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Palladium-Catalyzed Intramolecular Hydroarylation of 4-Benzofuranyl Alkynoates. Approach to Angelicin Derivatives

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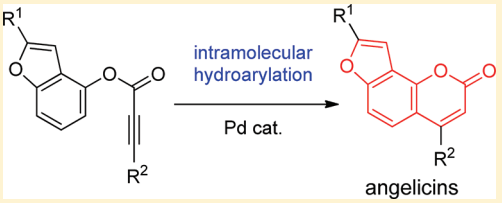
Supporting Information

ABSTRACT: Intramolecular hydroarylation of 4-benzofuranyl alkynoates using $Pd(OAc)_2$ as catalyst took place selectively and efficiently, giving angular furocoumarin derivatives in high yields. The parent angelicin was obtained in 80% yield by this method. The starting 4-benzofuranyl alkynoates were easily accessible from readily available 4-hydroxybenzofurans and alkynoic acids.



Furocoumarins are an important class of tricyclic aromatic compounds consisting of a fused structure of coumarin and furan nucleuses. They have long attracted much attention because of their biological and industrial applications. Among furocoumarin derivatives, psoralen (**1**) and angelicin (**2**) (shown in Figure 1) are naturally occurring or synthetic

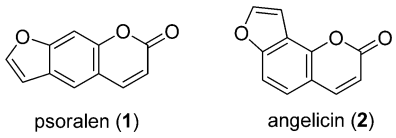


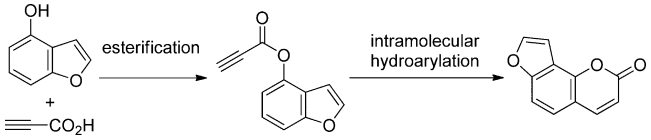
Figure 1. Representative furocoumarins.

compounds and are known to possess a high photobiological activity, as discussed in many reviews.[1] To summarize briefly, psoralen and its analogues cause cell damage by covalent binding to DNA on UVA irradiation (400−320 nm). Many human skin diseases, such as psoriasis, T-cell lymphoma, and vitiligo are commonly treated with a combination of psoralens and UVA radiation. However, the linear psoralens cause undesirable side effects such as genotoxicity[2] and risk of skin cancer[3] because of their cross-linking with DNA. Angelicin and its analogues exhibit interesting pharmacological activity, but the angular structure reduces the undesirable side effects.[4] Therefore, considerable attention has recently been paid to angular furocoumarins such as **2**.

For the reasons mentioned above, many synthetic methods for furocoumarins have been extensively developed so far.[1a,b,g,5] There are two main approaches to construct the furocoumarin skeleton, namely, furan-ring construction and pyrone-ring construction. Among these methods, the methodology fusing a furan ring on a coumarin nucleus has been traditionally and widely applied for the synthesis of furocoumarins.[1a,b] On the other hand, hydroxybenzofuran derivatives have been used for the furocoumarin synthesis via the pyrone-ring construction as starting materials, and the synthetic method involves the Perkin condensation,[6] the Pechmann reaction,[7] the Wittig reaction,[5d,8] and related reactions.[9]

Intramolecular hydroarylation of alkynes is an efficient and promising method for synthesizing carbocyclic and heterocyclic aromatic compounds.[10] Recently, several coumarin derivatives have been prepared by transition-metal-catalyzed hydroarylation reactions.[11] However, to the best of our knowledge, there are no reports on the synthesis of furocoumarins by the hydroarylation methodology (Scheme 1). In this paper, we

Scheme 1. Pyrone-Constructing Methodology Using Intramolecular Hydroarylation



report for the first time an efficient synthesis of furocoumarins by palladium-catalyzed intramolecular hydroarylation.

Starting 4-hydroxybenzofuran derivatives **2** were synthesized by conventional methods, as shown in Scheme 2. 4-Hydroxybenzofuran (**2a**) was readily prepared in 60% yield by aromatization of commercial 6,7-dihydro-1-benzofuran-4(5*H*)-one (**1**) using palladium charcoal and 1-dodecene.[12] 2-Hexyl-4-hydroxybenzofuran (**2b**) and 4-hydroxy-2-phenylbenzofuran (**2c**) were conveniently prepared by the Sonogashira−Hagihara coupling of 2-iodoresorcinol (**3**) with 1-octyne and phenylacetylene in 50 and 60% yields, respectively. Then, 4-benzofuranyl alkynoates **5** were prepared by condensation of 4-hydroxybenzofurans **2** with alkynoic acids **4** using dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) (Scheme 3). The results are given in Table 1.

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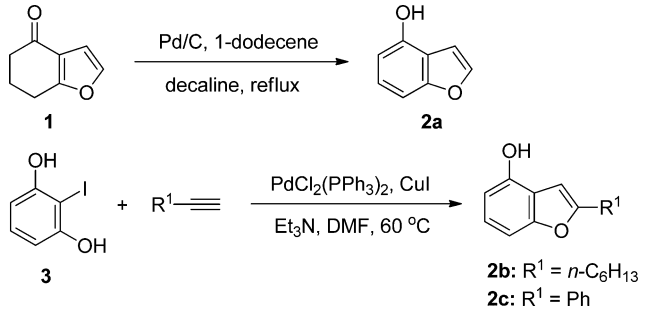
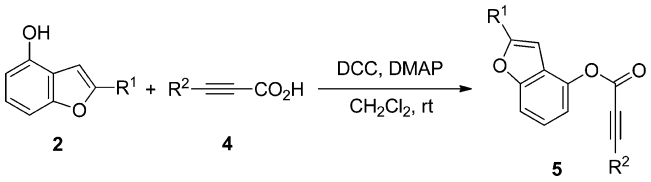
Scheme 2. Synthesis of 4-Hydroxybenzofurans 2



Scheme 3. Synthesis of 4-Benzofuranyl Alkynoates 5



Thus, 4-hydroxybenzofurans **2** can be readily prepared and can be transformed into 4-benzofuryl alkynoates **5**.

Table 1. Synthesis of 4-Benzofuranyl Alkynoates 5

entry[a]	hydroxybenzofuran **2**, R^1	alkynoic acid **4**, R^2	product **5**	yield[b] (%)
1	H	H	**5a**	66
2	H	Me	**5b**	74
3	H	n-C_5H_{11}	**5c**	84
4	H	Ph	**5d**	80
5	n-C_6H_{13}	H	**5e**	62
6	n-C_6H_{13}	Me	**5f**	74
7	n-C_6H_{13}	n-C_5H_{11}	**5g**	75
8	n-C_6H_{13}	Ph	**5h**	71
9	Ph	H	**5i**	69
10	Ph	Me	**5j**	90
11	Ph	n-C_5H_{11}	**5k**	90
12	Ph	Ph	**5l**	98

[a]Reaction conditions: **2** (3 mmol), **4** (3 mmol), DCC (3 mmol), DMAP (0.3 mmol), CH_2Cl_2 (3 mL), rt, 3 h. [b]Isolated yields by column chromatography on silica gel.

The intramolecular hydroarylation reaction of 4-benzofuranyl alkynoates was performed in the presence of palladium catalyst in a mixed solvent of TFA and CH_2Cl_2, as shown in Scheme 4. When the 4-benzofuranyl alkynoates were allowed to react at 30 °C for 5 h using 1 mol % of $Pd(OAc)_2$, the furanocoumarins were obtained in high yields. The results are given in Table 2. The reaction of unsubstituted 4-benzofuranyl propiolate **5a** gave furanocoumarin **6a**, i.e., angelicin, in 80% yield (entry 1). Even when the substituents on the acetylenic bond were alkyl

Scheme 4. Intramolecular Hydroarylation of 5

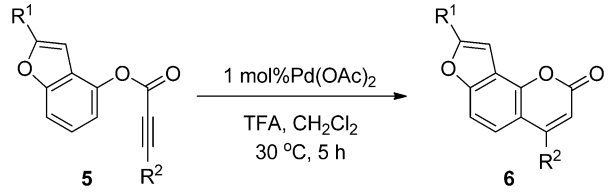


Table 2. Intramolecular Hydroarylation of 5

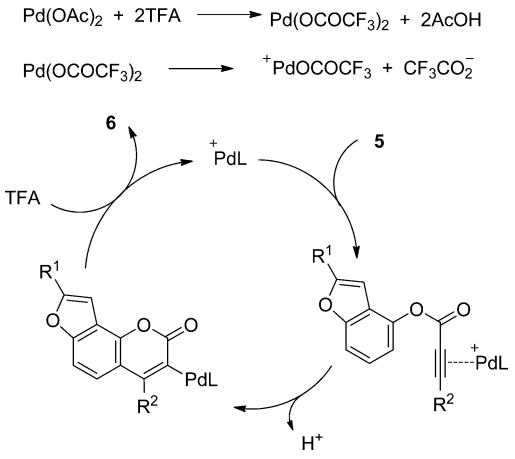
	alkynoate **5**			
entry[a]	R^1	R^2	furocoumarin **6**	yield[b] (%)
1	H	H	**6a**	80
2	H	Me	**6b**	84
3	H	n-C_5H_{11}	**6c**	80
4	H	Ph	**6d**	95
5	n-C_6H_{13}	H	**6e**	70
6	n-C_6H_{13}	Me	**6f**	71
7	n-C_6H_{13}	n-C_5H_{11}	**6g**	86
8	n-C_6H_{13}	Ph	**6h**	83
9[c]	Ph	H	**6i**	74
10	Ph	Me	**6j**	80
11	Ph	n-C_5H_{11}	**6k**	87
12	Ph	Ph	**6l**	81

[a]Reaction conditions: **5** (1 mmol), $Pd(OAc)_2$ (0.01 mmol), TFA (0.5 mL), CH_2Cl_2 (0.5 mL), 30 °C, 5 h. [b]Isolated yields by column chromatography on silica gel. [c]24 h.

and phenyl, the furocoumarin derivatives **6b–d** were obtained in high yields of 80–95% (entries 2–4). Moreover, even if the substituents like hexyl and phenyl groups existed on the benzofuran, the furocoumarin derivatives **6e–l** were obtained in high yields of 70–87% (entries 5–12). Therefore, the methodology using intramolecular hydroarylation is an excellent method for furocoumarin synthesis because of its convenient procedure and the high yield of products.

To understand the role of TFA, we attempted the intramolecular hydroarylation in the absence of TFA. The same reaction of **5j** (R^1 = Ph, R^2 = Me) was conducted in CH_2Cl_2 in the absence of TFA at 30 °C for 5 h. The product **6j** was not observed, and the starting material was recovered unchanged. Therefore, it is considered that TFA plays important roles in this intramolecular hydroarylation reaction. A possible mechanism is shown in Scheme 5. First, TFA

Scheme 5. Possible Mechanism for Intramolecular Hydroarylation Affording Furocoumarins



undergoes ligand exchange of $Pd(OAc)_2$ with acetate ion to generate $Pd(OCOCF_3)_2$,[13] which shows a higher reactivity due to the increased electrophilicity. Second, TFA promotes the protonation of the resulting palladium complex. Thus, the resulting reactive palladium species ($^+$PdL) coordinates with the triple bond to induce intramolecular electrophilic aromatic substitution, and then a furanocoumaryl palladium complex is

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formed. The resulting furanocoumaryl palladium complex undergoes protonation by TFA to give furocoumarin **6**, and the palladium species ($^{+}$PdL) is regenerated.

In summary, we have demonstrated a highly efficient synthesis of furocoumarins by palladium-catalyzed intramolecular hydroarylation of 4-benzofuranyl alkynoates. The 4-benzofuranyl alkynoates are readily prepared by condensation of easily available 4-hydroxybenzofurans and alkynoic acids. Because of the simplicity of the process and the high yield of the product, this procedure is the best method for angelicin derivatives.

EXPERIMENTAL SECTION

Synthesis of 2-Iodoresorcinol.[14] To resorcinol (1.10 g, 10 mmol) were added water (10 mL), iodine (2.72 g, 10.7 mmol), and $NaHCO_3$ (0.94 g, 11.2 mmol), and the mixture was stirred at room temperature for 20 min. After the reaction, the remaining iodine was quenched with aqueous sodium sulfite. The product was extracted with ether, concentrated under reduced pressure, and purified by column chromatography on silica gel with CH_2Cl_2/hexane as eluent. 2-Iodoresorcinol was obtained in 70% yield (1.65 g) as a colorless solid: mp 101.2−104.0 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.49(d, J = 8.1 Hz, 2H), 7.02 (t, J = 8.1 Hz, 1H), 8.73 (s, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 75.3, 106.9, 130.2, 158.4.

Synthesis of 4-Hydroxybenzofuran (2a).[12a] A mixture of 6,7-dihydro-1-benzofuran-4(5*H*)-one (**1**, 4.71 g, 34.6 mmol), Pd−C (3.1 g), 1-dodecene (10 mL), and decalin (60 mL) was refluxed for 24 h with stirring under argon atmosphere. After the reaction, ethanol was added to the reaction mixture, and the resulting precipitates were filtered off. The filtrate was concentrated under reduced pressure and submitted to column chromatography on silica gel. Elution with hexane/EtOAc gave 2.78 g (60%) of **2a** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 1H), 6.60−6.63 (m, 1H), 6.83 (d, J = 1.8 Hz, 1H), 7.11−7.12 (m, 2H), 7.51−7.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.3, 104.5, 107.9, 116.7, 124.9, 143.7, 149.1, 156.6.

Synthesis of Substituted 4-Hydroxybenzofurans 2. A mixture of 2-iodoresorcinol (**3**, 2.36 g, 10 mmol), 1-octyne or phenylacetylene (20 mmol), $PdCl_2(PPh_3)_2$ (246 mg, 0.35 mmol), CuI (100 mg, 0.525 mmol), Et_3N (20 mL), and DMF (25 mL) was heated at 60 °C with stirring under argon atmosphere. After reacting for 12 h, the reaction mixture was slightly acidified with diluted HCl and extracted with ether. The ethereal solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was submitted to column chromatography on silica gel. The product was isolated by elution with CH_2Cl_2/hexane.

2-Hexyl-4-hydroxybenzofuran (2b). The product was obtained in 50% yield as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.26−1.38 (m, 6H), 1.67−1.77 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 5.19 (s, 1H), 6.42 (s, 1H), 6.56−6.59 (m, 1H), 7.03−7.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 27.6, 28.4, 28.8, 31.6, 98.2, 104.1, 107.7, 117.9, 123.7, 148.4, 156.3, 158.7; HRMS (EI) calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1306.

4-Hydroxy-2-phenylbenzofuran (2c). The product was obtained in 60% yield as colorless crystals: mp 165−167 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.71−6.74 (m, 1H), 7.08−7.18 (m, 2H), 7.34−7.39 (m, 2H), 7.44- 7.50 (m, 2H), 7.90−7.93 (m, 2H), 8.91 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 99.7, 103.6, 108.8, 119.4, 125.3, 126.2, 129.2, 129.7, 131.3, 152.0, 154.9, 157.3. Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.83; H, 4.80.

Synthesis of 4-Benzofuranyl Alkynoates 5. A mixture of 4-hydroxybenzofuran **2** (3 mmol), alkynoic acid **4** (3 mmol), and DMAP (37 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C for 5 min. To the mixture was added DCC (619 mg, 3 mmol), stirred at 0 °C for 5 min, and then stirred at room temperature for 3 h. The resulting precipitates were filtered off, and the filtrate was treated with diluted HCl. The product was extracted with CH_2Cl_2, concentrated under reduced pressure, and isolated by column chromatography on silica gel with CH_2Cl_2/hexane as eluent.

4-Benzofuranyl Propiolate (5a). The product was obtained in 66% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 1H), 6.70−6.71 (m, 1H), 7.05−7.09 (m, 1H), 7.25−7.31 (m, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.9, 77.2, 103.6, 110.0, 114.9, 120.7, 124.4, 142.6, 145.3, 150.3, 156.1; HRMS (EI) calcd for $C_{11}H_6O_3$ 186.0317, found 186.0318.

4-Benzofuranyl Butynoate (5b). The product was obtained in 74% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 6.71 (s, 1H), 7.04 (d, J = 8 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6, 71.8, 88.4, 103.7, 109.6, 115.0, 120.9, 124.3, 142.9, 145.1, 151.2, 156.1; HRMS (EI) calcd for $C_{12}H_8O_3$ 200.0473, found 200.0470.

4-Benzofuranyl Octynoate (5c). The product was obtained in 84% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.30−1.43 (m, 4H), 1.58−1.65 (m, 2H), 2.40 (t, J = 7.2 Hz, 2H), 6.72−6.73 (m, 1H), 7.03−7.06 (m, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.40−7.43 (m, 1H), 7.60 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 13.7, 18.6, 21.9, 27.0, 30.8, 72.5, 92.6, 103.7, 109.6, 115.0, 120.9, 124.3, 143.0, 145.0, 151.3, 156.1; HRMS (EI) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1102.

4-Benzofuranyl Phenylpropiolate (5d). The product was obtained in 80% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, J = 1.2 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.28−7.33 (m, 1H), 7.37−7.51 (m, 4H), 7.61−7.67 (m, 3H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 80.0, 88.9, 103.7, 109.7, 115.0, 119.0, 120.9, 124.4, 128.5, 130.9, 133.0, 143.0, 145.1, 151.6, 156.1; HRMS (EI) calcd for $C_{17}H_{10}O_3$ 262.0630, found 262.0634.

2-Hexylbenzofuran-4-yl Propiolate (5e). The product was obtained in 62% yield as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77−0.81 (m, 3H), 1.16−1.30 (m, 6H), 1.58−1.67 (m, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.98 (s, 1H), 6.22 (s, 1H), 6.89 (d, J = 8.1 Hz, 1H), 7.05−7.11 (m, 1H), 7.21−7.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 27.4, 28.4, 28.8, 31.5, 74.2, 76.8, 98.9, 109.4, 114.6, 122.2, 123.2 141.8, 150.4, 155.9, 160.5; HRMS (EI) calcd for $C_{17}H_{18}O_3$ 270.1256, found 270.1257.

2-Hexylbenzofuran-4-yl Butynoate (5f). The product was obtained in 74% yield as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, J = 6.9 Hz, 3H), 1.17−1.32 (m, 6H), 1.61−1.66 (m, 2H), 1.96 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H), 6.23 (d, J = 0.6 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8, 13.9, 22.4, 27.4, 28.3, 28.8, 31.4, 72.0, 88.0, 98.9, 109.0, 114.7, 122.3, 123.1, 142.1, 151.3, 155.9, 160.3; HRMS (EI) calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1414.

2-Hexylbenzofuran-4-yl Octynoate (5g). The product was obtained in 75% yield as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−0.85 (m, 6H), 1.17−1.35 (m, 10H), 1.47−1.57 (m, 2H), 1.59−1.68 (m, 2H), 2.26−2.31 (m, 2H), 2.64 (t, J = 8.1 Hz, 2H), 6.24 (s, 1H), 6.88 (d, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.21 (d, J = 8. Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.0, 18.7, 22.0, 22.5, 27.1, 27.4, 28.3, 28.8, 30.9, 31.5, 72.6, 92.4, 99.0, 109.0, 114.7, 122.4, 123.1, 142.2, 151.5, 155.9, 160.2; HRMS (EI) calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2039.

2-Hexylbenzofuran-4-yl Phenylpropiolate (5h). The product was obtained in 71% yield as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (t, J = 6.9 Hz, 3H), 1.14−1.26 (m, 6H), 1.53−1.63 (m, 2H), 2.59 (t, J = 7.5 Hz, 2H), 6.25 (d, J = 0.9 Hz, 1H), 6.89−6.92 (m, 1H), 7.05 (t, J = 8.1 Hz, 1H), 7.18−7.32 (m, 4H), 7.45−7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 27.4, 28.4, 28.8, 31.5, 80.2, 88.8, 99.0, 109.2, 114.8, 119.3, 122.4, 123.2, 128.6, 131.0, 133.1, 142.2, 151.8, 155.9, 160.4; HRMS (EI) calcd for $C_{23}H_{22}O_3$ 346.1569, found 346.1570.

2-Phenylbenzofuran-4-yl Propiolate (5i). The product was obtained in 69% yield as white crystals: mp 88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 1H, CH), 6.94 (d, J = 0.9 Hz, 1H), 7.04−7.07 (m, 1H), 7.24−7.46 (m, 5H), 7.83−7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.2, 76.6, 98.2, 109.8, 115.2, 122.6, 124.3, 125.2, 128.8, 129.0, 129.8, 142.4, 150.4, 156.9, 156.6. Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.59; H, 3.94.

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2-Phenylbenzofuran-4-yl Butynoate (5j). The product was obtained in 90% yield as white crystals: mp 89−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 6.94 (d, J = 0.9 Hz, 1H), 7.02−7.05 (m, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.28−7.42 (m, 5H), 7.80−7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8, 71.9, 88.5, 98.3, 109.4, 115.2, 122.7, 124.3, 125.0, 128.7, 128.9, 129.8, 142.6, 151.3, 155.9, 156.3. Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.19; H, 4.37.

2-Phenylbenzofuran-4-yl Octynoate (5k). The product was obtained in 90% yield as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.1 Hz, 3H), 1.24−1.43 (m, 4H), 1.54−1.64 (m, 2H), 2.37 (t, J = 7.1 Hz, 2H), 6.95 (d, J = 0.9 Hz, 1H), 7.02−7.05 (m, 1H), 7.21−7.42 (m, 5H), 7.80−7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 18.7, 22.0, 27.0, 30.9, 72.5, 92.73, 98.3, 109.4, 115.2, 122.7, 124.2, 125.0, 128.7, 128.8, 129.7, 142.7, 151.4, 155.9, 156.2. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.51; H, 6.13.

2-Phenylbenzofuran-4-yl Phenylpropiolate (5l). The product was obtained in 98% yield as white crystals: mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, J = 0.6 Hz, 1H), 7.00−7.03 (m, 1H), 7.14−7.43 (m, 8H), 7.55−7.58 (m, 2H), 7.75−7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.2, 89.1, 98.4, 109.6, 115.3, 119.2, 122.8, 124.4, 125.1, 128.7, 128.8, 128.9, 129.9, 131.1, 133.2, 142.8, 151.8, 156.1, 156.4; HRMS (EI) calcd for $C_{23}H_{14}O_3$ 338.0943, found 338.0945.

Synthesis of Furocoumarins 6 by Pd-Catalyzed Intramolecular Hydroarylation. A mixture of alkynoate **5** (1 mmol) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) was stirred at 30 °C for 5 h. In the case of **6i** (R^1 = Ph, R^2 = H), the mixture was stirred for 24 h. The reaction mixture was neutralized with $NaHCO_3$, extracted with CH_2Cl_2, and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel using CH_2Cl_2/hexane as eluent.

2*H*-Furo[2,3-*h*]-1-benzopyran-2-one (6a). The product was obtained in 80% yield as white crystals: mp 135−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 9.6 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.8 (d, J = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.0, 108.7, 113.5, 114.1, 116.9, 123.8, 144.4, 145.8, 148.5, 157.3, 160.7. Anal. Calcd for $C_{11}H_6O_3$: C, 70.97; H, 3.25. Found: C, 70.57; H, 3.29.

4-Methyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6b). The product was obtained in 84% yield as white crystals: mp 186−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, J = 1.2 Hz, 3H), 6.24 (q, J = 1.2 Hz, 1H), 7.11 (dd, J = 0.9, 2.4 Hz, 1H), 7.41 (dd, J = 0.9, 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 104.2, 108.3, 112.7, 114.4, 116.8, 120.4, 145.7, 147.8, 153.5, 157.1, 160.7. Anal. Calcd for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 72.09; H, 4.12.

4-Pentyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6c). The product was obtained in 80% yield as white solid: mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 6.9 Hz, 3H), 1.41−1.43 (m, 4H), 1.68−1.79 (m, 2H), 2.80 (t, J = 7.7 Hz, 2H), 6.24 (s, 1H), 7.12 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.3, 28.0, 31.5, 32.4, 104.3, 108.2, 111.5, 113.8, 117.0, 120.2, 145.6, 148.1, 157.0, 157.5, 161.0. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.87; H, 6.33.

4-Phenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6d). The product was obtained in 95% yield as white crystals: mp 165−166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 7.15 (dd, J = 0.6, 2.4 Hz, 1H), 7.28−7.38 (m, 2H), 7.43−7.55 (m, 5H), 7.68 (d, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 108.2, 112.7, 113.4, 117.0, 122.9, 128.3, 128.7, 129.5, 135.8, 145.7, 148.4, 156.7, 157.2, 160.6. Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.84; H, 3.93.

8-Hexyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6e). The product was obtained in 70% yield as yellowish crystals: mp 62−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−0.95 (m, 3H), 1.32−1.40 (m, 6H), 1.67−1.81 (m, 2H), 2.79 (t, J = 7.5 Hz, 2H), 6.34 (d, J = 9.6 Hz, 1H), 6.71 (s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 27.4, 28.3, 28.8, 31.5, 99.1, 108.2, 113.3, 113.7, 118.2, 122.5, 144.6, 147.7, 157.0, 160.9, 161.1. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.53; H, 6.69.

8-Hexyl-4-methyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6f). The product was obtained in 71% yield as white crystals: mp 66−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87−0.92 (m, 3H), 1.29−1.42 (m, 6H), 1.69−1.79 (m, 2H), 2.42 (d, J = 1.2 Hz, 3H), 2.77 (t, J = 7.2 Hz, 2H), 6.16 (d, J = 1.2 H, 1H), 6.65 (d, J = 0.9 Hz, 1H), 7.26 (dd, J = 0.9, 8.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.1, 22.4, 27.3, 28.2, 28.6, 31.3, 99.0, 107.5, 112.2, 114.1, 117.9, 119.0, 146.9, 153.4, 156.7, 160.7, 160.8. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.90; H, 7.08.

8-Hexyl-4-pentyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6g). The product was obtained in 86% yield as white crystals: mp 61−62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76−0.83 (m, 6H), 1.18−1.33 (m, 10H), 1.55−1.65 (m, 4H), 2.60−2.68 (m, 4H), 6.05 (s, 1H), 6.56 (d, J = 0.9 Hz, 1H), 7.17 (dd, J = 0.9, 8.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.7, 22.1, 22.3, 27.2, 27.7, 28.0, 28.5, 31.2, 31.3, 32.0, 99.0, 107.4, 110.9, 113.3, 118.0, 118.7, 147.0, 156.4, 157.2, 160.6, 160.7. Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.69; H, 8.28.

8-Hexyl-4-phenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6h). The product was obtained in 83% yield as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3H), 1.33−1.41 (m, 6H), 1.72−1.82 (m, 2H), 2.81 (t, J = 7.4 Hz, 2H), 6.31 (s, 1H), 6.78 (s, 1H), 7.28 (s, 2H), 7.45−7.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.3, 27.2, 28.1, 28.6, 31.2, 99.1, 107.5, 112.3, 113.1, 118.2, 121.5, 128.2, 128.5, 129.3, 135.8, 147.5, 156.6, 156.7, 160.6, 160.9; HRMS (EI) calcd for $C_{23}H_{22}O_3$ 346.1569, found 346.1572.

8-Phenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6i). The product was obtained in 74% yield as white crystals: mp 220−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (d, J = 9.6 Hz, 1H), 7.26−7.49 (m, 6H), 7.77 (d, J = 9.6 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.2, 108.5, 113.7, 114.1, 118.7, 123.6, 125.1, 128.9, 129.2, 129.5, 144.4, 148.1, 157.0, 157.2, 160.8. Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.56; H, 3.95.

4-Methyl-8-phenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6j). The product was obtained in 80% yield as white crystals: mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (d, J = 1.2 Hz, 1H), 6.17 (d, J = 1.2 Hz, 1H), 7.19 (s, 1H), 7.33−7.45 (m, 5H), 7.75−7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 98.2, 107.9, 112.6, 114.5, 118.4, 120.1, 124.8, 128.8, 129.0, 129.3, 147.3, 153.4, 156.7, 156.8, 169.6. Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.32; H, 4.15.

4-Pentyl-8-phenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6k). The product was obtained in 87% yield as white crystals: mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 6.9 Hz, 3H), 1.36−1.49 (m, 4H), 1.69−1.79 (m, 2H), 2.82 (t, J = 7.7 Hz, 2H), 6.27 (s, 1H), 7.37−7.55 (m, 6H), 7. 88 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 27.8, 31.5, 32.3, 98.4, 107.9, 111.4, 113.9, 118.7, 119.9, 124.9, 128.8, 129.0, 129.4, 147.6, 156.6, 156.8, 157.4, 160.9. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.25; H, 6.14.

4,8-Diphenyl-2*H*-furo[2,3-*h*]-1-benzopyran-2-one (6l). The product was obtained in 81% yield as white crystals: mp 205−206 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1H), 7.37−7.56 (m, 11H), 7.86−7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.5, 108.0, 112.9, 113.8, 118.9, 122.8, 125.0, 128.4, 128.8, 128.9, 129.2, 129.5, 129.6, 135.9, 148.2, 156.8, 157.0, 157.1, 160.8. Anal. Calcd for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.81; H, 4.11.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of **2a−c**, **3**, **5a−l**, and **6a−l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) For recent reviews, see: (a) Santana, L.; Uriarte, E.; Roleira, F.; Milhazes, N.; Borges, F. *Curr. Med. Chem.* **2004**, *11*, 3239−61. (b) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887−916. (c) Caffieri, S. *Photochem. Photobiol. Sci.* **2002**, *1*, 149−157. (d) Kitamura, N.; Kohtani, S.; Nakagaki, R. *J. Photochem. Photobiol., C: Photochem. Rev.* **2005**, *6*, 168−185. (e) Gambari, R.; Lampronti, I.; Bianchi, N.; Zuccato, C.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Top. Heterocycl. Chem.* **2007**, *9*, 265−276. (f) Conforti, F.; Marrelli, M.; Menichini, F.; Bonesi, M.; Statti, G.; Provenzano, E.; Menichini, F. *Curr. Drug Ther.* **2009**, *4*, 38−58. (g) Traven, V. F. *Molecules* **2004**, *9*, 50−66. (h) Shim, S. C.; Jeon, Y. H.; Kim, D. W.; Han, G. S.; Yoo, D. J. *J. Photosci.* **1995**, *2*, 37−45. (i) Gasparro, F. P. *Photochem. Photobiol.* **1996**, *63*, 553−557.

(2) Gould, J. W.; Mercurio, M. G.; Elmets, C. A. *J. Am. Acad. Dermatol.* **1995**, *33*, 571−573.

(3) Stern, R. S. *Lancet* **1994**, *344*, 1644−1645.

(4) (a) Dall'Acqua, F.; Vedaldi, D.; Caffieri, S.; Guiotto, A.; Bordin, F.; Rodighiero, P. *Natl. Cancer Inst. Monogr.* **1984**, *66*, 55−60. (b) Carlassare, F.; Baccichetti, F.; Guiotto, A.; Rodighiero, P.; Gia, O.; Capozzi, A.; Pastorine, G.; Bordin, F. *J. Photochem. Photobiol., B: Biol.* **1990**, *5*, 25−39. (c) Bordin, F.; Dall'Acqua, F.; Guiotto, A. *Pharmacol. Ther.* **1991**, *52*, 331−363.

(5) (a) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Tetrahedron* **2002**, *58*, 4859−4863. (b) Clarke, D. J.; Robinson, R. S. *Tetrahedron* **2002**, *58*, 2831−2837. (c) Black, M.; Cadogan, J. I. G.; McNab, H.; MacPherson, A. D.; Roddam, V. P.; Smith, C.; Swenson, H. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2483−2493. (d) Lee, Y. R. *Tetrahedron* **1995**, *51*, 3087−3094. (e) Wulff, W. D.; McCallum, J. S.; Kunng, F.-A. *J. Am. Chem. Soc.* **1988**, *110*, 7419−7434.

(6) (a) Desai, S. M.; Trivedi, K. N. *Indian J. Chem., Sect. B* **1985**, *24B*, 47−50. (b) Kawase, Y.; Yamaguchi, S.; Aoyama, K.; Matsuda, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1907−1908.

(7) (a) Hishmat, O. H.; Abd-El-Rahman, A. H.; Khalil, K. M. A.; Moawad, M. I.; Atalla, M. M. *J. Pharm. Sci.* **1982**, *71*, 1046−1049. (b) Soman, S. S.; Trivedi, K. N. *J. Indian Chem., Soc.* **1990**, *67*, 997−999. (c) Soman, S. S.; Trivedi, K. N. *Indian J. Chem., Sect. B* **1994**, *33B*, 1075−1079.

(8) Ahluwalia, V. K.; Gupta, R.; Grover, M.; Mukherjee, I.; Khanduri, C. H. *Indian J. Chem., Sect. B* **1988**, *27B*, 1138−1139.

(9) (a) Royer, R.; Renè, L.; Buisson, J. P.; Demerseman, P.; Averbeck, D. *Eur. J. Med. Chem.* **1978**, *13*, 213−218. (b) Ratiner, B. D.; Elia, L. P.; Otsuki, T. *Chem. Express* **1990**, *5*, 225−228. (c) Vettori, L. P.; Auzzi, G.; Papini, P.; Bruni, F. *Farmaco, Edizione Sci.* **1975**, *30*, 754−760.

(10) For reviews: (a) Nevado, C.; Echavarren, A. E. *Synthesis* **2005**, 167−182. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885−3903. (c) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42−64. (d) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403−424. (e) Kirsch, S. F. *Synthesis* **2008**, 3183−3204. (f) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111−1125. (g) Wang, X.; Zhou, L.; Lu., W. *Curr. Org. Chem.* **2010**, *14*, 289−307.

(11) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu., W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516−7522. (c) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669−3671. (d) Yoon, M. Y.; Kim, J. H.; Choi, D. S.; Shin, U. S.; Lee, J. Y.; Song, C. E. *Adv. Synth. Catal.* **2007**, *349*, 1725−1737.

(12) (a) Bodendiek, S. B.; Mahieux, C.; Hänsel, W.; Wulff, H. *Eur. J. Med. Chem.* **2009**, *44*, 1838−1852. (b) Kneen, G.; Maddocks, P. J. *Synth. Commun.* **1986**, *16*, 1635−1640.

(13) Marson, A.; Bart van Oort, A.; Mul, W. P. *Eur. J. Inorg. Chem.* **2002**, 3028−3031.

(14) Tsujiyama, S.-i.; Suzuki, K. *Org. Synth.* **2007**, *84*, 272−284. *Organic Syntheses*; Wiley: New York, 2009; Collect Vol. *XI*, pp 448−497.