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Synthesis of 2,5-Diaryl Nonsymmetric Furans C6-Platform Chemicals *via* Catalytic Conversion of Biomass and the Formal Synthesis of Dantrolene

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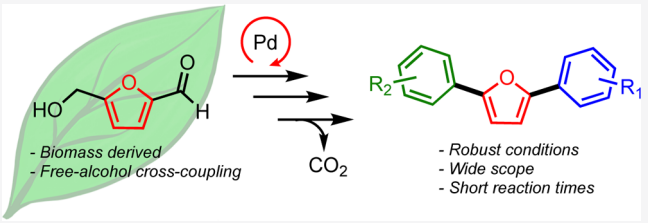
ABSTRACT: Biomass-derived commodity chemical 5-hydroxymethyl furfural is an underutilized C6-platform chemical derived from cellulose that is ideal to prepare next-generation value-added products. We have developed an efficient synthetic strategy to access 2,5-diaryl nonsymmetric furans from 5-hydroxymethyl furfural utilizing decarboxylative cross-couplings. A key finding was that the presence of the hydroxymethyl handle enhances the yields of the palladium-catalyzed decarboxylative cross-coupling reaction. The method provides access to a broad-range nonsymmetric 2,5-diaryl furans where each arene can be systematically introduced as required. Additionally, this green synthetic strategy was employed for a formal synthesis of the muscle relaxant Dantrolene in excellent yields.



INTRODUCTION

The exponential growth of the demand on organic chemical materials has led to an uncontrolled exploitation of petroleum feedstock sources.[1−3] To reduce dependence on petroleum derivatives and mitigate climate change in the chemical sectors, the employment of alternative production systems is required. Toward this end, biomass has been explored as a potential renewable resource for the production of fuels and starting materials for chemical synthesis.[4,5] Initial efforts from academic research are now moving into pilot plants as evidenced by the recent efforts of the Avantium-BASF[6] joint venture for 50,000 MT/year production of biomass-derived furans and the ADM-DuPont[7,8] pilot plant for the production of carbohydrate-derived platform chemicals.

Within biomass, furans derived from carbohydrates have been highlighted as "sleeping giants"[9] in terms of their potential use in a diverse range of applications. The breakdown of cellulose and cyclodehydration of common hexoses leads to 5-hydroxymethyl furfural (HMF),[10] which serves as a platform chemical for the production of the fuel alternatives 2,5-dimethylfuran, 2,5-dihydroxymethyl furan (DHMF), 2,5-furan dicarboxylic acid (terephthalic acid replacement molecule in PET polymers),[11−13] and γ-valerolactone[14] (food additive), among others.[15−17] It is highly important to develop chemical tools that allow chemists to perform transformations on these biomass-derived starting materials to obtain value-added next-generation chemicals.[18] On this note, the synthesis of aryl-substituted furans remains an important transformation because of the ubiquitous presence of this moiety in a variety of compound classes including natural products,[19] active pharmaceutical ingredients,[20] polymer synthesis,[21] among others.[22,23] Several reports have described the synthesis of 2,5-diaryl furans **10**. The employment of coinage metals such as Cu, Ag, and Au toward the synthesis of substituted furans has been reported with reactions including cyclization of alkynes with tethered nucleophiles,[24] cycloaddition reactions,[25] radical cyclization of haloalkenes or haloalkynes,[26] among others.[27] These methodologies, although helpful, require the synthesis of complex starting materials that are often not commercially available, which results in a nonmodular approach that could limit their synthetic utility. Other reports have utilized preformed furan cores. The Yin group reported the α-arylation of furans through cleavage of a primary alcohol utilizing boronic esters as the coupling partners (Scheme 1, **1**→**2**),[28] and the advances on C−H activation by the Doucet group[29,30] have allowed for the arylation of furan in combination with decarboxylative couplings (Scheme 1, **4**→**5**→**6** and **1**→**3**.). Although helpful, these methodologies rely on C5 furan starting materials obtained from pentoses (derived from hemicellulose), which are less abundant when compared to the hexoses (derived from cellulose) and C6 derivatives, such as HMF (**7**).

In our approach, we propose the utilization of cellulose-derived HMF **7** and sequential decarboxylative cross-

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Scheme 1. Reported Synthetic Strategies for the Synthesis of 2,5-Nonsymmetric Diaryl Furans and the Proposed Present Work

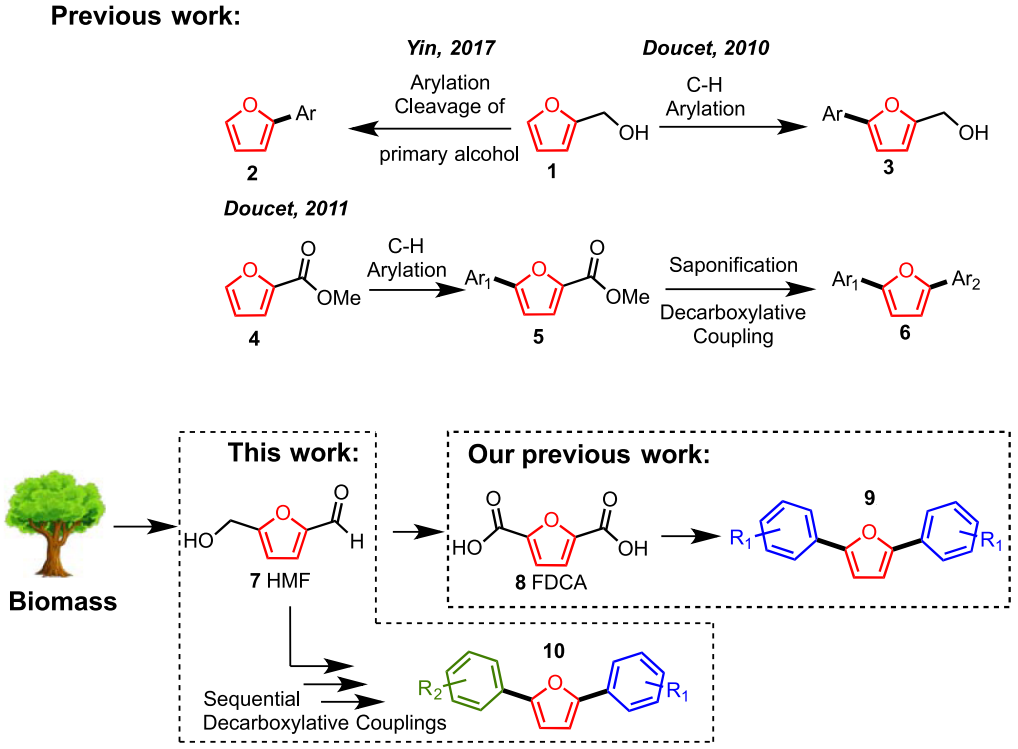
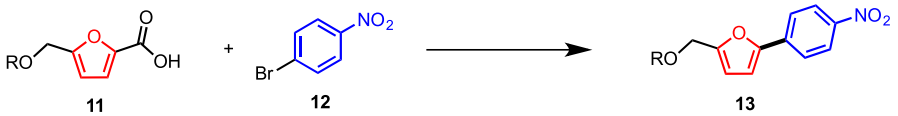


Table 1. Optimization of the Initial Decarboxylative Cross-Coupling[a]



entry	R	Pd source	ligand	yield (%)
1	TBDMS	$Pd(OAc)_2$	none	0
2	TBDMS	$Pd(OAc)_2$	P(*t*-Bu)$_3$	23
3	TBDMS	$PdCl_2$	P(*t*-Bu)$_3$	28
4	H	$PdCl_2$	P(*t*-Bu)$_3$	54
5	H	Pd[P(*t*-Bu$_3$)]$_2$	None	61
6	H	$Pd(dba)_2$	P(*t*-Bu)$_3$	51
7	H	$Pd(dba)_2$	PCy_3	44
8	H	$Pd(acac)_2$	P(*t*-Bu)$_3$	67
9	H	$Pd(acac)_2$	MePhos	85
10	H	$Pd(acac)_2$	JohnPhos	93

[a]General conditions: Furan substrate 0.4 mmol, *p*-bromo nitrobenzene 0.2 mmol, Cs_2CO_3 (1.5 equiv), *n*-Bu_4NCl (30 mol %), Pd source (5 mol %), ligand (10 mol %), DMF [0.1 M], 170 °C μw, 8 min, 900 rpm.

coupling[31−37] steps to circumvent long-standing stepwise transformations of nonaromatic precursors. This approach circumvents the formation of heavy stoichiometric organometallic waste, usually produced from classical Pd-mediated methodologies. Previously, we reported the employment of a double decarboxylative cross-coupling reaction on biomass-derived 2,5-furandicarboxylic acid (FDCA, **8**) for the synthesis of symmetric 2,5-diaryl furans (**9**) with good to excellent yields.[38] Herein, we aim to expand the scope of biomass-derived starting materials by generating 2,5-diaryl nonsymmetric furans from HMF (Scheme 1, **7**→**10**). This route would provide significant additional value by allowing for differentiation between the 2- and 5-positions of the furan while also utilizing a C6 biomass-derived starting material (HMF) that is upstream in the biorefinery process, relative to the previously employed FDCA.

RESULTS AND DISCUSSION

The proposed synthetic approach comprises a first oxidation of the aldehyde moiety of HMF to obtain HMFA (**11**, R═H). There have been several strategies reported for this transformation, typically employing transition metals supported on heterogeneous media for catalysis.[39−42] Our group previously reported the utilization of a solvent-free mechanochemical disproportionation of HMF into DHMF and HMFA in quantitative yields,[43] and we employed this method to obtain the required substrate for the inital cross-coupling reactions (Table 1).

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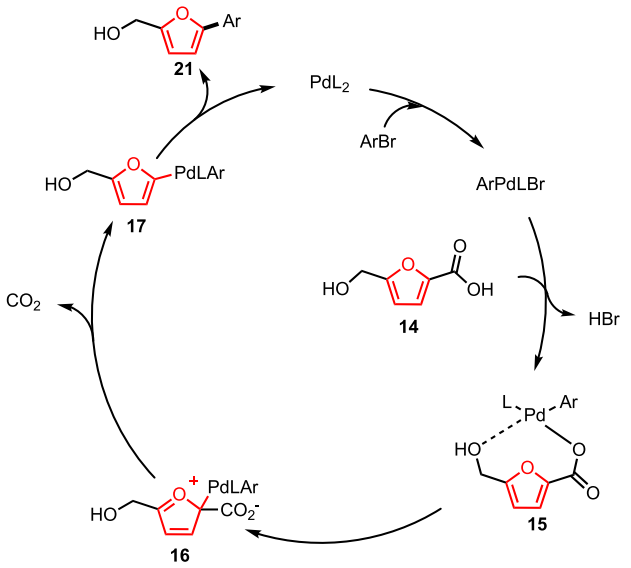
We prepared the silyl ether-protected HMFA (**11**, R= tBuMe$_2$Si) and evaluated the reaction with previously reported decarboxylative cross-coupling conditions. In the absence of a phosphine ligand (Table 1, entry 1), the reaction did not yield the desired product, but when P(t-Bu)$_3$ was added, a 23% yield was obtained for the desired cross-coupling product (entry 2). PdCl$_2$ provided the product in a similar yield as Pd(OAc)$_2$ (entries 2 and 3). To our surprise, employing the unprotected alcohol (HMFA) in the cross-coupling, resulted in higher yields (entries 4–7), which led us to hypothesize that the hydroxymethyl handle may be acting to facilitate the cross-coupling. Finally, employing a combination of Pd(acac)$_2$ and Buchwald-type ligands[44] yielded the desired product in excellent yields (entries 9–10).

Previous reports had demonstrated that free alcohols and phenol functionalities when present on the aryl-bromide electrophilic cross-coupling partner were not tolerated for related palladium-mediated decarboxylative arylations.[38] Based on our initial results, we hypothesized that the employment of HMFA (**14**) in the decarboxylative cross-coupling (Scheme 2), which includes a free hydroxymethyl group in the nucleophilic cross-coupling partner, could potentially aid in the stabilization of key intermediate **15** and facilitate the electrophilic palladation (Scheme 2, **15**→**16**) required for the cross-coupling reaction.

Scheme 2. Proposed Catalytic Cycle for the Pd-Mediated Cross-Coupling of HMFA (15) and Aryl Bromides



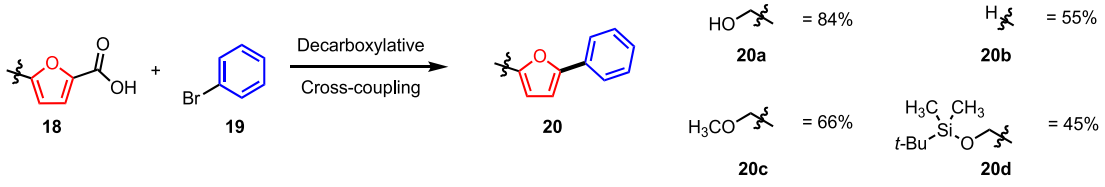
In order to evaluate the influence of the hydroxymethyl handle on the decarboxylative cross-couplings, single experiments were designed to modify this group. Replacing the alcohol group with the corresponding methyl ether resulted in a lower yield (66%, Scheme 3, **18c**→**20c**). Furoic acid **18b** provided an even lower yield of 55% of the desired cross-coupling product **20c**. Finally, the previously synthesized t-butyldimethylsilyl ether **18d** led to a 45% yield of **20d**. These experiments supported that there was an intrinsic beneficial overall effect of having the free hydroxymethyl handle on the furoic acid coupling partner.

Competition experiments were subsequently conducted to further evaluate the importance of the hydroxymethyl stabilizing group effect (Scheme 4). In the initial experiment (Scheme 4, Top), HMFA **18a** was compared with furoic acid **18b**, from which a ratio of 1.5:1.0 (**20a**:**20b**) of the corresponding products was obtained in favor of the product-derived HMFA. However, because the electronics of the furan ring were different for the two starting materials, we performed a subsequent competition experiment (Scheme 4, bottom), in which the C5-position was substituted for all starting materials, while varying the steric environment around the oxygen atom. The composition of the reaction crude mixture was found to be predominantly of product **20a** (from HMFA), and lower quantities of **20c** (from **18c**) and **20d** (from **18d**) were obtained, which suggests an energetically favored reaction pathway for the starting material bearing the hydroxymethyl handle. Overall, these experiments suggest that the free hydroxyl group on the HMFA is responsible for the improved yields. These possible interactions (hypothesized in Scheme 2) of distal weakly coordinating functional groups in palladium catalysis have been reported in related systems by the Yu[45,46] group based on the initial findings of van Leeuwen[47] and the Sanford group.[48] Ongoing studies in our group are being carried out to better describe the nature of these interactions and their impact on the decarboxylative cross-couplings.

Oxidation of furfuryl alcohols to the corresponding carboxylic acids remains a challenge because the typically harsh oxidative conditions often lead to unwanted by-products and have low functional group tolerance. In order to avoid these issues, we evaluated a catalytic TEMPO-NaOCl oxidation with NaClO$_2$ (Table 2, entries 1 and 2), but the corresponding products were obtained in a low yield.[49] We hypothesized that the electron-rich nature of this model substrate (**21a**) may be problematic and thus prepared a second model substrate with an electron-deficient substituent (p-CF$_3$, **21b**), that improved the yield toward the aldehyde (**22b**), but only a small quantity of the desired carboxylic acid (**23b**) was obtained (entry 2). Oxidative conditions that involve acidic media were noncompatible with the hydroxymethyl furan derivatives as they induce the formation of nondesired side products (entry 3). Interestingly, when metal catalysis with peroxide was employed,[50] a mixture between the desired acid and the aldehyde derivative was obtained (entries 4 and 5).

Replacement of the BiCl$_3$ with CuBr$_2$ led to the selective formation of the aldehyde in moderate yields.[51] Harsher

Scheme 3. Cross-Coupling of HMFA Derivatives with Bromobenzene: Individual Reaction Yields



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Scheme 4. Competition Decarboxylative Cross-Coupling Reactions Between Furoic Acid Derivatives

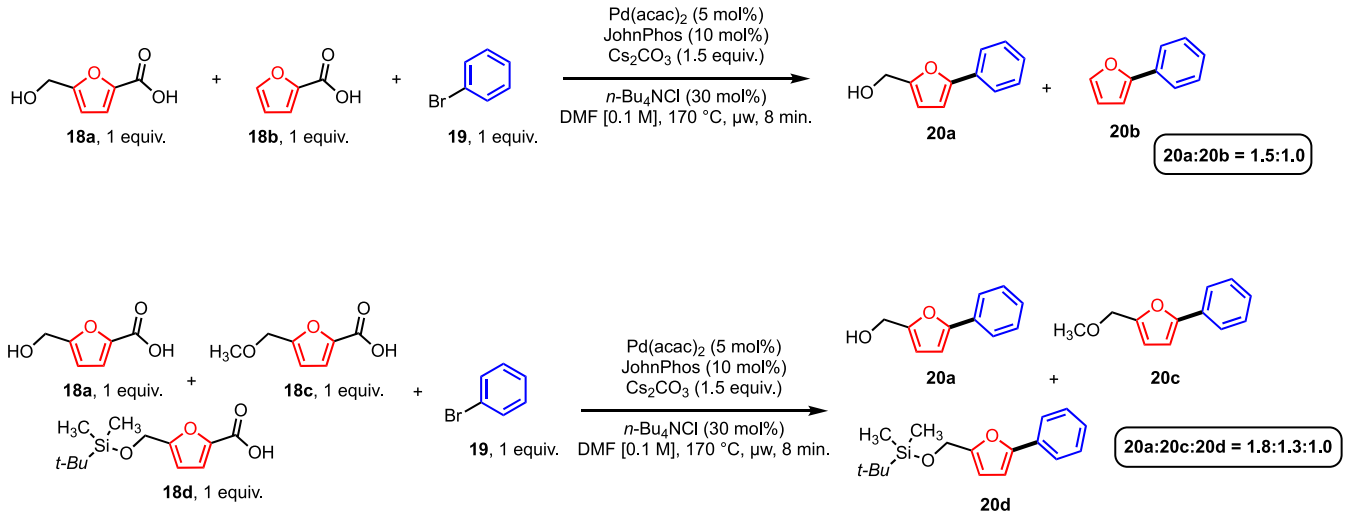
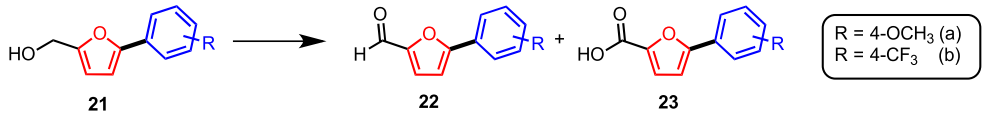


Table 2. Oxidation of the Methyl Alcohol Moiety



entry	R	conditions[a]	%22	%23
1	4-OCH_3	$NaClO_2$, NaOCl, TEMPO	20	0
2	4-CF_3	$NaClO_2$, NaOCl, TEMPO	48	<5
3	4-CF_3	Jones Reagent	0	0
4	4-CF_3	$BiCl_3$, *t*-BuOOH	<5	68
5	4-OCH_3	$BiCl_3$, *t*-BuOOH	45	19
6	4-OCH_3	$SiO_2/KMnO_4$	0	0
7	4-CF_3	$CuBr_2$, *t*-BuOOH	68	0
8	4-OCH_3	$CuBr_2$, *t*-BuOOH	43	0
9	4-CF_3	$Fe(NO_3)_3 9H_2O$, TEMPO, O_2	>98	0
10	4-OCH_3	$Fe(NO_3)_3$ $9H_2O$, TEMPO, O_2	90	0
11	4-CF_3	$[Cu(CH_3CN)_4]PF_6$, DBED, O_2	>99	0
12	4-OCH_3	$[Cu(CH_3CN)_4]PF_6$, DBED, O_2	94	0
13	4-CF_3	1.$[Cu(CH_3CN)_4]PF_6$, DBED, O_2 2.$NaClO_2$, sulphamic acid	0	95
14	4-OCH_3	1.$[Cu(CH_3CN)_4]PF_6$, DBED, O_2 2.$NaClO_2$, sulphamic acid	0	89

[a]Full description of the reaction conditions can be found in Experimental Section. [b]60% of 4-methoxybenzoic acid was recovered.

oxidation conditions ($KMnO_4$ adsorbed on silica[52]) cleaved the furan moiety to produce the corresponding benzoic acid (entry 6). Aerobic oxidation using TEMPO/O_2 with Fe-$(NO_3)_3$ gave excellent yields of the aldehyde derivative.[53] Given the high cost of TEMPO, we envisioned that this step would be nonoptimal, particularly for potential industrial applications.[54] To address this issue, we subsequently employed a biomimetic copper system,[55] in which the reaction is performed at room temperature under an O_2 atmosphere, obtaining high yields of the corresponding aldehydes in significantly shorter reaction times. We subsequently employed a two-step oxidation (entries 13 and 14) with the conditions reported in entries 11 and 12, including an adapted Pinnick oxidation[56,57] to obtain the desired carboxylic acids (**23**).

With the carboxylic acids prepared, we subjected the furoic acids to a second decarboxylative cross-coupling based on the conditions optimized for the first reaction with a wide variety of coupling partners (Table 3). As expected, electron-deficient carboxylic acids (entries 1−3 and 7−9) typically produced the corresponding product in higher yields. Correspondingly, electron-neutral and -rich carboxylic acids (entries 4−6 and 10−12) provided the products in lower yields, possibly because of the higher energetic barrier to overcome in the decarboxylation step. Overall, a wide scope of 2,5-diaryl nonsymmetric furans were prepared that tolerated different functionalities, including substrates bearing sterically challenging *ortho* substituents (entries 7, 9, and 11) in good to excellent yields.

Formal Synthesis of Dantrolene. Dantrolene **26** is a hydantoin derivative furan that acts as a postsynaptic muscle relaxant with important applications in the prevention and treatment of malignant hyperthermia.[20,58] The reported patented synthesis[59,60] involves the preparation of a diazonium salt, followed by a Cu-catalyzed Meerwein arylation and an iminium formation with 2-aminohydantoin to form the target

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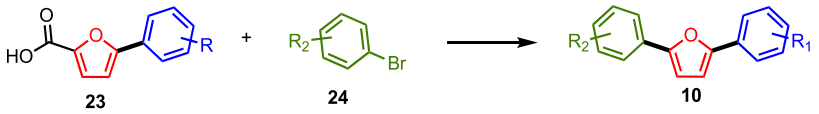
Table 3. Scope of the Second-Decarboxylative Cross-Coupling Arylation



Entry	Product	Yield (%)
1	**10a**	77
2	**10b**	72
3	**10c**	91
4	**10d**	69
5	**10e**	76
6	**10f**	82
7	**10g**	83
8	**10h**	69
9	**10i**	64
10	**10j**	74
11	**10k**	83
12	**10m**	87

[a]General conditions: furan carboxylic acid (1.5 equiv), aryl bromide 1 mmol, $Pd(acac)_2$ (5 mol %), JohnPhos (10 mol %) Cs_2CO_3 (1.5 equiv), *n*-Bu_4NCl (30 mol %) DMF [0.1 M], 170 °C μw, 8 min, 900 rpm.

drug. Despite this synthetic approach involving only three steps, it presents a challenge in the efficiency of the arylation because of the very low yield (<20%) and requires the preparation of the potentially dangerous diazonium salt. Other methodologies have been reported that explore the C−H arylation of C5-derived furans with solid-supported catalysis (TiO_2)[61] and Pd-mediated C−H arylations.[62]

We propose employing a C6 biomass-derived starting material for the synthesis of this drug molecule based on the currently reported method (Scheme 5). HMFA (**18a**) was obtained from HMF (**7**) through a solvent-free mechanochemical base-promoted disproportionation and used as the starting material for the decarboxylative cross-coupling with *p*-bromo nitrobenzene to obtain (**13a**). This step is critical because it circumvents the two main problems of the patented route, the low yield for the cross-coupling, and the commercial availability of the starting materials. This compound was subjected to a biomimetic Cu-catalyzed aerobic oxidation to obtain the corresponding aldehyde (**25**) in quantitative yield. The overall yield for this three-step

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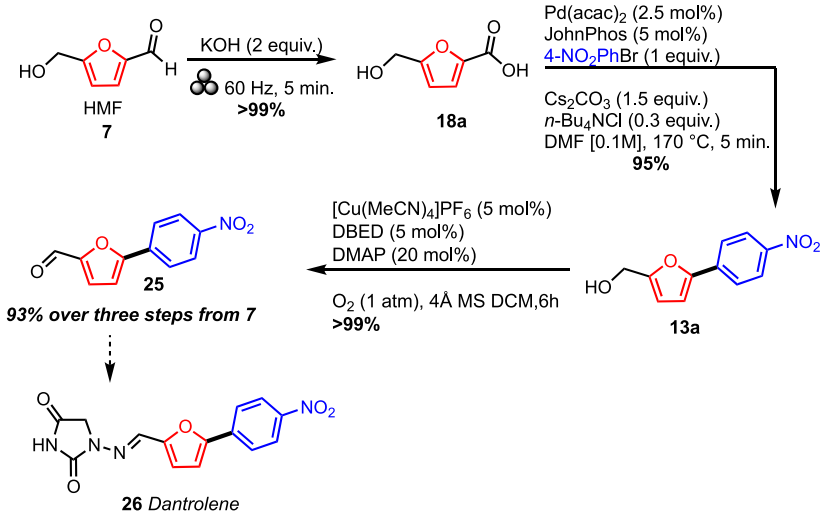
Scheme 5. Synthetic Route for the Formal Synthesis of Dantrolene from Biomass-derived HMF



process to the key aldehyde intermediate (**25**) of 93% starting from biomass-derived HMF is the most efficient synthesis reported to date for Dantrolene.

■ CONCLUSIONS

Highlighting the importance of employing C6 biomass-derived furans, this work presents a new method to obtain 2,5-diaryl nonsymmetric furans from cellulose-derived HMF with good to excellent yields. Single and competition reactions support the idea of a distal weakly coordinating stabilizing effect of the hydroxyl handle that results in improved yields. With a commitment toward green synthetic chemistry methodologies, a biomimetic Cu-catalyzed aerobic oxidation was employed in a two-step reaction sequence to obtain the key synthetic intermediates to synthesize the double-arylated products. Furthermore, with this key intermediate, a new formal synthetic pathway for the commercially available muscle relaxant Dantrolene was achieved, with excellent yields and improved synthetic efficiency than those obtained from previously reported routes. This work highlights the importance of the employment of renewable resources as starting materials for high-value synthetic targets.

■ EXPERIMENTAL SECTION

General Considerations. Flash chromatography was carried out using 40−63 μm silica gel (SiliCycle), and some compounds were isolated using a CombiFlash Teledyne Isco. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and were stored under an inert atmosphere with activated 3 or 4 Å molecular sieves. Distilled water was obtained from an in-house water distillery. All other reagents and chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in CDCl3 or d^6-DMSO using a Varian Inova 500 MHz spectrometer. Spectra were referenced to the residual solvent signal or the TMS signal. Spectral features are tabulated in the following order: chemical shift (δ, ppm), multiplicity (*s*-singlet, *d*-doublet, *t*-triplet, *q*-quartet, *dd*-doublet of doublets, *m*-multiplet, and *ddd*-doublet of doublets of doublets), coupling constants (J and Hz), and number of protons. High-resolution mass spectra were obtained with an LTQ Orbitrap Velos ETD (positive and negative mode) mass spectrometer. Microwave reactions were carried out in sealed vials using a Biotage Initiator EXP US 355302 system (300 W and 2450 MHz).

General Procedure for the Decarboxylative Cross-Coupling of HMFA and Aryl Bromides. To an oven-dried microwave vial (2−5 mL), with a stir bar, was added 114 mg of HMFA (0.8 mmol, 2 equiv), 6.1 mg of Pd(acac)$_2$ (0.02 mmol, 5 mol %), 11.9 mg of JohnPhos (0.08 mmol, 10 mol %), 195 mg of Cs_2CO_3 (0.6 mmol, 1.5 equiv.), 0.4 mmol of the corresponding aryl bromide, 33 mg of *n*-Bu_4NCl (0.12 mmol, 30 mol %), and 4 mL of anhydrous DMF. The reaction is prestirred for 30 s and then subjected to microwave irradiation to achieve 170 °C for 8 min at 900 rpm. The reaction crude is transferred to a 125 mL separating funnel, diluted with 30 mL of EtOAc, and washed with brine (2 × 20 mL) and $NaHCO_3$(sat) (1 × 20 mL). The combined aqueous phases are reextracted with EtOAc (1 × 15 mL), and the combined organics are dried over Na_2SO_4. The solvent is removed under vaccuo, and the crude is purified by silica gel chromatography to obtain the pure desired product. This procedure was scaled up in a 20 mL sealed microwave vial, with 516 mg (3.6 mmol, 2 equiv) of HMFA and 340 mg (1.8 mmol, 1 equiv) of 4-bromo anisole, 27 mg (5 mol %) of Pd(acac)$_2$, 55 mg (10 mol %) of JohnPhos, 150 mg (30 mol %) of *n*-Bu_4NCl, 870 mg (2.7 mmol, 1.5 equiv), and 18 mL of anhydrous DMF. In this case, the reaction was subjected to microwave irradiation at 170 °C for 20 min. Work-up was done as previously described, with extensive (six times) brine washing to assure removal of DMF. Purification was done using an 80 g silica column on CombiFlash with hexanes/DCM/EtOAC (4:4:2) to afford 332 mg of the desired product (91%, pale-yellow solid).

Cu-Catalyzed Oxidation of the Primary Alcohol to the Aldehyde. In a nitrogen glovebox, a Schlenk tube equipped with a stir bar was charged with alcohol (0.5 mmol), $[Cu(CH_3CN)_4]PF_6$ (0.025 mmol), DBED (0.025 mmol), DMAP (0.1 mmol), 4 Å molecular sieves (100 mg), and CH_2Cl_2 (4 mL). The tube was sealed, brought out of the glovebox, the nitrogen headspace was evacuated, and then replaced at a constant pressure of 1 atm O_2. The resulting mixture was stirred at room temperature for 6 h. After this time, 10% wt. $NaHSO_4$ (15 mL) was added to quench the reaction. The product was extracted with additional CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated to afford the product. Purification was done (when needed) with silica gel CombiFlash using hexanes/EtOAc (10:0 to 8:2) as the eluent. This reaction was scaled up according to the corresponding yield of the first cross-coupling.

Adapted Pinnick Oxidation of the Aldehyde to the Carboxylic Acid. The corresponding aldehyde (1 equiv) was added in a 10 mL round-bottom flask and equipped with a stir bar. To this flask, was added MeCN/H_2O (3:1, 0.65 M to the corresponding alcohol), NaH_2PO_4 (0.26 equiv), $NaClO_2$ (1.39 equiv), and H_2O_2 30% (1 equiv). The flask was covered with aluminum foil to avoid photoinduced decomposition and stirred at room temperature for 18 h. In those cases where the reaction was not completed in 18 h (electron-rich substrates), the reaction vessel was

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opened and $NaClO_2$ (1.05 equiv) and H_2O_2 30% (1 equiv) was added and stirred for another 18 h. When the reaction was completed, the stir bar was removed and the MeCN was removed under vaccuo. The aqueous remaining solution was checked for high acidity (pH 2, adjusted with 2 M HCl when necessary) and extracted with EtOAc (3 × 10 mL). The combined organics were dried with Na_2SO_4, and the solvent was removed under vaccuo to obtain the desired product. When needed, purification of the product can be done with acid-base extraction or silica gel chromatography with DCM/MeOH (10:0 to 8:2, and a trace amount of AcOH).

General Procedure for the Decarboxylative Cross-Coupling of 5-Aryl-2-furoic Acids and Aryl Bromides. To an oven-dried microwave vial (0.5−2 mL), with a stir bar, was added 0.2 mmol of the 5-aryl-2-furoic acid (1 equiv), 3.1 mg of $Pd(acac)_2$ (0.01 mmol, 5 mol %), 6.0 mg of JohnPhos (0.02 mmol, 10 mol %), 98 mg of Cs_2CO_3 (0.3 mmol, 1.5 equiv.), 0.4 mmol of the corresponding aryl bromide, 16 mg of *n*-Bu_4NCl (0.06 mmol, 30 mol %), and 2 mL of anhydrous DMF. The reaction is prestirred for 30 s and then subjected to microwave irradiation to achieve 170 °C for 8 min at 900 rpm. The reaction crude is transferred to a 125 mL separating funnel, diluted with 30 mL of EtOAc, and washed with brine (2 × 20 mL) and $NaHCO_3$(sat) (1 × 20 mL). The combined aqueous phases are reextracted with EtOAc (1 × 15 mL), and the combined organics are dried over Na_2SO_4. The solvent is removed under vaccuo, and the crude is purified by silica gel chromatography to obtain the pure desired product.

3a: (5-(4-nitrophenyl)furan-2-yl)methanol.[29] Purified by CC (R_f = 0.42) hexanes/DCM/EtOAc (4:4:2), 81 mg (93%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.23 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 3.4 Hz, 1H), 6.46 (d, J = 3.4 Hz, 1H), 4.71 (s, 2H), 1.86 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 155.8 (1C), 151.6 (1C), 146.4 (1C), 136.2 (1C), 124.3 (2C), 123.9 (2C), 110.5 (1C), 109.7 (1C), 57.6 (1C). HRMS (ESI): m/z Calcd for $C_{11}H_8NO_4^-$ $[M - 1]^{-\bullet}$ 218.0459. Found: 218.0455 (−1.8 ppm).

3b: (5-(4-methoxyphenyl)furan-2-yl)methanol.[29] Purified by CC (R_f = 0.53) hexanes/DCM/EtOAc (4:4:2), 78 mg (95%) yield as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.60 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.46 (d, J = 3.2 Hz, 1H), 6.34 (d, J = 3.2 Hz, 1H), 4.64 (s, 2H), 3.83 (s, 3H), 2.19 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 159.1 (1C), 154.2 (1C), 152.9 (1C), 125.3 (2C), 123.8 (1C), 114.1 (2C), 109.9 (1C), 104.1 (1C), 57.6 (1C), 55.3 (1C). HRMS (ESI): m/z Calcd for $C_{12}H_{11}O_3^-$ $[M - 1]^{-\bullet}$ 203.0708. Found: 203.0705 (−1.3 ppm).

3c: (5-(4-(trifluoromethyl)phenyl)furan-2-yl)methanol.[29] Purified by CC (R_f = 0.30) hexanes/DCM/EtOAc (4:4:2), 85 mg (88%) yield as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.74 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 6.70 (d, J = 3.3 Hz, 1H), 6.40 (d, J = 3.3 Hz, 1H), 4.68 (s, 2H), 2.34 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 154.7 (1C), 152.4 (1C), 133.7 (1C), 129.0 (q, C−F, $^2J_{C-F}$ = 32.5 Hz, 1C), 125.7 (q, C−F, $^3J_{C-F}$ = 3.9 Hz, 2C), 124.1 (q, C−F, $^1J_{C-F}$ = 271.2 Hz, 1C), 123.7 (2C), 110.1 (1C), 107.7 (1C), 57.5 (1C). HRMS (EI): m/z Calcd For $C_{12}H_8F_3O_2^-$ $[M - 1]^{-\bullet}$ 241.0477. Found: 241.0472 (−1.9 ppm).

3d: (5-Phenylfuran-2-yl)methanol.[63] Purified by CC (R_f = 0.34) hexanes/DCM/EtOAc (4:4:2), 54 mg (78%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.69 (m, 2H), 7.39 (m, 2H), 7.28 (m, 1H), 6.61 (d, J = 3.3 Hz, 1H), 6.39 (d, J = 3.3 Hz, 1H), 4.68 (s, 2H), 1.98 (br s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 154.0 (1C), 153.6 (1C), 130.7 (1C), 128.7 (2C), 127.5 (1C), 123.8 (2C), 110.0 (1C), 105.7 (1C), 57.7 (1C). HRMS (ESI): m/z Calcd for $C_{11}H_9O_2^-$ $[M - 1]^{-\bullet}$ 173.0603. Found: 173.0599 (−2.1 ppm).

10a: 2-(4-nitrophenyl)-5-(p-tolyl)furan. Purified by CC (R_f = 0.42) hexanes/DCM (1:1), 43 mg (77%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.25 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H) 6.95 (d, J = 3.6 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 155.9 (1C), 150.6 (1C), 146.1 (1C), 138.3 (1C), 136.4 (1C), 129.5 (2C), 127.3 (1C), 124.4 (2C), 124.1 (2C), 123.6 (2C), 111.4 (1C), 107.2 (1C), 21.4 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{13}NO_3$ $[M^{+\bullet}]$: 279.0895. Found: 279.0898 (1.1 ppm).

10b: 2-(3-methoxyphenyl)-5-(4-nitrophenyl)furan. Purified by CC (R_f = 0.36) hexanes/DCM (1:1), 42 mg (72%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.25 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.36 (d, J = 5.1 Hz, 2H), 7.30 (dt, J = 2.4, 0.9 Hz, 1H), 6.96 (d, J = 3.6 Hz, 1H), 6.91−6.87 (m, 1H), 6.80 (d, J = 3.6 Hz, 1H), 3.90 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 160 (1C), 155.4 (1C), 150.9 (1C), 146.2 (1C), 136.2 (1C), 131.2 (1C), 124.37 (2C), 123.7 (2C), 116.74 (1C), 113.6 (1C), 111.3 (1C), 109.8 (1C), 108.1 (1C), 55.37 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{13}NO_4$ $[M^{+\bullet}]$: 295.0845. Found: 295.0851 (2.0 ppm).

10c: 2-(4-nitrophenyl)-5-(3-(trifluoromethyl)phenyl)furan. Purified by CC (R_f = 0.38) hexanes/DCM (1:1), 61 mg (91%) yield as an orange/yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.29 (d, J = 9.0 HZ, 2H), 7.99 (m, 1H), 7.93 (m, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.57 (m, 2H), 7.00 (d, J = 3.6 Hz, 1H), 6.91 (d, J = 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 153.8 (1C), 151.7 (1C), 146.5 (1C), 135.8 (1C), 131.4 (q, C−F, $^2J_{C-F}$ = 32.5 Hz, 1C), 130.7 (1C), 129.4 (1C), 127.1(q, C−F, $^4J_{C-F}$ = 1.4 Hz, 1C), 124.6(q, C−F, $^3J_{C-F}$ = 3.8 Hz, 1C), 124.4 (2C), 124.0 (q, C−F, $^1J_{C-F}$ = 272.0 Hz, 1C), 123.9 (2C), 120.7(q, C−F, $^3J_{C-F}$ = 3.9 Hz, 1C), 111.2 (1C), 109.1 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{10}F_3NO_3$ $[M^{+\bullet}]$: 333.0613. Found: 333.0618 (1.5 ppm).

10d: 2-(4-methoxyphenyl)-5-(p-tolyl)furan.[64] Purified by CC (R_f = 0.43) hexanes/DCM (1:1), 36 mg (69%) yield as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.70−7.65 (m, 2H), 7.65−7.60 (m, 2H), 7.23−7.18 (m, 2H), 6.98−6.91 (m, 2H), 6.66 (d, J = 3.4 Hz, 1H), 6.59 (d, J = 3.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 158.9 (1C), 153 (1C), 152.9 (1C), 136.9 (1C), 129.3 (2C), 128.2 (1C), 125.1 (2C), 124 (1C), 123.5 (2C), 114.1 (2C), 106.4 (1C), 105.5 (1C), 55.3 (1C), 21.2 (1C). HRMS (ESI): exact mass calculated for $C_{18}H_{16}O_2$ $[M^{+\bullet}]$: 264.1150. Found: 264.1152 (0.8 ppm).

10e: 2-(4-methoxyphenyl)-5-(3-nitrophenyl)furan. Purified by CC (R_f = 0.31) hexanes/DCM (7:3), 45 mg (76%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.51 (ddd, J = 2.2, 1.6, 0.4 Hz, 1H), 8.06 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 7.98 (ddd, J = 8.0, 1.6, 1.0 Hz, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.55 (dd, J = 8.0, 0.4 Hz, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 3.5 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 159.5 (1C), 154.8 (1C), 150 (1C), 148.7 (1C), 132.4 (1C), 129.6 (1C), 128.8 (2C), 125.5 (1C), 123.1 (1C), 121.2 (1C), 118,08 (1C), 114.2 (2C), 109.5 (1C), 105.8 (1C), 55.36 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{13}NO_4$ $[M^{+\bullet}]$: 295.0845. Found: 295.0852 (2.4 ppm).

10f: 2-(4-methoxyphenyl)-5-(4-nitrophenyl)furan. Purified by CC (R_f = 0.38) hexanes/DCM (7:3), 48 mg (82%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.24 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 3.6 Hz, 1H), 6.67 (d, J = 3.56 Hz, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 159.8 (1C), 155.8 (1C), 150.3 (1C), 146.0 (1C), 136.4 (1C), 125.6 (2C), 124.4 (2C), 123.4 (2C), 122.9 (2C), 114.3 (1C), 111.5 (1C), 106.4 (1C), 55.4 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{13}NO_4$ $[M^{+\bullet}]$: 295.0845. Found: 295.0851 (2.0 ppm).

10g: 2-(2-methyl-4-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)-furan. Purified by CC (R_f = 0.58) hexanes/DCM (7:3), 57 mg (83%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.63 (d, J = 2.5 Hz, 1H), 8.05 (dd, J = 8.4, 2.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H), 6.82 (d, J = 3.6 Hz, 1H), 2.67 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 152.6 (1C), 151.6 (1C), 146.6 (1C), 141.6 (1C), 133.2 (q, C−F, $^4J_{C-F}$ = 1.4 Hz, 1C), 132.3 (1C), 130.8 (1C), 129.5 (q, C−F, $^2J_{C-F}$ = 32.6 Hz, 1C), 125.9 (q, C−F, $^3J_{C-F}$ = 3.8 Hz, 2C), 124.0 (q, C−F, $^1J_{C-F}$ = 271.7 Hz, 1C), 124.0 (2C), 121.9 (1C), 121.7 (1C), 112.7 (1C), 109.1 (1C), 22.3 (1C).

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HRMS (EI): exact mass Calcd for $C_{18}H_{12}F_3NO_3$ [$M^{+\bullet}$]: 347.0769. Found: 347.0774 (1.4 ppm).

10h: 2-(4-fluorophenyl)-5-(4-(trifluoromethyl)phenyl)furan. Purified by CC (R_f = 0.39) hexanes/DCM (7:3), 42 mg (69%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.81 (d, J = 7.4 Hz, 2H), 7.72 (m, 2H), 7.65 (d, J = 7.4, 2H), 7.12 (m, 2H), 6.84 (d, J = 3.5 Hz, 1H), 6.70 (d, J = 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 162.4 (d, C−F, $^1J_{C-F}$ = 248.3 Hz, 1C), 153.6 (1C), 151.8 (1C), 133.7 (q, C−F, $^4J_{C-F}$ = 1.23 Hz, 2C), 128.9 (q, C−F, $^2J_{C-F}$ = 32.8 Hz, 1C), 126.7, 125.7 (q, C−F, $^3J_{C-F}$ = 3.8 Hz, 2C), 125.7 (d, C−F, $^3J_{C-F}$ = 8.0 Hz, 2C), 124.2 (q, C−F, $^1J_{C-F}$ = 271.4 Hz, 1C), 123.6 (1C), 115.8 (d, C−F, $^2J_{C-F}$ = 22.0 Hz, 2C), 109.2 (1C), 107.1 (d, C−F, $^4J_{C-F}$ = 1.4 Hz, 1C). HRMS (ESI): m/z Calcd for $C_{17}H_{10}F_4O$ [$M^{+\bullet}$]: 306.0668. Found: 306.0669 (0.3 ppm).

10i: Methyl 3-Methyl-4-(5-(4-(trifluoromethyl)phenyl)furan-2-yl)benzoate. Purified by CC (R_f = 0.38) hexanes/DCM (7:3), 46 mg (64%) yield as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.90 (m, 2H), 7.87 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 3.5 Hz, 1H), 6.80 (d, J = 3.5 Hz, 1H), 3.94 (s, 3H), 2.62 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 166.8 (1C), 153.1 (1C), 152.3 (1C), 134.3 (1C), 133.5 (2C), 132.6 (1C), 129.3 (q, C−F, $^2J_{C-F}$ = 32.3 Hz, 1C), 128.8 (1C), 127.3 (1C), 126.5 (1C), 125.8 (q, C−F, $^3J_{C-F}$ = 3.8 Hz, 2C), 124.1 (q, C−F, $^1J_{C-F}$ = 272.0 Hz, 1C), 123.8 (2C), 112.6 (1C), 109.1 (1C), 52.1 (1C), 22.2 (1C). HRMS (ESI): m/z Calcd for $C_{20}H_{15}F_3O_3$ [$M^{+\bullet}$]: 360.0973. Found: 360.0979 (1.7 ppm).

10j: Ethyl 4-(5-phenylfuran-2-yl)benzoate. Purified by CC (R_f = 0.41) hexanes/DCM (7:3), 43 mg (74%) yield as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.08 (d, J = 8.7 Hz, 2H), 8.08 (d, J = 8.7 Hz, 2H), 7.76 (m, 2H), 7.42 (m, 2H), 7.30 (m, 1H), 6.87 (d, J = 3.5 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 166.3 (1C), 154.4 (1C), 152.3 (1C), 134.5 (1C), 130.4 (2C), 130.1 (1C), 128.8 (1C), 128.7 (2C), 127.8 (1C), 123.9 (2C), 123.2 (2C), 109.5 (1C), 107.5 (1C), 61.0 (1C), 14.4 (1C). HRMS (ESI): m/z Calcd for $C_{19}H_{16}O_3$ [$M^{+\bullet}$]: 292.1099. Found: 292.1105 (2.1 ppm).

10k: 2-(2-methyl-4-nitrophenyl)-5-phenylfuran. Purified by CC (R_f = 0.40) hexanes/DCM (7:3), 46 mg (74%) yield as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.63 (d, J = 2.5 Hz, 1H), 8.01 (dd, J = 8.3, 2.5 Hz, 1H), 7.75 (m, 2H), 7.44 (dd, J = 8.4, 7.2 Hz, 2H), 7.39 (dd, J = 8.4, 0.8 Hz, 1H), 7.32 (m, 1H), 6.80 (d, J = 3.5 Hz, 1H), 6.78 (d, J = 3.5 Hz, 1H), 2.65 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 154.2 (1C), 150.5 (1C), 146.6 (1C), 141.3 (1C), 132.2 (1C), 131.1 (1C), 130.1 (1C), 128.8 (2C), 128.0 (1C), 124.0 (2C), 121.4 (1C), 121.4 (1C), 112.6 (1C), 107.1 (1C), 22.4 (1C). HRMS (ESI): m/z Calcd for $C_{17}H_{13}NO_3$ [$M^{+\bullet}$]: 279.0895. Found: 279.0893 (−0.7 ppm).

10m: 2-(3-ethylphenyl)-5-phenylfuran. Purified by CC (R_f = 0.52) hexanes/DCM (7:3), 41 mg (83%) yield as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.76 (m, 2H), 7.72 (m, 1H), 7.43 (m, 2H), 7.31 (m, 2H), 6.79 (d, J = 3.4 Hz, 1H), 6.64 (d, J = 3.4 Hz, 1H), 2.97 (q, J = 7.5 Hz, 2H), 1.35 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ ppm 153.4 9 (1C), 153.2 (1C), 141.2 (1C), 130.9 (1C), 129.7 (1C), 129.5 (1C), 128.7 (2C), 128.0 (1C), 127.9 (1C), 127.3 (1C), 125.9 (1C), 123.7 (2C), 110.3 (1C), 106.8 (1C), 27.4 (1C), 15.4 (1C). HRMS (ESI): m/z Calcd for $C_{18}H_{16}O$ [$M^{+\bullet}$]: 248.1201. Found: 248.1203 (0.8 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02236.

Supporting Information ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

FDCA	2,5-furandixylic acid
HMF	5-hydroxymethyl furfural
DHMF	bis-2,5-hydroxymethyl furan
μw	microwave.

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