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High-Pressure-Promoted Diels–Alder Approach to Biaryls: Application to the Synthesis of the Cannabinols Family

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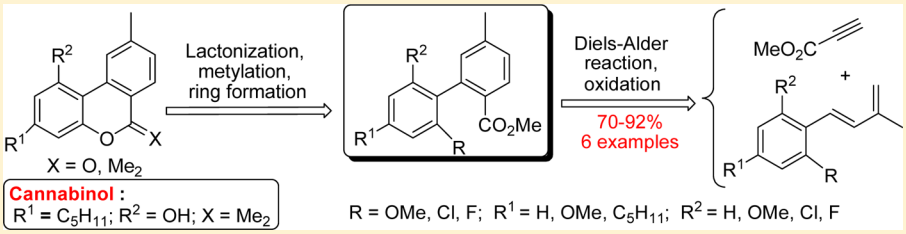
Supporting Information



ABSTRACT: Diels–Alder reactions of a range of 1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes with methyl propiolate carried out in a green ethanolic medium under 9 kbar pressure were investigated. The use of high pressure as activating method of the Diels–Alder reactions allows efficient and regioselective generation of a series of cyclohexadienylbenzene cycloadducts that are oxidized to the corresponding biaryls. The alkoxy/alkyl/halogen-substituted biaryls produced are useful precursors for accessing substituted *6H*-benzo[*c*]chromen-6-ones and the cannabinols family.

INTRODUCTION

Biaryls represent a key structural motif in a wide variety of natural products[1] and pharmacologically active drugs,[2] as well as in high-performance molecules like organic semiconductors, liquid crystals,[3] and chiral auxiliaries.[4] Thus, the construction of the biaryl structure continues to generate considerable synthetic attention. One of the main challenges in the construction of this structural motif involves the palladium-catalyzed, cross-coupling reaction of aryl halides with organometallics,[5] such as tin (Stille coupling),[6] boron derivatives (Suzuki–Miyaura coupling),[7] and to a lesser extent, organozinc (Negishi coupling), organomagnesium (Kumada coupling), and organosilicon (Hiyama) reagents.[8] However, documented reports of the significant cost of the necessary coupling partners (e.g., aryl halide or boronic acid) for traditional metal-mediated approaches to highly functionalized biaryls, and the limited availability of the aryl halides and/or aryl metal species, have made alternate strategies more attractive.[9,10] Furthermore, the methods reported are sometimes not attractive, as they can be environmentally unsafe because of harsh reaction conditions and toxic catalysts.[9] Thus, considering also the profound need to have this class of compounds as "ultra pure" material for modern electronic application (e.g., metals and residual halogens need to be in the low ppm to ppb levels), the development of a nonmetal-mediated method for the construction of biaryl compounds[11] is desiderable. Relatedly, high pressure technology could be a useful clean nondestructive activation mode because it can markedly improve both reaction yields and reaction selectivities (i.e., stereoselectivity, regioselectivity) of organic reactions (particularly, the Diels–Alder cycloadditions) under milder reaction conditions with no need for a metallic catalyst and/or high temperatures.[12] Furthermore, this technique is also energy-economical because the energy input is limited to the compression step at the onset of the reaction, in sharp contrast with a classical heating that triggers continuous energy consumption until completion.[12] Instead, the uncatalyzed synthesis of this class of compounds remains little investigated,[13] and to our knowledge, an energy-saving high-pressure[12] activation method for biaryls has never been reported.

Although the Diels–Alder reaction might represent an efficient method for the synthesis of functionalized biaryls, there are only a few synthetic approaches to biaryls in the literature that are based on the Diels–Alder reaction.[11,14] Recently, the Carter group[11] described a rapid and efficient synthesis of a wide range of tetra-ortho-substituted biaryl compounds utilizing the Diels–Alder reaction of phenylacetylenes as dienophiles with oxygenated dienes.

One particular attraction to the powerful Carter's strategy is the ability to construct biaryl compounds possessing four different atoms (N, Cl/Br, O and P) at the four ortho positions that would not be readily accessible from the traditional methods. However, because of the low reactivity of the alkyne triple bond as a dienophile, the cycloaddition reactions required harsh reaction conditions (80–155 °C), and they were only successful using phenylacetylenes that have an electron-withdrawing *ortho*-nitrophenyl moiety. This thus only allowed the access of nitro-substituted biaryl compounds, strongly limiting the flexibility of this approach.[11]

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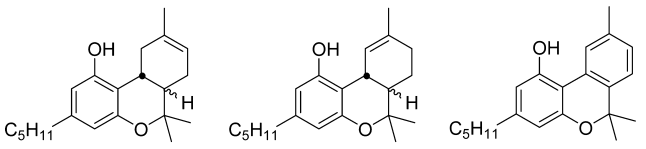
These results and the importance of this class of compounds as precursors for accessing complex polyaromatic systems (i.e., the polyphenilenes family) and broadly substituted natural products (i.e., the cannabinols family) prompted as to study competitive, environmentally safe routes that allow the synthesis of a wide range of broadly substituted biaryls. Recently, we reported a high-yielding and eco-friendly synthetic route to polysubstituted 6*H*-tetrahydro-benzo[*c*]chromene templates (i.e., the tetrahydro-cannabinols family),[15] which was based on high-pressure Diels–Alder reactions. We highlighted in our investigations the great benefit of using high pressure as an activating method in the Diels–Alder key step of the strategy, to access the *cis*- and *trans*-tetrahydrocannabinol (THC) families with excellent yields under milder and noncatalytic reaction conditions,[16] and in green solvents (e.g., ethanol and water) as reaction medium.[17] For example, using hydroxy-substituted 3-cyano-coumarins or alkoxy-benzylideneacetones as the dienophiles, we exploited this Diels–Alder approach for the synthesis of Δ^8-*cis*-THC and Δ^8-*trans*-THC **1** and their analogues.[16d] Instead, the Diels–Alder reactions of 1-(alkoxy/alkyl-substituted phenyl)buta-1,3-dienes with methyl vinyl ketone or methyl acrylate opened a route to Δ^9-*cis*-THC and Δ^9-*trans*-THC **2** and their analogues.[16e] Together with Δ^8-THC **1** and Δ^9-THC **2**, another prominent member of the natural cannabinoids family[18] is cannabinol **3** (Figure 1). This deceptively simple natural product continues to focus the attention of synthetic chemists, and new approaches to this continue to appear.[19]



Δ^8-*cis*-THC, β-H (**1a**) Δ^9-*cis*-THC, β-H (**2a**) Cannabinol (**3**)

Δ^8-*trans*-THC, α-H (**1b**) Δ^9-*trans*-THC, α-H (**2b**)

Figure 1. Tetrahydrocannabinols (THC) and cannabinol.

Thus, in connection with our ongoing studies, as a flexible method for accessing cannabinol **3** and its analogues, we envisioned a strategy based on the Diels–Alder reaction of substituted 1-aryl-3-methyl-1,3-butadienes with methyl propiolate (**5**) (Scheme 1). This strategy allows uncatalyzed access to a wide range of ortho-substituted biaryls **7**, which are useful precursors for accessing 6*H*-benzo[*c*]chromen-6-ones **8** and cannabinols **3** (Scheme 1).

In this report, we present (i) a study of the Diels–Alder reaction of 3-methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes **4** with methyl propiolate (**5**); (ii) oxidation of the cycloadducts **6** into their corresponding ortho-substituted biaryls **7**; and (iii) application of this approach to the synthesis of important molecules, such as 6*H*-benzo[*c*]-chromen-6-ones **8** and cannabinol **3** (Scheme 1).

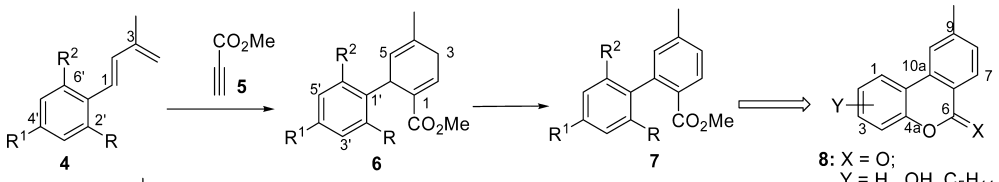
RESULTS AND DISCUSSION

3-Methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes Synthesis. The synthesis of 1,3-butadienes **4a–d** was reported previously;[16d,e] according to the same procedure, the novel dienes **4e** and **4f** were synthesized in 77 and 70% yields, respectively, using the Wittig reaction[20] of the corresponding (*E*)-benzylideneacetones.[16d]

Diels–Alder Reactions of 3-Methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes 4 with Methyl Propiolate 5 under Atmospheric and High-Pressure Conditions. The Diels–Alder reaction between **4** and **5** is the key step of our strategy, as this allows access to a wide range of alkoxy/alkyl/halogen-substituted biaryls **7**, which are useful precursors for accessing substituted 6*H*-benzo[*c*]-chromen-6-ones **8** and cannabinol **3** (see Scheme 1). There are relatively few examples of Diels–Alder reactions of 1-aryl-1,3-butadienes in the literature,[21] and examples of cycloaddition reactions of dienes of type **4** with methyl propiolate (**5**) are particularly rare. For example, it has been reported that 4-aryl-2-silyloxybuta-1,3-dienes react with methyl propiolate (**5**) and other electron-deficient alkynes under thermal conditions (100 °C, for 20 h, in benzene), to give the adducts in low to moderate yields (47–64%) after acidic workup.[22] However, to the best of our knowledge, no examples of Diels–Alder reactions between 3-methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)-1,3-butadienes **4** and methyl propiolate (**5**) have been reported. Thus, it became clear that improving the chemical and environmental efficiency of the Diels–Alder reaction of **4** with **5** would not be a trivial task, and this was our first aim.

First, the Diels–Alder reactions of (*E*)-3-methyl-1-(2′-methoxyphenyl)buta-1,3-diene (**4a**) with methyl propiolate (**5**) were chosen as representative, and they were investigated

Scheme 1. Diels–Alder Approach to Biaryls 7 and Its Application to the Synthesis of 6*H*-Benzo[*c*]chromen-6-ones 8 and Cannabinols 3



4, 6, 7	a	b	c	d	e	f
R	OMe	OMe	OMe	OMe	Cl	Cl
R^1	H	OMe	H	C_5H_{11}	H	H
R^2	H	H	OMe	OMe	Cl	F

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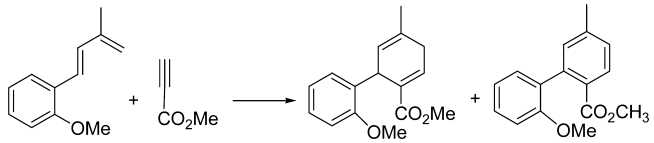
Table 1. Diels–Alder Reactions of (*E*)-3-Methyl-1-(2′-methoxyphenyl)buta-1,3-diene (4a) with Methyl Propiolate (5) under Atmospheric and High-Pressure Conditions

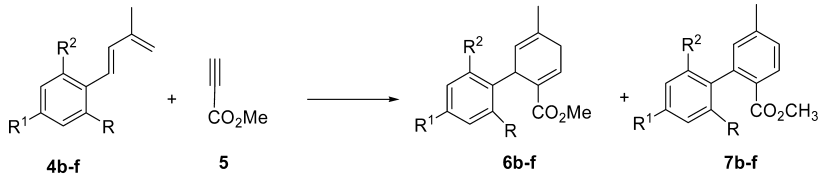


4a 5 6a 7a

entry	medium[a,b]	time (h)	pressure (bar)	temperature (°C)	products[c]	yield[d] (%)
1	H_2O	24	1	100	**6a**/**7a** (4:1)	18, (27)[e]
2	H_2O	150	1	50	**6a**/**7a** (1.5:1)	40, (65)[e]
3	EtOH	100	1	80	**6a**/**7a** (19:1)	44, (50)[e]
4	EtOH/H_2O (1:1)	56	1	80	**6a**/**7a** (2.1:1)	22, (41)[e]
5	PhMe	27	1	110	**6a**/**7a** (9:1)	31, (38)[e]
6	CH_2Cl_2[f]	1	1	−10		
7	CH_2Cl_2[g]	5	1	−10		
8	SolFC[h]	15	1	80	**6a**/**7a** (1:0)	48
9	CH_2Cl_2	40	9×10^3	35	**6a**/**7a** (1:0)	84
10	EtOH	40	9×10^3	35	**6a**/**7a** (1:0)	91

[a]Diene concentration, 0.1 M. [b]2 equiv of **5** were used. [c]Ratio determined by gas chromatography and/or ^{1}H NMR analysis. [d]Yield of purified cycloadduct **6a**. [e]Combined isolated yields of compounds **6a** and **7a**. [f]In the presence of 0.5 equiv of $EtAlCl_2$. [g]In the presence of 0.5 equiv of $HfCl_4$·2THF. [h]Performed in a sealed steel reactor using 6 equiv of **5**.

Table 2. Diels–Alder Reactions of (*E*)-3-Methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes 4b–f with Methyl Propiolate (5) under Atmospheric and High-Pressure Conditions



4b-f 5 6b-f 7b-f

	b	c	d	e	f
R	OMe	OMe	OMe	Cl	Cl
R^1	OMe	H	C_5H_{11}	H	H
R^2	H	OMe	OMe	Cl	F

entry	diene[a,b]	medium	time (h)	pressure (bar)	temperature (°C)	products[c]	yield[d] (%)
1	**4b**	H_2O	30	1	100	**6b**/**7b** (9:1)	23, (30)[e]
2	**4b**	H_2O	95	1	50	**6b**/**7b** (1.5:1)	39, (55)[e]
3	**4b**	EtOH	100	1	80	**6b**/**7b** (9:1)	50, (70)[e]
4	**4b**	PhMe	32	1	110	**6b**/**7b** (49:1)	30
5	**4b**	SolFC[f]	4	1	80	**6b**/**7b** (1:0)	43
6	**4b**	CH_2Cl_2	44	9×10^3	40	**6b**/**7b** (32:1)	76
7	**4b**	EtOH	44	9×10^3	40	**6b**/**7b** (49:1)	85
8	**4c**	EtOH	120	1	80	**6c**/**7c** (3:1)	43, (75)[e]
9	**4c**	CH_2Cl_2	44	9×10^3	40	**6c**/**7c** (49:1)	90
10	**4c**	EtOH	44	9×10^3	40	**6c**/**7c** (19:1)	92
11	**4d**	EtOH	120	1	80	**6d**/**7d** (3.2:1)	45, (73)[e]
12	**4d**	CH_2Cl_2	48	9×10^3	40	**6d**/**7d** (19:1)	77
13	**4d**	EtOH	48	9×10^3	40	**6d**/**7d** (24:1)	83
14	**4e**	EtOH	120	1	80	**6e**/**7e** (4:1)	37, (45)[e]
15	**4e**	CH_2Cl_2	48	9×10^3	45	**6e**/**7e** (19:1)	60
16	**4e**	EtOH	48	9×10^3	45	**6e**/**7e** (32:1)	70
17	**4f**	EtOH	120	1	80	**6f**/**7f** (4.9:1)	27, (40)[e]
18	**4f**	CH_2Cl_2	52	9×10^3	45	**6f**/**7f** (9:1)	65
19	**4f**	EtOH	52	9×10^3	45	**6f**/**7f** (16:1)	71

[a]Diene concentration, 0.1 M. [b]2 equiv of **5** were used. [c]Ratio determined by gas chromatography and/or ^{1}H NMR analysis. [d]Yield of purified cycloadduct **6**. [e]Combined isolated yields of compounds **6** and **7**. [f]Performed in a sealed steel reactor using 6 equiv of **5**.

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under various atmospheric and high-pressure conditions, in methylene chloride, toluene and in green solvents (e.g., ethanol and water) as reaction medium,[17] and under solvent free conditions, to search for high-yielding and eco-friendly conditions for these transformations. All the Diels–Alder reactions were carried out in the presence of a few crystals of hydroquinone as radical scavenger, in order to prevent the diene polymerization.[16] The results of this optimization study are summarized in Table 1.

Under atmospheric (1 bar) or high-pressure conditions (9×10^3 bar), the cycloadditions of **4a** with **5** were always totally regioselective.

When the cycloaddition of diene **4a** with **5** was performed at normal pressure and high temperature (50–110 °C) in toluene, water and ethanol, this always led to mixtures of cycloadduct **6a** and the biaryl product **7a**, which was derived from **6a** by the dehydrogenation reaction[23] (Table 1, entries 1–5). In water, at 100 °C and at 50 °C, mixtures of the cycloadduct **6a** and the aromatic product **7a** were obtained in low yields in the ratios of 4:1 and 1.5:1, respectively (Table 1, entries 1, 2); separation by chromatography on silica gel led to pure cycloadducts **6a** in 18 and 40% yields, respectively.

Under ambient pressure in ethanol and toluene solutions, and under solvent free conditions, the cycloadditions of **4a** with **5** were more selective, producing mixtures of **6a**/**7a** in the ratios of 19:1, 9:1 and 1:0, respectively, although they again gave low yields of the isolated cycloadduct **6a** (31–48%) (Table 1, entries 3, 5, 8). However, attempted cycloadditions between **4a** and **5** with conventional and mild Lewis acids, such as $EtAlCl_2$ and $HfCl_4 \cdot 2THF$, at low temperature (−10 °C) produced complex mixtures in which compounds **6a** and **7a** were not detected at all (Table 1, entries 6, 7).

Thus, on the basis of our experience in the high-pressure field,[12e,g,16a–e] and in view of the excellent results achieved recently in our laboratory using high pressure as an activation method for the Diels–Alder reactions of diene **4a**,[16e] we studied the cycloaddition of **4a** with methyl propiolate (**5**) under high-pressure conditions.

Accordingly, cycloadduct **6a** was obtained with total selectivity and in high isolated yield (84%) when a solution of **4a** and methyl propiolate (**5**) in methylene chloride was treated for 35 h under 9×10^3 bar pressure at low temperature (35 °C). Changing the solvent from methylene chloride to ethanol improved the yield to 91%, again at reduced temperature (35 °C) (Table 1, entries 9, 10).

This study was then extended to the Diels–Alder reactions of other 3-methyl-1-(alkoxy/alkyl/halogen-substituted phenyl)-buta-1,3-dienes **4b–f** with methyl propiolate (**5**), to determine the flexibility of this approach to biaryls and the cannabinols family. The results of the optimized thermal and high-pressure reaction conditions are reported in Table 2.

As with **4a**, the [4 + 2] cycloadditions reactions of dienes **4b–f** with **5** carried out under normal and high-pressure conditions were always totally regioselective (Table 2), showing to proceed exclusively to [1,3] adducts.[24] This regiochemical bias was expected because it is the normal path in the Diels–Alder reactions of electron-rich 1,3-substituted-1,3-dienes with electron–deficient alkenes and alkynes, in accord with frontier molecular orbital theory.[24] Thus, for example, this regiochemical bias has been maintained for the reactions of 2-cyclohexenones with 2-methyl-1,3-pentadiene,[24] for those of 4-aryl-2-silyloxybuta-1,3-dienes with methyl propiolate,[22] and for all the cycloadditions reactions, studied by Carter,[11] between nitrophenyl-alkynes and oxygenated dienes, where the strong directing ability of the *ortho*-nitrophenyl moiety in the alkyne is able to guide the regiochemistry of the cycloadditions even in the presence of additional electron-withdrawing groups.

At normal pressure (1 bar), heating at high temperatures (50–110 °C) for long reaction times (30–95 h), (*E*)-3-methyl-1-(2′, 4′-dimethoxyphenyl)buta-1,3-diene (**4b**) with **5** in water and in toluene solution led to mixtures of cycloadduct **6b** and biaryl **7b**, from which **6b** was isolated in low yields (23–39%) by column chromatography on silica gel (Table 2, entries 1, 2, 4). As with **4a**, the same reaction at ambient pressure under SolFC gave the cycloadduct **6b** selectively in a shorter reaction time (4 h), although the isolated yield of **6b** still remained unsatisfactory (43%) (Table 2, entry 5). At normal pressure, the best isolated yield (70%) of a 9:1 mixture of **6b**/**7b** was obtained when ethanol was used as the reaction medium, at 80 °C for 100 h (Table 2, entry 3). Similarly, the thermal cycloadditions of dienes **4c** and **4d** with **5** in ethanol as the reaction medium at 80 °C for 120 h provided mixtures of **6c**/**7c** and **6d**/**7d** in 75 and 73% yields, respectively (Table 2, entries 8, 11). Analogous to previous reports on the cycloadditions of dienes **4** with methyl vinyl ketone or methyl acrylate,[16e] the higher electron-donating character of the phenyl moiety of diene **4b–d** with respect to **4a** (due to the introduction of a second methoxy electron-donating-group) did not translate into higher yields at normal pressure.

The unsatisfactory results obtained under thermal conditions (low–moderate yields of mixtures **6**/**7**, at high reaction temperatures for long reaction times) prompted us to study the cyloaddition of dienes **4b–d** with **5** under hyperbaric conditions, to investigate more efficient and eco-friendly conditions for all of these transformations. Thus, as with diene **4a**, using hyperbaric conditions (9×10^3 bar), the cycloadditions of **4b–d** with **5** occurred in methylene chloride at low temperature (40 °C), to give the corresponding cycloadducts **6b–d** selectively in 76–90% isolated yields (Table 2, entries 6, 9, 12). When the reaction medium was changed from methylene chloride to ethanol under identical conditions, the same cycloadditions gave again slightly better isolated yields of the cycloadducts **6b–d** (83–92%) (Table 2, entries 7, 10, 13).

Next, we extended the study to halogenated dienes, such as 3-methyl-1-(2′,6′-dichlorophenyl)buta-1,3-diene (**4e**) and 3-methyl-1-(2′-chloro-6′-fluoro-phenyl)buta-1,3-diene (**4f**), to explore the potential of our approach in the synthesis of halogenated biaryls, which are versatile precursors for the construction of complex molecules (e.g., organic semiconductors, natural products) (Table 2, entries 14–19). The cycloadditions of **4e** and **4f** with **5** under normal and high-pressure conditions always gave reduced yields with respect to dienes **4a–d**. This was the result of the deactivation of the dienic components **4e** and **4f** with respect to **4a–d**, due to the electron-withdrawing character of the two halogens in the phenyl moiety.

However, we observed that the 9×10^3 bar pressure cycloadditions of **4e** and **4f** with **5** in methylene chloride again proceeded well, selectively yielding cycloadducts **6e** and **6f** in reasonable isolated yields (60 and 65%, respectively) (Table 2, entries 15, 18). Furthermore, under the same reaction conditions, use of the ethanol as reaction medium improved the isolated yields of **6e** and **6f** to 70 and 71%, respectively (Table 2, entries 16, 19), thus showing that electron-

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withdrawing substituents on the phenyl moiety of the dienes were also well tolerated under high-pressure conditions.

Thus, the comparison across the data reported in Tables 1 and 2 indicates once again that high pressure was a very efficient and eco-friendly method of activation. Indeed, under 9 × 10^3 bar pressure in methylene chloride and in ethanol as reaction media we always obtained remarkably superior yields of purified cyclohexadienylbenzenes cycloadduct **6**, by cycloaddition of both electron-rich and electron-poor dienes. In addition, it should be noted that reaction temperatures and/or reaction times were reduced compared with the thermal conditions, and that the cycloadducts **6** were obtained selectively without any consistent contamination of the aromatic compounds **7** (Figure 2). This thus allowed for easily purified **6**, obtained in excellent yields, using short column chromatography on silica gel.

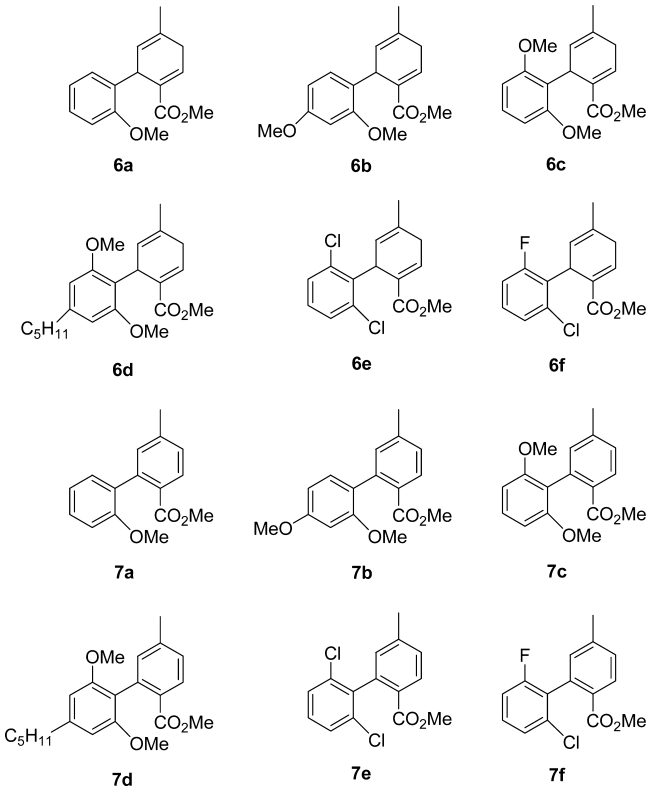
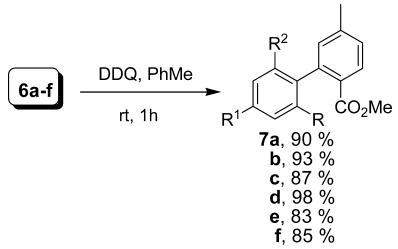


Figure 2. Diels–Alder cycloadducts **6** and biaryls **7**.

On the basis of the above findings (e.g., the presence of aromatized compounds **7** in the Diels–Alder reaction mixtures), it was expected that performing the Diels–Alder reactions between dienes **4** and dienophile **5** in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as an oxidant would directly favor the formation of aromatized products **7**. Despite our considerable efforts with a wide range of conditions (e.g., 1–10 mol equiv of DDQ at normal and high pressure), we were not able to effect a one-step Diels–Alder reaction/oxidation to biaryls **7a–f**. However, it is worth noting that the selective access to cyclohexadienylbenzenes cycloadduct **6** with two carbon–carbon double bonds with different chemical reactivities (one isolated and the other conjugated to the carbomethoxyl function) remains valuable and promising, as these compounds would be useful molecular scaffolds for additional functionalizations.

Application to the Synthesis of Ortho-Substituted Biaryls, 6*H*-Benzo[*c*]chromenones, and the Cannabinols Family. With the alkoxy/halogen-substituted cyclohexadienylbenzenes **6** in hand, we then turned our attention to the synthesis of biaryls **7**, and their conversion into the corresponding 6*H*-benzo[*c*]chromenones **8** and cannabinol **3**. Thus, aromatization of the pure cycloadducts **6a–f** (or the thermal Diels–Alder reaction mixtures **6**/**7**) with 1.5 mol equiv of DDQ in toluene solution at room temperature for 1 h resulted in the formation of the corresponding biaryls **7a–f** in excellent yields (Scheme 2).

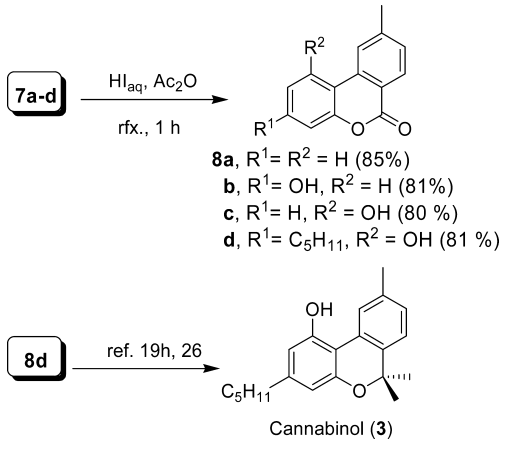
Scheme 2. Oxidation Reactions of Cycloadducts 6 to Biaryls 7



Then, with biaryl esters **7** in hand, it appeared useful to synthesize the corresponding 6*H*-benzo[*c*]chromen-6-one derivatives **8**, which are useful precursors of important molecules, such as the cannabinoids (i.e., cannabinol **3** and its analogues).

Thus, in agreement with the literature,[19h,26] demethylative lactonization of selected biaryls **7a–d** with 57% aqueous hydrogen iodide in acetic anhydride at reflux temperatures for 1 h gave the corresponding 6*H*-benzo[*c*]chromenones **8a** (85%),[25] **8b** (81%), **8c** (80%) and **8d** (81%)[19h,26] (Scheme 3). The synthesis of cannabinol **3** from chromenone **8d**

Scheme 3. Synthesis of 6*H*-Benzo[*c*]chromenones 8a–d and Cannabinol 3



through methylation with methylmagnesium iodide and the subsequent treatment of the crude product with *p*-TsOH has been described in the literature[19h,26] (Scheme 3).

Structural Analysis. The structures of all of the compounds were inferred from the analysis of their ^{1}H NMR and ^{13}C NMR spectra. The pertinent data are given in the Experimental Section. The (*E*)-configurations of the carbon–carbon double bond for the 3-methyl-1-(2′,6′-dichlorophenyl)-

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buta-1,3-diene (**4e**) and the 3-methyl-1-(2′-chloro,6′fluorophenyl)buta-1,3-diene (**4f**) were confirmed from the 16.5 Hz coupling constants measured for $^3J_{1,2}$.

All of the cycloadducts **6**, biaryl compounds **7**, and chromenones **8** prepared in this study were new compounds, except **8a**[25] and **8d**.[19h] The structures of all of the new compounds were assigned mainly on the basis of the comparison of their NMR data with those of similar compounds.[11a,25] The regiochemistry of the methyl group at C-4 of all of the compounds was confirmed by two-dimensional correlation spectroscopy, COSY, NOESY and HMQC experiments performed on **6d** and **7d**. Inspection of the ^{1}H−^{1}H and ^{1}H−^{13}C connectivities of compounds **6d** and **7d**, together with the presence of NOESY correlation peaks between the H-5, H-6 and 4-Me protons for **6d** and between the H-5 and 4-Me protons for **7d**, revealed the regiochemistry of the methyl group at C-4. Confirmation of the structures assigned to adducts **6** followed also from the conversion of **6a** and **6d** into the known chromenones **8a**[25] and **8d**,[19h,26] respectively.

CONCLUSIONS

A novel high-yielding strategy for the synthesis of a range of ortho-substituted biaryls was developed via the Diels−Alder reaction of 1-(alkoxy/alkyl/halogen-substituted phenyl)buta-1,3-dienes with methyl propiolate. The results described in this report show that activation by high pressure allows the [4 + 2] cycloaddition reactions to occur in excellent yields in a green ethanolic medium, under mild reaction temperatures, and without any metal catalyst, thus making this approach to the biaryls chemically efficient and environmentally friendly. Another particular attraction to this strategy is the efficient high pressure activation of the Diels−Alder reactions of 1-aryl-3-methyl-1,3-butadienes with both electron-donating (e.g., alkoxy/alkyl groups) and electron-withdrawing (e.g., halogen) substituents. This allows access to highly functionalized biaryl compounds that are not readily accessible from the traditional palladium-catalyzed cross-coupling reactions. This also provides an ideal complement to the powerful Diels−Alder approach of Carter et al.,[11] which remains useful for the synthesis of nitro-substituted biaryls.

Furthermore, in connection with our ongoing studies on the synthesis of Δ^8-THCs and Δ^9-THCs, this chemistry has been applied to the synthesis of a series of 6*H*-benzo[*c*]-chromenones, including the synthesis of the benzo[*c*]chromene natural product cannabinol. However, our proposed strategy for the construction of the 6*H*-benzo[*c*]chromenes-based *privileged*[15,16] structures can also be applied to the synthesis of other naturally occurring derivatives for use in bioassays or SAR studies. Extension of this methodology to the synthesis of other natural products is under active investigation.

EXPERIMENTAL SECTION

General Methods. All of the compounds were purified by column chromatography or by recrystallization. NMR spectra were recorded at 400 MHz for protons, 376.3 MHz for fluorine and 100.6 MHz for carbon nuclei. Gas chromatography−mass spectrometry (GC−MS) analysis was carried out using a 70 eV electron energy EI. GC analysis was performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter) on an "on column" injector system and with a flame ionization detector with hydrogen as the carrier gas. Infrared (IR) spectra were recorded with a FT-IR instrument, using $CHCl_3$ as solvent. Melting points are uncorrected. The aryl buta-1,3-dienes **4a**−**d**[16e] were prepared previously in our laboratory. Hyperbaric experiments were conducted on a Unipress LV30/16 apparatus. The synthesis of aryl buta-1,3-dienes **4e**,**f** was achieved according a previous procedure using the Wittig reaction of the corresponding (*E*)-benzylideneacetones.[16d,e,20] Dienophile **5** was purchased and used without further purification. The products were purified by column chromatography carried out on silica gel (230−400 mesh), using petroleum ether−ethyl acetate or petroleum ether−diethyl ether mixtures as eluent.

The complete NMR structure assignments for all of the new compounds were based on the relevant $J_{H,H}$ coupling constant values and on COSY, NOESY and HETCOR experiments.

2′,6′-Dichloro-1-((*E*)-3-methylbuta-1,3-dienyl)benzene (4e). Light yellow oil: 2.21 g, (13.5 mmol) 77% yield; IR ($CHCl_3$) 1560, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H, CH_3), 5.19 (s broad, 2H, Hs-4), 6.58 (d, 1H, J = 16.5 Hz, H-2), 6.92 (d, 1H, J = 16.5 Hz, H-1), 7.10 (t, 1H, J = 8.0 Hz, H-4′), 7.33 (d, 2H, J = 8.0 Hz, H-3′, H-5′); ^{13}C NMR ($CDCl_3$) δ18.2, 119.0, 122.7, 127.9, 128.4, 132.0, 134.4 (2C), 134.8, 139.8, 141.7; MS *m*/*e* (rel intensity) 70 (10), 75 (10), 115 (15), 141 (58), 142 (110), 143 (12), 162 (22), 177 (44), 179 (14), 212 (M$^+$, 12). Anal. Calcd for $C_{11}H_{10}Cl_2$: C, 62.00; H, 4.73. Found: C, 62.05; H, 4.70.

2′-Chloro-6′-fluoro-1-((*E*)-3-methylbuta-1,3-dienyl)benzene (4f). Yellow oil: 1.86 g, (13.5 mmol) 70% yield; IR ($CHCl_3$) 1566, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 3H, CH_3), 5.19 (s broad, 2H, Hs-4), 6.66 (d, 1H, J = 16.5 Hz, H-2), 7.00 (m, 1H, H-3′), 7.07−7.14 (m, 2H, H-1, H-5′), 7.19 (m, 1H, H-4′); ^{19}F NMR ($CDCl_3$) δ −111,41 (dd, 1F, J = 10.9, 5.64 Hz, F-6′); ^{13}C NMR ($CDCl_3$) δ 18.1, 114.5 ($^2J_{CF}$ = 24.1 Hz), 119.2, 119.4, 124.3 ($^2J_{CF}$ = 14.1 Hz), 125.5, 127.8 ($^4J_{CF}$ = 10.1 Hz), 134.4, 138.8 ($^3J_{CF}$ = 12.9 Hz), 142.3, 161.1 ($^1J_{CF}$ = 252.5 Hz); MS *m*/*e* (rel intensity) 99 (15), 133 (33), 145 (22), 146 (100), 147 (17), 159 (26),160 (M$^+$, 16), 161 (100), 162 (15), 196 (M$^+$, 36). Anal. Calcd for $C_{11}H_{10}ClF$: C, 67.18; H, 5.13. Found: C, 67.45; H, 5.17.

General Procedure for the Diels−Alder Reaction of 1-Arylbuta-1,3-dienes (4a−f) with Methyl Propiolate (5). The cycloaddition reactions of 1-arylbuta-1,3-dienes **4** with **5** were accomplished (A) at normal pressure and (B) under 9 kbar pressure conditions. The details are given in Tables 1 and 2.

Condition (A). Methyl propiolate (**5**) (3 mmol) and a few crystals of hydroquinone were added to a solution of arylbutadiene **4** (1.5 mmol) in 15 mL of the solvent, and the resulting mixture was poured into an oil bath under magnetic stirring at the indicated reaction temperature and for the indicated reaction time. The cooled mixture was then poured into saturated brine (15 mL) and extracted twice with diethyl ether. The dried extract (Na_2SO_4) was evaporated under a vacuum and chromatographed over silica gel. Elution with 10−20% mixtures of ethyl acetate/petroleum ether gave the pure cycloadducts **6**.

Condition (B). A solution of arylbutadiene **4** (1.5 mmol) in 10 mL of solvent was placed in a 15 mL Teflon vial. Dienophile **5** (3 mmol) and a few crystals of hydroquinone were then added, and the vial was filled with the solvent. The vial was closed and kept at 9 kbar at the indicated temperature for the appropriate time. After depressurizing, the mixture was worked up and purified as above, giving the pure cycloadducts **6**.

Methyl 6-(2′-methoxyphenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6a). White solid: mp 42−43 °C (*n*-hexane); 0.352 g, 91% yield; IR ($CHCl_3$) 1713 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H, CH_3), 2.84 (m, 2H, Hs-3), 3.59 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.84 (s broad, 1H, H-6), 5.52 (s, 1H, H-5), 6.84 (dd, 1H, J = 1.0, 7.5 Hz H-3′), 6.86 (t, 1H, J = 8.0 Hz, H-5′), 6.94 (dd, 1H, J = 1.8, 7.6 Hz, H-6′), 7.15 (dt, 1H, J = 1.8, 7.9 H-4′), 7.21 (dt, 1H, J = 0.9, 4.5 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 22.6, 31.9, 35.2, 51.5, 55.7, 110.8, 120.8, 123.3, 127.1, 127.4, 127.6, 130.9, 132.9, 137.8, 156.5, 167.1; MS *m*/*e* (rel intensity) 59 (18), 65 (15), 77 (28), 91 (37), 108 (20), 128 (20), 139 (16), 152 (38), 153 (22), 165 (39), 166 (15), 167 (18), 168 (29), 169 (18), 181 (24), 183 (41), 184 (23), 195 (46), 196 (28), 199 (21), 210 (23), 211 (100), 225 (59), 226 (84), 227 (18), 258 (M$^+$, 9). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.35; H, 7.08.

Methyl 6-(2′,4′-dimethoxyphenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6b). White solid: mp 86−87 °C (*n*-hexane);

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0.367 g, 85% yield; IR ($CHCl_3$) 1714 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 3H, CH_3), 2.83 (m, 2H, Hs-3), 3.60 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.74 (s, 1H, H-6), 5.50 (s, 1H, H-5), 6.38 (dd, 1H, J = 2.4, 8.4 Hz, H-5′), 6.46 (d, 1H, J = 2.4 Hz, H-3′), 6.83 (d, 1H, J = 8.4 Hz, H-6′), 7.18 (t broad, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 22.6, 31.8, 34.7, 51.4, 55.2, 55.7, 98.7, 104.4, 123.6, 125.4, 127.1, 128.1, 131.0, 137.4, 157.4, 159.0, 167.2; MS m/e (rel intensity) 91 (13), 115 (15), 138 (16), 153 (14), 165 (18), 197 (23), 198 (20), 213 (57), 214 (26), 225 (37), 226 (39), 227 (32), 228 (29), 229 (26), 241 (100), 255 (47), 256 (79), 288 (M^+, 56). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.76; H, 7.03.

Methyl 6-(2′,6′-dimethoxyphenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6c). White solid: mp 90−91 °C (*n*-hexane); 0.397 g, 92% yield; IR ($CHCl_3$) 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3H, CH_3), 2.81 (m, 2H, Hs-3), 3.56 (s, 3H, OCH_3), 3.76 (s, 6H, OCH_3, OCH_3), 4.99 (s, 1H, H-6), 5.30 (s, 1H, H-5), 6.53 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.04 (s broad, 1H, H-2), 7.11 (t, 1H, J = 8.3 Hz, H-4′); ^{13}C NMR ($CDCl_3$) δ 22.6, 32.2, 32.2. 51.2, 56.2 (2C), 104.9 (2C), 120.0, 121.6, 127.2, 128.4, 130.4, 136.4, 158.7 (2C), 167.3; MS m/e (rel intensity) 77 (19), 91 (28), 115 (29), 128 (21), 138 (33), 139 (18), 141 (17), 152 (27), 153 (28), 165 (31), 169 (18), 181 (36), 183 (17), 197 (42), 198 (42), 199 (19), 210 (22), 213 (51), 225 (100), 226 (100), 227 (20), 240 (50), 241 (100), 242 (28), 255 (100), 256 (100), 288 (M^+, 18). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.78; H, 6.93.

Methyl 6-(2′,6′-dimethoxy-4′-pentylphenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6d). Light yellow solid: mp 60−61 °C (*n*-hexane); 0.446 g, 83% yield; IR ($CHCl_3$) 1711 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz, CH_3), 1.28−1.36 (m, 4H, CH_2CH_2), 1.58−1.65 (m, 2H, CH_2), 1.69 (s, 3H, CH_3), 2.53 (t, 2H, J = 7.8 Hz, CH_2), 2.79 (m, 2H, Hs-3), 3.58 (s, 3H, OCH_3), 3.78 (s, 6H, OCH_3, OCH_3), 4.95 (s broad, 1H, H-6), 5.31 (s broad, 1H, H-5), 6.36 (s, 2H, H-3′, H-5′), 7.03 (s broad, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 14.0 (C-5″), 22.5 (C-4″), 22.6 (4-CH_3), 30.9 (C-2″), 31.7 (C-3″), 32.0 (C-6), 32.2 (C-3), 36.4 (C-1″), 51.1 (CH_3OC=O), 56.2 (2′-OCH_3, 6′-OCH_3), 105.1 (C-3′, C-5′), 117.2 (C-1′), 121.9 (C-5), 128.2 (C-1), 130.5 (C-4′), 136.3 (C-2), 142.3 (C-4), 158.5 (C-2′, C-6′), 167.3 (C=O); MS m/e (rel intensity) 91 (30), 152 (92), 153 (26), 165 (44), 181 (27), 195 (45), 211 (40), 213 (41), 225 (100), 240 (40), 254 (44), 267 (33), 295 (100), 311 (100), 325 (100), 326 (73), 358 (M^+, 43). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.75; H, 8.41.

Methyl 6-(2′,6′-dichlorophenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6e). Light yellow solid: mp 76−77 °C (*n*-hexane); 0.312 g, 70% yield; IR ($CHCl_3$) 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H, CH_3), 2.86 (m, 2H, Hs-3), 3.61 (s, 3H, OCH_3), 5.0 (s, 1H, H-6), 5.34 (s, 1H, H-5), 6.88 (t, 1H, J = 9.2 Hz, H-2), 7.03−7.10 (m, 1H, H-4′), 7.15 (m, 2H, H-3′, H-5′); ^{13}C NMR ($CDCl_3$) δ 22.5, 32.1, 51.5, 114.6, 119.3(2C), 127.8, 128.3, 130.3, 132.1, 134.9, 138.5, 142.8, 158.6, 166.6; MS m/e (rel intensity) 91 (27), 165 (65), 166 (43), 170 (41), 221 (33), 233 (27), 245 (100), 265 (23), 280 (34). Anal. Calcd for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.75. Found: C, 60.66; H, 4.78.

Methyl 6-(2′-chloro-6′-fluorophenyl)-4-methylcyclohexa-1,4-diene-1-carboxylate (6f). Light yellow oil: 0.299 g, 71% yield; IR ($CHCl_3$) 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H, CH_3), 2.87 (m, 2H, 3-CH_2), 3.61 (s, 3H, OCH_3), 4.99 (s broad, 1H, H-6), 5.33 (s broad, 1H, H-5), 6.88 (t, 1H, J = 9.2 Hz, H-2), 7.05−7.11 (m, 1H, H-5′), 7.15 (m, 2H, H-3′, H-4′); ^{19}F NMR ($CDCl_3$) δ −113,94 (s broad, 1F, F-6′); ^{13}C NMR ($CDCl_3$) δ 22.5 (2C), 32.1, 51.5, 114.6 ($^2J_{CF}$ = 22.33 Hz), 119.4, 125.6, 127.8 ($^3J_{CF}$ = 10.06 Hz), 128.3, 130.4, 134.9 (2C), 138.5, 162.1 ($^1J_{CF}$ = 267.59 Hz), 166.6; MS m/e (rel intensity) 59 (48), 91 (43), 119 (21), 143 (21), 165 (94), 166 (52), 170 (54), 183 (68), 186 (37), 221 (35), 233 (25), 245 (100), 265 (22), 280 (M^+, 30). Anal. Calcd for $C_{15}H_{14}ClFO_2$: C, 64.18; H, 5.03. Found: C, 64.13; H, 5.00.

Oxidation of Cycloadducts 6 to Biaryls 7. To a solution of the cycloadducts **6** (0.35 mmol) in toluene (4.35 mL) was added DDQ (0.118 g, 0.521 mmol). The mixture was stirred at room temperature for 1 h and then poured into saturated aqueous $NaHCO_3$ and extracted twice with diethyl ether. The dried extract (Na_2SO_4) was concentrated under a vacuum and purified by silica gel column chromatography (20% diethyl ether/petroleum ether) to give biaryls **7**.

Methyl 2′-methoxy-4-methyl-1′,6-biphenyl-1-carboxylate (7a). Yellow oil: 80.6 mg, 90% yield; IR ($CHCl_3$) 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 6.90 (d, 1H, J = 8.0 Hz, H-3), 7.04 (t, 1H, J = 7.5 Hz, H-5′), 7.15 (s, 1H, H-5), 7.20 (d broad, 1H, J = 7.5 H-6′), 7.24 (dd, 1H, J = 1.6, 7.5 Hz, H-3′), 7.33 (dt, 1H, J = 1.6, 7.5 H-4′), 7.80 (d, 1H, J = 8.0 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.4, 51.5, 55.2, 110.0, 120.6, 127.8, 128.6, 128.7, 129.6, 129.7, 130.8, 132.0, 138.9, 142.0, 156.1, 168.4; MS m/e (rel intensity) 115 (19), 139 (18), 151 (18), 152 (62), 153 (37), 163 (43), 165 (38), 181 (100), 182 (56), 195 (41), 210 (100), 225 (100), 226 (66), 256 (M^+, 100). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.93; H, 6.23.

Methyl 2′,4′-dimethoxy-4-methyl-1′,6-biphenyl-1-carboxylate (7b). White solid: mp 59−60 °C (*n*-hexane); 93.1 mg, 93% yield; IR ($CHCl_3$) 1713 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.48 (d, 1H, J = 2.3 Hz, H-3′), 6.56 (dd, 1H, J = 2.3, 8.3 Hz, H-5′), 7.11 (s, 1H, H-5), 7.16 (d, 1H, J = 8.3 Hz, H-6′), 7.17 (d, 1H, J = 7.9 Hz, H-3), 7.76 (d, 1H, J = 7.9 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.4, 51.5, 55.2, 55.3, 98.2, 104.2, 123.6, 127.5, 128.7, 129.5, 130.1, 132.2, 138.6, 141.9, 157.1, 160.4, 168.7; MS m/e (rel intensity) 115 (16), 139 (11), 163 (21), 169 (11), 197 (28), 225 (13), 240 (61), 255 (100), 256 (19), 286 (M^+, 86). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.38; H, 6.29.

Methyl 2′,6′-dimethoxy-4-methyl-1′,6-biphenyl-1-carboxylate (7c). White solid: mp 93−94 °C (*n*-hexane); 87.1 mg, 87% yield; IR ($CHCl_3$) 1724 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3, OCH_3), 6.64 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.13 (s, 1H, H-5), 7.20 (d, 1H, J = 7.9 Hz, H-3), 7.28 (t, 1H, J = 8.3 Hz, H-4′), 7.88 (d, 1H, J = 7.9 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.5, 51.4, 55.9 (2C), 104.0 (2C), 119.3, 127.8, 128.5, 129.9, 132.9, 135.2, 141.6 (2C), 157.1 (2C), 167.9; MS m/e (rel intensity) 115 (16), 163 (41), 169 (16), 181 (15), 197 (17), 225 (12), 240 (30), 255 (100), 256 (16), 286 (M^+, 50). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.29; H, 6.30.

Methyl 2′,6′-dimethoxy-4-methyl-4′-pentyl-1′,6-biphenyl-1-carboxylate (7d). Light yellow solid: mp 48−49 °C (*n*-hexane); 122.1 mg, 98% yield; IR ($CHCl_3$) 1723 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.0 Hz, CH_3), 1.34−1.44 (m, 4H, CH_2CH_2), 1.67−1.73 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.65 (t, 2H, J = 7.8 Hz, CH_2), 3.62 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3, OCH_3), 6.46 (s, 2H, H-3′, H-5′), 7.13 (s, 1H, H-5), 7.17 (d, 1H, J = 7.9 Hz, H-3), 7.85 (d, 1H, J = 7.9 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 14.1 (C-5″), 21.5 (4-CH_3), 22.6 (C-4″), 31.1 (C-2″), 31.6 (C-3″), 36.7 (C-1″), 51.4 (CH_3OC=O), 55.8 (2′-OCH_3, 6′-OCH_3), 104.3 (C-3′, C-5′), 116.6 (C-1′), 127.6 (C-5), 128.7 (C-1), 129.8 (C-3), 133.2 (C-2), 135.3 (C-4′), 141.4 (C-6), 143.8 (C-4), 156.8 (C-2′, C-6′), 168.1 (C=O); MS m/e (rel intensity) 152 (10), 163 (15), 165 (14), 181 (14), 225 (21), 237 (21), 253 (75), 254 (20), 268 (100), 269 (18), 299 (17), 325 (31), 356 (M^+, 62). Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.90.

Methyl 2′,6′-dichloro-4-methyl-1′,6-biphenyl-1-carboxylate (7e). Light yellow oil: 85.5 mg, 83% yield; IR ($CHCl_3$) 1726 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 7.03−7.09 (m, 1H, H-4′), 7.1 (s broad, 1H, H-5), 7.24−7.29 (m, 2H, H-3′, H-5′), 7.31 (m, 1H, H-3), 8.03 (d, 1H, J = 8.0 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.5, 51.9, 113.5, 113.7, 124.7, 127.1, 129.1, 130.8, 132.1, 134.1, 142.8 (2C), 158.6, 161.0, 166.5; MS m/e (rel intensity) 157 (15), 181 (17), 183 (100), 184 (65), 199 (32), 200 (16), 228 (93), 229 (15), 243 (100), 244 (80), 247 (31). Anal. Calcd for $C_{15}H_{12}Cl_2O_2$: C, 61.04; H, 4.10. Found: C, 61.01; H, 4.07.

Methyl 2′-chloro-6′-fluoro-4-methyl-1′,6-biphenyl-1-carboxylate (7f). Light yellow solid: 82.9 mg, 85% yield; mp 67−68 °C (*n*-hexane); IR ($CHCl_3$) 1727 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 7.02−7.08 (m, 1H, H-5′), 7.1 (s, 1H, H-5), 7.26 (m, 2H, H-3′, H-4′), 7.31 (d broad, 1H, J = 8.4 Hz, H-3), 8.02 (d, 1H, J = 8.4 Hz, H-2); ^{19}F NMR ($CDCl_3$) δ −111,64 (s

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broad, 1F, F-6′);^{13}C NMR ($CDCl_3$) δ 21.5, 51.9, 113.6 ($^2J_{CF}$ = 22.94 Hz), 124.7, 127.2, 128.9 ($^3J_{CF}$ = 9.35 Hz), 129.3, 130.8, 132.2, 134.2, 142.9 (2C), 159.7, 160.4 ($^1J_{CF}$ = 246.84 Hz), 166.5; MS *m*/*e* (rel intensity) 183 (23), 184 (13), 199 (6), 228 (19), 243 (100), 244 (16). Anal. Calcd for $C_{15}H_{12}ClFO_2$: C, 64.64; H, 4.34. Found: C, 64.65; H, 4.37.

Demethylative Lactonization of Biaryls 7a−d to Benzo[*c*]-chromenones 8a−d. To a hot solution of **7a−d** (0.184 mmol) in acetic anhydride (1 mL) was added dropwise 57% aq HI (1 mL), and the mixture was refluxed for 1 h. This was then cooled to room temperature, poured into water, and extracted with diethyl ether. The combined extracts were washed successively with 20% aqueous Na_2SO_3, 1 M aqueous solution of $NaHCO_3$, and water and dried over Na_2SO_4. Then, the solvent was evaporated, and the residue was purified by two crystallizations (*n*-hexane and chloroform) to give chromenones **8a**,[25] **8b**, **8c** and **8d**.[19h,26]

3-Hydroxy-9-methyl-6*H*-benzo[*c*]chromen-6-one (8b). White solid: mp 245−246 °C (*n*-hexane); 33.7 mg, 85% yield; IR ($CHCl_3$) 3425 (OH), 1733 (C═O) cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$) δ 2.52 (s, 3H, CH_3), 6.78 (m, 1H, H-2), 6.88 (m, 1H, H-4), 7.36 (m, 1H, H-8), 8.03 (m, 1H, H-1), 8.12 (m, 1H, H-10), 9.17 (d, 1H, *J* = 5.1 Hz, H-7); ^{13}C NMR ($(CD_3)_2CO$) δ 21.2, 103.3, 110.3, 112.9, 117.4, 121.5, 124.6, 128.8, 129.7, 135.4, 146.1, 153.0, 159.8, 160.6. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.29; H, 4.42.

1-Hydroxy-9-methyl-6*H*-benzo[*c*]chromen-6-one (8c). White solid: mp 242−243 °C (*n*-hexane); 33.3 mg, 80% yield; IR ($CHCl_3$) 3349 (OH), 1732 (C═O) cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$) δ 2.52 (s, 3H, CH_3), 6.86 (d, 1H, *J* = 8.2 Hz, H-4), 6.92 (d, 1H, *J* = 8.2 Hz, H-2), 7.33 (t, 1H, *J* = 8.2 Hz, H-3), 7.44 (d, 1H, *J* = 8.1 Hz, H-8), 8.22 (d, 1H, *J* = 8.1 Hz, H-7), 9.03 (s, 1H, H-10); ^{13}C NMR ($(CD_3)_2CO$) δ 21.6, 106.8, 108.6, 111.9, 118.5, 127.7, 129.0, 129.7, 129.9, 134..9, 145.6, 153.5, 156.4, 160.4. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.38; H, 4.45.

1-Hydroxy-9-methyl-3-pentyl-6*H*-benzo[*c*]chromen-6-one (8d).[26] White solid: mp 183−184 °C (*n*-hexane) (lit.[26] 191−192 °C); 44.1 mg, 81% yield; IR ($CHCl_3$) 3358 (OH), 1732 (C═O) cm^{-1}; ^{1}H NMR ($(CD_3)_2CO$) δ 0.87 (t, 3H, *J* = 8.3 Hz, CH_3), 1.34 (m, 4H, $-CH_2CH_2-$), 1.65 (m, 2H, $-CH_2-$), 2.51 (s, 3H, CH_3), 2.61 (t, 2H, *J* = 7.5 Hz, $-CH_2-$), 6.73 (d, 1H, *J* = 1.6 Hz, H-4), 6.78 (d, 1H, *J* = 1.6 Hz, H-2), 7.39 (d, 1H, *J* = 8.0 Hz, H-8), 8.19 (d, 1H, *J* = 8.0 Hz, H-7), 8.97 (s, 1H, H-10); ^{13}C NMR ($(CD_3)_2CO$) δ 13.4, 21.6, 22.3, 30.4, 31.3, 35.2, 104.5, 108.4, 112.0, 118.1, 127.3, 128.5, 129.7, 135.1, 145.5, 145.7, 153.0, 156.1, 160.6. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.96; H, 6.76.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all of the new compounds. 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.

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