%). R_f (1:2 EtOAc/pet.) = 0.26. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.3 (s, 1H), 9.68 (s, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.18 (m, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H), 6.04 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 158.7, 152.4, 148.9, 148.6, 141.0, 122.6, 122.4, 113.8, 113.3, 112.5, 110.9, 108.2, 102.0, 56.0, 55.9. IR: ν (cm^{-1}) = 1626 (m), 1520 (m), 1256 (s), 1227 (s) 1025 (s). MS (EI) m/z 302 (100, $[M]^{+\bullet}$ $C_{16}H_{14}O_6$). HRMS (EI) m/z: $[M]^{+\bullet}$ calcd for $C_{16}H_{14}O_6$ 302.0790; found 302.0788.

7-(3,4-Dihydroxyphenyl)-6-hydroxybenzo[d][1,3]dioxole-5-carbaldehyde (5). Boron tribromide (1.0 M solution in DCM, 8.34 mmol, 2.1 equiv) was added dropwise to a solution of biphenyl **7** (1.20 g, 3.97 mmol, 1.0 equiv) in 45 mL of anhydrous DCM at 0 °C under nitrogen. The solution was slowly warmed to room temperature and stirred for 1.5 h at which time it was poured into ice water. The mixture was extracted exhaustively with EtOAc, and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography on silica using EtOAc/pet. = 3:2 as the

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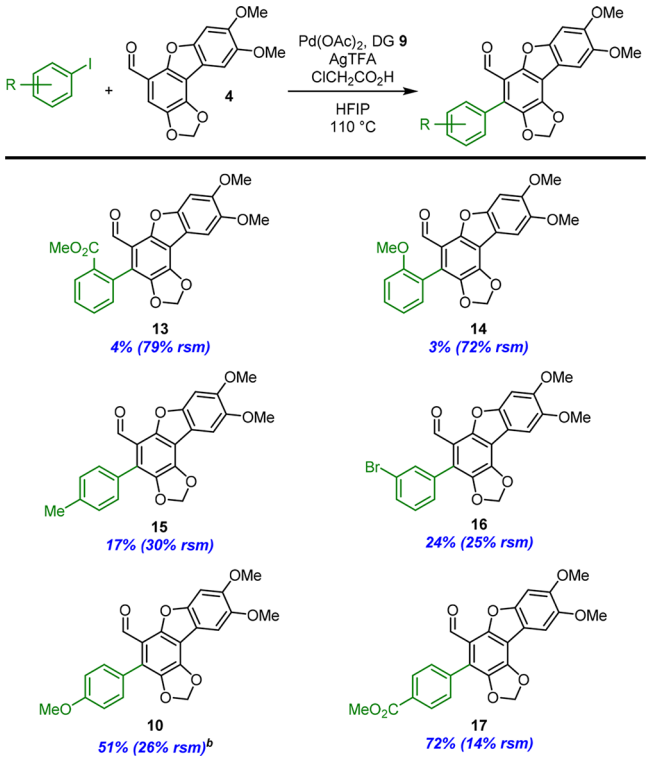
Scheme 3. Scope of the Directed *ortho*-C(sp^2)−H Arylation Reaction with Benzaldehyde 4[a]



[a]Reaction conditions: benzaldehyde **4** (0.110 mmol, 1 equiv), aryl iodide (3 equiv), $Pd(OAc)_2$ (10 mol %), DG **9** (40 mol %), $ClCH_2CO_2H$ (10 equiv), AgTFA (2 equiv), HFIP (0.6 mL), 110 °C, 20 h. Isolated yields (rsm yields). [b]Reaction conditions: benzaldehyde **4** (0.457 mmol, 1 equiv), *p*-iodoanisole (2 equiv), $Pd(OAc)_2$ (10 mol %), DG **9** (40 mol %), $ClCH_2CO_2H$ (10 equiv), AgTFA (2 equiv), HFIP (2.3 mL), 100 °C, 22 h. Isolated yields (rsm yields).

eluent, affording the title compound as a yellow solid (889 mg, 3.24 mmol, 82%). R_f (2:1 EtOAc/pet.) = 0.48. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 12.4 (br s, 1H), 9.76 (s, 1H), 7.97 (br s, 2H), 7.15 (d, J = 2.0 Hz, 1H), 7.10 (s, 1H), 7.01 (dd, J = 8.2, 2.0 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 196.1, 159.4, 153.5, 145.9, 145.4, 142.1, 123.0, 122.8, 118.2, 115.6, 114.8, 113.3, 109.0, 103.1. IR: ν (cm^{-1}) = 3486 (m), 3283 (br), 1608 (s), 1409 (s), 1307 (s), 1249 (s), 1039 (s). MS (EI) m/z 274 (100, $[M]^{+\bullet}$ $C_{14}H_{10}O_6$). HRMS (EI) m/z: $[M]^{+\bullet}$ calcd for $C_{14}H_{10}O_6$ 274.0477; found 274.0476.

*8,9-Dimethoxybenzo[b][1,3]dioxolo[4,5-e]benzofuran-5-carbaldehyde (**4**).* Biphenyl catechol **5** (274 mg, 1.00 mmol, 1.0 equiv) was dissolved in 58 mL of solvent (DCM/MeOH = 7:1) at 0 °C under nitrogen. $PhI(OAc)_2$ (451 mg, 1.40 mmol, 1.4 equiv) was added to the solution in one portion and stirred for 1 h at which time an additional 0.2 equiv of $PhI(OAc)_2$ was added. After 0.5 h, the solvent was removed *in vacuo* and the residue was redissolved in 10 mL of DMF. Potassium carbonate (1.38 g, 10.0 mmol, 10 equiv) was added to the solution followed by methyl iodide (1.14 g, 8.00 mmol, 8.0 equiv), and the mixture was stirred at room temperature under nitrogen for 17 h, at which time the reaction was diluted with water and EtOAc. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification was achieved using flash column chromatography on silica using DCM/pet/EtOAc = 8:2:1 as the eluent affording the title compound as a colorless solid (135 mg, 0.451 mmol, 45%). R_f (1:1 EtOAc/pet.) = 0.32. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 7.31 (s, 1H), 7.30 (s, 1H), 7.15 (s, 1H), 6.22 (s, 2H), 3.99, (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 155.9, 151.8, 150.4, 146.7, 145.3, 143.8, 114.2, 111.7, 109.9, 103.4, 103.3, 102.9, 95.7, 56.6, 56.3. IR: ν (cm^{-1}) = 1671 (m), 1503 (m), 1396 (m), 1261 (s), 1112 (s). MS (EI) m/z 300 (100, $[M]^{+\bullet}$ $C_{16}H_{12}O_6$). HRMS (EI) m/z: $[M]^{+\bullet}$ calcd for $C_{16}H_{12}O_6$ 300.0634; found 300.0633.

*8,9-Dimethoxy-4-(4-methoxyphenyl)benzo[b][1,3]dioxolo[4,5-e]-benzofuran-5-carbaldehyde (**10**).* In a sealed tube, benzaldehyde **4** (137 mg, 0.457 mmol, 1.0 equiv), *p*-iodoanisole (214 mg, 0.914 mmol, 2.0 equiv), $Pd(OAc)_2$ (10.3 mg, 0.0457 mmol, 10 mol %), DG **9** (18.8 mg, 0.183 mmol, 40 mol %), AgTFA (202 mg, 0.914 mmol, 2.0 equiv), and $ClCH_2CO_2H$ (432 mg, 4.57 mmol, 10 equiv) were suspended in 2.3 mL of HFIP, and the mixture was stirred for 10 min and then heated to 100 °C in an oil bath covered in aluminum foil to minimize exposure to light. After 22 h, the reaction was cooled to room temperature and 3.00 g of sodium bicarbonate were added. The suspension was stirred vigorously for 10 min and then filtered through Celite using EtOAc, and the filtrates were concentrated *in vacuo*. Purification was achieved via flash column chromatography on silica using DCM/pet/EtOAc = 8:2:1 as the eluent affording the title compound as a brown amorphous solid (94 mg, 0.246 mmol, 51% isolated yield, 26% recovered starting material). R_f (1:1 EtOAc/pet.) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.43−7.41 (m, 2H), 7.34 (s, 1H), 7.29 (s, 1H), 7.04−7.02 (m, 2H), 6.23 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 159.8, 153.8, 152.2, 150.3, 146.7, 143.8, 140.9, 132.2, 123.8, 123.6, 113.9, 112.9, 111.5, 109.3, 103.1, 102.7, 96.1, 56.6, 56.3, 55.4. IR: ν (cm^{-1}) = 2926 (w), 1683 (m), 1597 (m), 1475 (m), 1249 (s), 1199 (s), 1174 (s), 1124 (s). MS (ESI) m/z 445 (55, $[M + K]^+$ $C_{23}H_{18}O_7K$), 429 (100, $[M + Na]^+$ $C_{23}H_{18}O_7Na$), 407 (20, $[M + H]^+$ $C_{23}H_{19}O_7$). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{23}H_{18}O_7Na$ 429.0950; found 429.0951.

*4-(4′,5-Dimethoxy-[1,1′-biphenyl]-2-yl)-8,9-dimethoxybenzo[b]-[1,3]dioxolo[4,5-e]benzofuran-5-carbaldehyde (**11**).* In a sealed tube, benzaldehyde **4** (35 mg, 0.12 mmol, 1.0 equiv), *p*-iodoanisole (192 mg, 0.819 mmol, 7.0 equiv), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol, 10 mol %), DG **9** (4.8 mg, 0.047 mmol, 40 mol %), AgTFA (51.7 mg, 0.234 mmol, 2.0 equiv), and $ClCH_2CO_2H$ (111 mg, 1.17 mmol, 10 equiv) were suspended in 0.6 mL of HFIP, and the mixture was stirred for 10 min and then heated to 110 °C in an oil bath covered in aluminum foil to minimize exposure to light. After 36 h, the reaction was cooled to room temperature and 300 mg of sodium bicarbonate were added. The suspension was stirred vigorously for 10 min, then filtered through Celite, and concentrated *in vacuo*. The NMR yields were determined using dibromomethane as the internal standard. The NMR yields of benzaldehydes **4**, **10**, and **11** were 10%, 41%, and 10%, respectively. Separation of **10** and **11** proved to be difficult due to the highly similar R_f values, and a pure sample for characterization could be obtained via flash column chromatography using a gradient eluent system (pet/EtOAc = 5:1 to 4:1). R_f (1:4 EtOAc/pet.) = 0.06. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.29 (s, 1H), 7.25 (s, 1H), 7.09−7.07 (m, 2H), 7.02−6.98 (m, 2H), 6.70−6.68 (m, 2H), 6.12 (d, J = 1.1 Hz, 1H), 5.80 (d, J = 1.1 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 160.0, 158.7, 153.9, 152.1, 150.3, 146.7, 143.74, 143.65, 141.2, 133.1, 132.9, 130.1, 123.4, 122.4, 115.5, 113.4, 113.0, 112.6, 111.5, 109.3, 103.1, 102.5, 96.2, 56.6, 56.3, 55.4, 55.1. IR: ν (cm^{-1}) = 2930 (w), 1685 (m), 1603 (m), 1494 (m), 1475 (m), 1309 (m), 1248 (m), 1200 (s), 1175 (s), 1127 (s). MS (ESI) m/z 551 (20, $[M + K]^+$ $C_{30}H_{24}O_8K$), 535 (100, $[M + Na]^+$ $C_{30}H_{24}O_8Na$), 513 (30, $[M + H]^+$ $C_{30}H_{25}O_8$). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{25}O_8$ 513.1544; found 513.1538.

*4-Formyl-7,8-dimethoxy-3-(4-methoxyphenyl)dibenzo[b,d]furan-1,2-diyl Diacetate (**12**).* Compound **10** (46.7 mg, 0.115 mmol, 1.0 equiv) was suspended in 1.0 mL of toluene, and phosphorus pentachloride (79.8 mg, 0.384 mmol, 3.3 equiv) was added. The mixture was then heated to 60 °C in an oil bath under nitrogen. After 2 h, the temperature was increased to 80 °C and 0.8 mL of 1 M HCl(aq) solution was added and stirred for 0.5 h at which time 2 mL of sat. $NaHCO_3$(aq) solution and 2 mL of EtOH were added and heated to 90 °C for 1.5 h. The mixture was cooled to room temperature, acidified with 1 M HCl(aq) solution, and extracted with

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EtOAc. The organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to afford the crude which was immediately subjected to the next step. The crude material was dissolved in 1.5 mL of DCM under nitrogen at 0 °C, and acetic anhydride (32.8 mg, 0.322 mmol, 2.8 equiv) was added slowly. Subsequently, triethylamine (116 mg, 1.15 mmol, 10 equiv) was added dropwise and the reaction was stirred at room temperature for 15 min at which time sat. NH_4Cl(aq) solution was added and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was subjected to flash column chromatography on silica using a gradient elution of EtOAc/pet. = 3:2 to 1:1, affording the title compound as a pale yellow paste (45.7 mg, 0.0956 mmol, 83% over two steps). R_f (1:1 EtOAc/pet.) = 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.32 (s, 1H), 7.30−7.28 (m, 2H), 7.17 (s, 1H), 7.00−6.98 (m, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 2.51 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 168.5, 167.0, 159.9, 153.2, 152.6, 151.1, 146.9, 140.1, 136.9, 136.2, 132.0, 124.2, 120.0, 118.4, 113.7, 112.2, 103.2, 96.2, 56.6, 56.3, 55.4, 20.5, 20.1. IR: ν (cm^{-1}) = 2937 (w), 1779 (m), 1477 (m), 1201 (s), 1171 (s), 1124 (s). MS (ESI) m/z 501 (100, $[M + Na]^+$ $C_{26}H_{22}O_9Na$). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{22}O_9Na$ 501.1162; found 501.1167.

*Boletopsin 11 (**1**).* Dibenzofuran **12** (56.6 mg, 0.118 mmol, 1.0 equiv) was dissolved in 1.7 mL of DCM, and sodium bicarbonate (49.7 mg, 0.592 mmol, 5.0 equiv) was added followed by *m*-CPBA (40.8 mg, 0.236 mmol, 2.0 equiv). The mixture was stirred under nitrogen at room temperature for 18 h at which time potassium carbonate (65.2 mg, 0.472 mmol, 4.0 equiv) and 1.5 mL of EtOH and 0.4 mL of water were added and stirred at room temperature for 6 h. The solvent was removed *in vacuo*, and the residue was redissolved in 4 mL of acetone, which was subsequently treated with potassium carbonate (130 mg, 0.944 mmol, 8.0 equiv) and methyl iodide (134 mg, 0.944 mmol, 8.0 equiv); the suspension was stirred under nitrogen at room temperature for 17 h. The mixture was filtered through a small plug of silica (DCM/pet/EtOAc = 8:2:1 as the eluent), and the filtrate was concentrated under reduced pressure. The crude was purified by flash column chromatography on silica using DCM/pet/EtOAc = 8:2:1 as the eluent, affording boletopsin 11 (**1**) as a colorless solid (26.0 mg, 0.0542 mmol, 46%). Spectral data match the previously reported data of the isolated natural product.[1b] R_f (8:2:1 DCM/pet./EtOAc) = 0.48. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.30 (m, 2H), 7.15−7.14 (m, 2H), 6.97−6.95 (m, 2H), 3.99 (s, 3H), 3.963 (s, 3H), 3.956 (s, 3H), 3.86 (s, 3H), 2.47 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.0, 159.0, 151.6, 151.0, 146.4, 145.9, 140.7, 136.0, 131.5, 131.1, 125.4, 124.9, 119.3, 113.8, 113.5, 103.5, 95.7, 61.0, 56.5, 56.3, 55.2, 20.5, 20.2. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.37 (s, 1H), 7.28 (s, 1H), 7.28−7.26 (m, 2H), 7.03−7.00 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.85 (s, 3H), 2.49 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 168.9, 168.7, 160.2, 152.5, 152.2, 148.0, 146.6, 141.3, 137.4, 132.5, 132.3, 126.5, 125.9, 120.2, 114.3, 114.2, 104.7, 96.9, 61.3, 56.8, 56.6, 55.5, 20.4, 20.2. IR: ν (cm^{-1}) = 2937 (w), 1773 (m), 1478 (m), 1280 (m), 1208 (s), 1189 (s), 1172 (s). MS (ESI) m/z 519 (50, $[M + K]^+$ $C_{26}H_{24}O_9K$), 503 (100, $[M + Na]^+$ $C_{26}H_{24}O_9Na$), 481 (10, $[M + H]^+$ $C_{26}H_{25}O_9$). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{24}O_9Na$ 503.1318; found 503.1321.

General Procedure for the Synthesis of Compounds 13−17.[7a] In a sealed tube, benzaldehyde **4** (33.0 mg, 0.110 mmol, 1.0 equiv), aryl iodide (0.330 mmol, 3.0 equiv), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 10 mol %), DG **9** (4.5 mg, 0.044 mmol, 40 mol %), $ClCH_2CO_2H$ (104 mg, 1.10 mmol, 10 equiv), and AgTFA (48.6 mg, 0.220 mmol, 2.0 equiv) were dissolved in 0.6 mL of HFIP and the mixture was stirred at room temperature for 10 min. The tube was then sealed and heated to 110 °C in an oil bath for 20 h covered in aluminum foil. The mixture was then cooled to room temperature, and 300 mg of sodium bicarbonate were added. The suspension was vigorously stirred for 10 min and filtered through Celite using EtOAc as the eluent. The filtrate was concentrated and subjected to flash column chromatography to afford the various *p*-terphenyl products.

*Methyl 2-(5-Formyl-8,9-dimethoxybenzo[b][1,3]dioxolo[4,5-e]-benzofuran-4- yl)benzoate (**13**).* Compound **13** was obtained from benzaldehyde **4** following the general procedure, using 2-iodobenzoate as the aryl iodide. Flash column chromatography on silica using DCM/pet./EtOAc = 8:2:1 afforded compound **13** (2.0 mg, 0.0046 mmol, 4%) along with recovered benzaldehyde **4** (26.2 mg, 0.0873 mmol, 79%). R_f (8:2:1 DCM/pet./EtOAc) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.13 (dd, J = 7.7, 1.1 Hz, 1H), 7.65−7.61 (m, 2H), 7.56−7.52 (m, 2H), 7.38 (dd, J = 7.0, 1.0 Hz, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 6.17 (s, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 166.7, 154.7, 152.2, 150.3, 146.7, 143.7, 140.9, 133.8, 132.3, 132.0, 130.7, 130.6, 128.7, 122.4, 112.7, 111.7, 109.5, 103.2, 102.8, 96.0, 56.6, 56.3, 52.1. IR: ν (cm^{-1}) = 2926 (w), 1725 (m), 1685 (m), 1606 (m), 1476 (m), 1310 (m), 1256 (m), 1200 (s), 1127 (s). MS (ESI) m/z 473 (45, $[M + K]^+$ $C_{24}H_{18}O_8K$), 457 (100, $[M + Na]^+$ $C_{24}H_{18}O_8Na$), 435 (15, $[M + H]^+$ $C_{24}H_{19}O_8$). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{19}O_8$ 435.1074; found 435.1074.

*8,9-Dimethoxy-4-(2-methoxyphenyl)benzo[b][1,3]dioxolo[4,5-e]-benzofuran-5-carbaldehyde (**14**).* Compound **14** was obtained from benzaldehyde **4** following the general procedure, using *o*-iodoanisole as the aryl iodide. Flash column chromatography on silica using DCM/pet./THF = 25:10:1 afforded compound **14** (1.2 mg, 0.030 mmol, 3%) along with recovered benzaldehyde **4** (23.9 mg, 0.0800 mmol, 72%). R_f (25:10:1 DCM/pet./THF) = 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.48−7.43 (m, 1H), 7.39 (dd, J = 7.6, 1.9 Hz, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.12−7.08 (m, 1H), 7.04−7.02 (m, 1H), 6.24 (d, J = 1.1 Hz, 1H), 6.19 (d, J = 1.1 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 157.0, 153.6, 152.3, 150.3, 146.7, 144.1, 141.2, 132.0, 130.5, 120.7, 120.6, 119.8, 112.8, 111.6, 111.0, 109.6, 103.2, 102.7, 96.2, 56.6, 56.3, 55.6. IR: ν (cm^{-1}) = 2936 (w), 1687 (m), 1597 (m), 1476 (m), 1310 (m), 1245 (m), 1199 (s), 1127 (s). MS (ESI) m/z 445 (35, $[M + K]^+$ $C_{23}H_{18}O_7K$), 429 (100, $[M + Na]^+$ $C_{23}H_{18}O_7Na$), 407 (20, $[M + H]^+$ $C_{23}H_{19}O_7$). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}O_7$ 407.1125; found 407.1121.

*8,9-Dimethoxy-4-(p-tolyl)benzo[b][1,3]dioxolo[4,5-e]benzofuran-5-carbaldehyde (**15**).* Compound **15** was obtained from benzaldehyde **4** following the general procedure, using 4-iodotoluene as the aryl iodide. Flash column chromatography on silica using DCM/pet./THF = 25:10:1 afforded compound **15** (7.4 mg, 0.019 mmol, 17%) along with recovered benzaldehyde **4** (10 mg, 0.033 mmol, 30%). R_f (25:10:1 DCM/pet./THF) = 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.39−7.37 (m, 2H), 7.35 (s, 1H), 7.32−7.28 (m, 3H), 6.22 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 153.8, 152.3, 150.4, 146.7, 143.8, 140.9, 138.6, 130.8, 129.1, 128.7, 123.8, 112.9, 111.5, 109.4, 103.1, 102.8, 96.2, 56.6, 56.3, 21.3. IR: ν (cm^{-1}) = 2923 (w), 1684 (m), 1597 (m), 1476 (m), 1309 (m), 1199 (s), 1176 (s), 1126 (s). MS (ESI) m/z 429 (65, $[M + K]^+$ $C_{23}H_{18}O_6K$), 413 (100, $[M + Na]^+$ $C_{23}H_{18}O_6Na$). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{19}O_6$ 391.1176; found 391.1169.

*4-(3-Bromophenyl)-8,9-dimethoxybenzo[b][1,3]dioxolo[4,5-e]-benzofuran-5-carbaldehyde (**16**).* Compound **16** was obtained from benzaldehyde **4** following the general procedure, using 3-bromoiodobenzene as the aryl iodide. Flash column chromatography on silica using DCM/pet./THF = 25:10:1 afforded compound **16** (11.8 mg, 0.0259 mmol, 24%) along with recovered benzaldehyde **4** (8.3 mg, 0.028 mmol, 25%). R_f (25:10:1 DCM/pet./THF) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.67−7.66 (m, 1H), 7.59 (ddd, J = 7.4, 1.8, 1.7 Hz, 1H), 7.42−7.33 (m, 3H), 7.29 (s, 1H), 6.24 (s, 2H), 4.00 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 154.2, 152.4, 150.6, 146.8, 144.0, 141.0, 134.0, 133.5, 131.6, 129.8, 129.6, 122.5, 121.4, 112.5, 111.3, 109.9, 103.2, 103.0, 96.1, 56.6, 56.4. IR: ν (cm^{-1}) = 2927 (w), 1686 (m), 1606 (m), 1472 (m), 1310 (m), 1200 (s), 1127 (s). MS (ESI) m/z 479 (99, $[M + 2 + Na]^+$ $C_{22}H_{15}O_6{}^{81}BrNa$), 477 (100, $[M + Na]^+$ $C_{22}H_{15}O_6{}^{79}BrNa$). HRMS (ESI) m/z: $[M + 2 + H]^+$ calcd for $C_{22}H_{16}O_6{}^{81}Br$ 457.0104; found 457.0100.

*Methyl 4-(5-Formyl-8,9-dimethoxybenzo[b][1,3]dioxolo[4,5-e]-benzofuran-4-yl)benzoate (**17**).* Compound **17** was obtained from benzaldehyde **4** following the general procedure, using 4-iodobenzoate as the aryl iodide. Flash column chromatography on silica using

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DCM/pet./EtOAc = 8:2:1 afforded compound **17** (34.8 mg, 0.0802 mmol, 72%) along with recovered benzaldehyde **4** (4.8 mg, 0.016 mmol, 14%). R_f (8:2:1 DCM/pet./EtOAc) = 0.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.16 (m, 2H), 7.57 (m, 2H), 7.34 (s, 1H), 7.28 (s, 1H), 6.23 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 166.6, 154.3, 152.4, 150.6, 146.9, 144.0, 141.0, 136.8, 130.9, 130.1, 129.5, 121.8, 112.4, 111.3, 109.9, 103.2, 102.9, 96.1, 56.6, 56.3, 52.3. IR: ν (cm^{-1}) = 2952 (w), 1720 (s), 1685 (m), 1608 (m), 1435 (m), 1310 (s), 1277 (s), 1201 (s), 1127 (s). MS (ESI) m/z 473 (25, $[M + K]^+$ $C_{24}H_{18}O_8K$), 457 (100, $[M + Na]^+$ $C_{24}H_{18}O_8Na$), 435 (20, $[M + H]^+$ $C_{24}H_{19}O_8$). HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{24}H_{18}O_8Na$ 457.0899; found 457.0895.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00792.

^{1}H and ^{13}C NMR spectra of novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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the addition of extra portons of $Pd(OAc)_2$ (5−10 mol%) and transient DG **9** (20 mol%) were unsuccessul. A higher loading of AgTFA (2.5 equiv) led to a diminished yield (38%).

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