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Full Paper

Isocoumarin-Fused Enediynes

Towards Isocoumarin-Fused Enediyne Systems through the Electrophilic Cyclization of Methyl *o*-(Buta-1,3-diynyl)benzoates

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Abstract: The synthesis of enediynes fused to an isocoumarin core was achieved through the electrophilic cyclization of *o*-(buta-1,3-diynyl)benzoates as a key step, followed by the Sonogashira coupling of the resulting 3-ethynyl-4-iodoisocoumarins with acetylenes. This approach allowed different substituents to be introduced to both ethynyl moieties with complete regiocontrol. The ability of the isocoumarin-fused enediynes to undergo Bergman cyclization was studied by differential scanning calorimetry.

Introduction

Isocoumarin and its derivatives make up an important class of oxygen-containing heterocycles, as they occur in many natural products with a wide range of biological activities.[1] Considerable efforts have been devoted to the synthesis of isocoumarins.[1a,2] Of the methods for the synthesis of an isocoumarin core, the electrophilic cyclization of 2-(alk-1-ynyl)benzoic acids and esters is the most attractive.[3] These reactions can be mediated by Brønsted acids[4] or transition-metal salts (Cu,[5] Hg,[6] Pd,[7] Ag[8]). The corresponding 4-chalcogeno derivatives have been synthesized using *p*-$NO_2C_6H_4SCl$ or PhSeCl as electrophilic reagents.[9a] Moreover, the electrophilic cyclization of methyl 2-ethynylbenzoates has been found to be a general strategy for the synthesis of 4-haloisocoumarin derivatives. Reagents such as iodine and ICl[9] or *N*-iodosuccinimide (NIS)[10] gave 4-iodoisoscoumarins, whereas bromolactonization of methyl 2-ethynylbenzoates with *N*-bromosuccinimide[10] or *N*-methylpyrrolidin-2-one hydrotribromide[11] led to 4-bromoisocoumarins.

It should be noted that depending on the reaction conditions and the structure of the acetylene starting materials, 5-*exo*-*dig* cyclization may take place to give isobenzofuranone byproducts along with the 6-*endo*-*dig* ring closure.[9a] Nevertheless, many isocoumarins, including naturally occurring compounds, have been synthesized by this approach. For example, this strategy has been used for the solution-phase synthesis of a 167-membered library of isocoumarins,[12a] for the synthesis of polyheterocyclic compounds,[12b] and for the solid-phase synthesis of 4-haloisocoumarin derivatives.[13]

The electrophilic cyclization of methyl *o*-ethynylbenzoates has been investigated in detail, but only a few examples of the cyclization of methyl *o*-(buta-1,3-diynyl)benzoates have been reported. The ICl-induced double cyclization of dimethyl 2,2′-(buta-1,3-diyn-1,4-diyl)dibenzoate to give biisocoumarin[9a] was described. The second reported example was a double iodocyclization of asymmetrically substituted 1,4-diarylbutadiynes to give biheterocyclic compounds bearing one isocoumarin ring.[12b] The formation of 3-ethynyl-4-iodoisocoumarin as an intermediate in the double cyclization was observed once.[12b]

Recently, we reported the iodocyclization of diacetylene derivatives of thioanisole, anisole, and *N*,*N*-dimethylaniline. Only one of the triple bonds was affected, and heteroindenes bearing an ethynyl moiety and an iodine atom were formed in one step. This cyclization was used as a key step in a simple and convenient approach to acyclic and macrocyclic enediynes fused to heteroindenes.[14] In this paper, we extend this approach, and report the synthesis of isocoumarin-fused enediynes by the electrophilic cyclization of methyl *o*-(buta-1,3-diynyl)benzoates and subsequent Sonogashira coupling.

It is noteworthy that enediynes are coming to the attention of the synthetic community as a result of the fact that naturally occurring enediynes with a (*Z*)-3-ene-1,5-diyne scaffold incorporated into a 9- or 10-membered macrocycle can damage DNA.[15] Thus, enediyne antibiotics represent some of the strongest antitumor and antibacterial compounds among other natural products.[16] However, their clinical application is restricted due to their high instability, toxicity, allergenicity, and structural complexity. This motivates chemists to search for synthetic analogues of enediynes.[17]

Results and Discussion

For the synthesis of starting methyl *ortho*-(buta-1,3-diynyl)-benzoates **3a**–**3d**, we used the Sonogashira coupling[18] of 2-iodobenzoate with terminal diacetylenes or TMS (trimethylsilyl)

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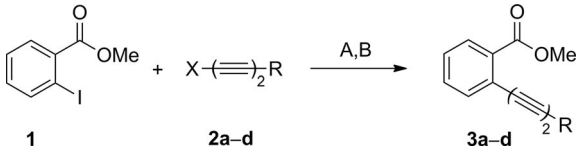
protected diacetylenes using conditions for one-pot TMS-group removal and C–C coupling (Table 1).

Table 1. Synthesis of methyl *o*-(buta-1,3-diynyl)benzoates **3a**–**3d**.



1 **2a–d** **3a–d**

Entry	R	X	Diacetylene[a]	Conditions[b]	Product (isolated yield [%])
1	Ph	H	**2a**	A	**3a** (75)
2	TMS	H	**2b**	A	**3b** (48)
3	C_5H_{11}	TMS	**2c**	B	**3c** (84)
4	$(CH_2)_2OH$	TMS	**2d**	B	**3d** (77)

[a] Diacetylenes **2a** and **2b** were synthesized by known procedures,[14a] and were used in the Sonogashira coupling without purification. [b] A: $Pd(PPh_3)_4$ (5 mol-%), CuI (15 mol-%), Et_3N, 40 °C, 3–18 h; B: $Pd(PPh_3)_4$ (5 mol-%), CuI (15 mol-%), diisopropanolamine [DIPA-$(OH)_2$] (4 equiv.), KF (5 equiv.), MeOH (10 equiv.), DMF, 40 °C, 1–2 h.

Thus phenylbuta-1,3-diyne (**2a**) and (trimethylsilyl)buta-1,3-diyne (**2b**), derived from 2-methyl-6-phenylpenta-3,5-diyn-2-ol and 1,4-bis(trimethylsilyl)butadiyne, respectively, were easily coupled with methyl 2-iodobenzoate (**1**) under the Sonogashira reaction conditions (A) that has been used previously for the synthesis of other *o*-functionalized aryldiacetylenes[14a] (Table 1, entries 1 and 2).

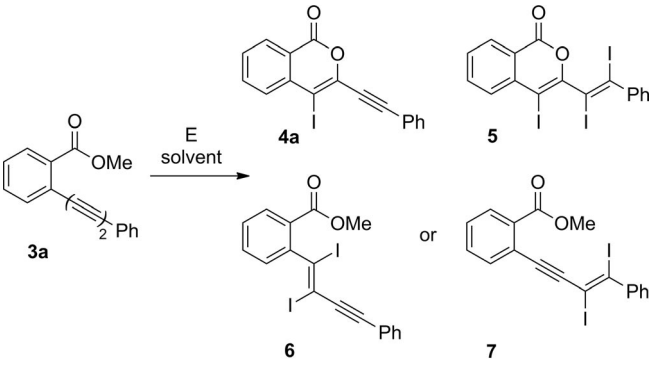
For the introduction of diacetylene moieties with alkyl and hydroxyalkyl substituents, another method (B) was used. In this case, TMS-group removal and Sonogashira coupling were carried out in one pot. This technique has been used previously with Ag^I/Pd^0 catalysts, and with K_2CO_3/MeOH acting as both a TMS-deprotection reagent and a base for the Sonogashira coupling.[19]

We found that a similar approach using Cu^I/Pd^0 in the presence of K_2CO_3/MeOH or a milder KF/MeOH system was very efficient in the synthesis of aryl diacetylenic alcohols, and for the introduction of eneyne scaffolds.[14a,14d]

The Sonogashira coupling of diynes **2c** and **2d** using KF/MeOH for one-pot TMS-group removal gave diacetylenes **3c** and **3d** in high yields, without affecting the ester group (Table 1, entries 3 and 4).

Electrophilic cyclization of methyl *o*-(4-phenylbuta-1,3-diynyl)benzoate (**3a**) with iodine (3 equiv.) in MeCN at 40 °C gave a mixture of products. The mixture was separated by preparative TLC, and analysed by MS. On the basis of the analytical data, the desired isocoumarin (**4a**), an isocoumarin with an iodinated triple bond **5**, and an iodinated starting ester **6** (or **7**) were identified along with the starting diyne (**3a**), which was detected in the reaction mixture even after 5 d (Table 2, entry 1). To avoid iodination of the triple bonds, starting ester **3a** and I_2 were used in an equimolar ratio (Table 2, entry 2). However, the conversion of the ester to the desired iodoisocoumarin (**4a**) was poor, and iodination of a triple bond in the starting material (**3a**) occurred again.

Table 2. Optimization of reaction conditions for the electrophilic cyclization of methyl *o*-(4-phenylbuta-1,3-diynyl)benzoate **3a**.



E = I_2, I_2/CAN, NIS; solvent = MeCN, DCM

Entry	Solvent [a]	E (equiv.)	Reaction time[b]	Ratio **4a**/**5**/**6** or **7**/**3a**[c]
1	MeCN	I_2 (3)	5 d	1:0.8:0.25:0.05
2	MeCN	I_2 (1)	28 h	1:–:2:0.1
3	MeCN	NIS (1)	5 d	1:0.3:0.2:1
4	MeCN	I_2/CAN (1:1.1)[d]	20 h	1:–:0.2:1.5
5	CH_2Cl_2	I_2 (1)	28 h	1:<0.05:–:0.1
6	CH_2Cl_2	I_2 (1.5)	20 h	1:0.16:–: <0.05
7	CH_2Cl_2	I_2 (1.2)	20 h	1:–:–: <0.05

[a] Reactions were carried out at 40 °C. [b] Reaction times were evaluated by ^{1}H NMR spectroscopy because of the close R_f values of compounds **3**–**7**. [c] The ratio was determined by ^{1}H NMR spectroscopy. [d] The experiment was run at room temp.

We then examined other electrophilic agents. Unfortunately, neither NIS nor an I_2/CAN system, which have been used previously for the O-cyclization of monoacetylenes,[10,20] gave only the desired product (**4a**) without iodinated by-products. Moreover the conversion of ester **3a** was still low (Table 2, entries 3 and 4).

Bearing in mind the fact that the rate of iodocyclization of *o*-(buta-1,3-diynyl)thioanisoles and -*N*,*N*-dimethylanilynes was higher when CH_2Cl_2 was used as a solvent rather than acetonitrile,[14a] we next tested CH_2Cl_2 as a solvent. We found that when the cyclization was carried out in CH_2Cl_2 with an equimolar amount of iodine, iodination of a triple bond in starting ester **3a** was avoided, the formation of by-product **5** decreased significantly, and the conversion of ester **3a** into iodoisocoumarin **4a** increased (Table 2, entry 5). To reach full conversion, an excess of iodine (1.5 equiv.) was used. But despite the fact that almost full conversion was obtained, these conditions led to increased amounts of isocoumarin with an iodinated triple bond **5** (Table 2, entry 6).

Finally, optimal conditions were found. The use of iodine (1.2 equiv.) in CH_2Cl_2 at 40 °C gave only traces of unconverted ester **3a**, and did not give iodinated by-products (Table 2, entry 7). Under these conditions, compound **4a** was isolated in 64 % yield (Table 3, entry 1).

For the reactions shown in Table 3, entries 2–4, the amount of iodine was reduced to 1.1 equiv. Iodocyclization of methyl *o*-(buta-1,3-diynyl)benzoates **3c** and **3d** gave the desired pro-

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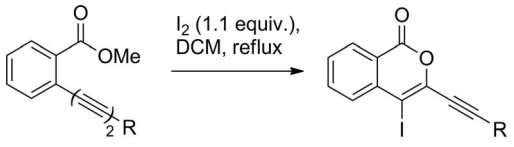
Table 3. Electrophilic cyclization of methyl *o*-(buta-1,3-diynyl)benzoates **3a**–**3d**.



3a–d **4a–c**

Entry	R	Ester	Reaction time	Ratio **4**/**3**[a]	Product (isolated yield [%])
1	Ph	**3a**	20[b]	1:0.05	**4a** (64)
2	TMS	**3b**	24	[c]	(–)
3	C_5H_{11}	**3c**	21	1:0.07	**4b** (59)
4	$(CH_2)_2OH$	**3d**	24	1:0.25	**4c** (40)

[a] The ratio was determined by ^1H NMR spectroscopy. [b] 1.2 equiv. of I_2 was used. [c] The ratio was not determined; a complex mixture was obtained.

ducts (i.e., **4b** and **4c**, respectively), and the formation of iodinated isocoumarins did not take place. However in the case of the hydroxyalkyl substituent, the electrophilic cyclization proceeded with a worse conversion of the starting material under these conditions, and the corresponding isocoumarin (**4c**) was formed in only moderate yield (Table 3, entry 4). Unfortunately, all attempts to induce TMS-substituted diacetylene ester **3b** to undergo cyclization gave complex mixtures of unidentified products and unconverted starting material (Table 3, entry 2).

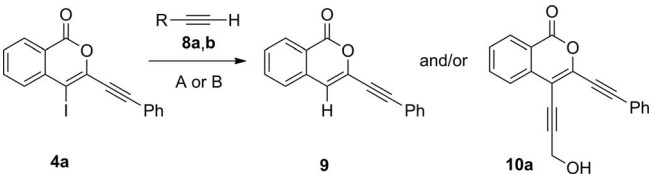
Despite the fact that according to Baldwin's rules, digonal ring closures are generally of the *endo* type,[21] the formation of both 5-*exo*-*dig* and 6-*endo*-*dig* products have been observed with *o*-ethynylbenzoates.[9a] We found that all the reactions of diacetylene derivatives **3** proceeded regioselectively as 6-*endo*-*dig* processes with the formation of only the isocoumarin ring.[22]

Next, iodoisocoumarins **4a**–**4c** were used as substrates for the synthesis of acyclic enediyne systems fused to an isocoumarin core by Sonogashira coupling with terminal acetylenes **8**. Iodoisocoumarin **4a** was chosen for optimization of the conditions (Table 4).

Surprisingly, the reaction of iodoisocoumarin **4a** with hexyne (**8a**) under conditions used recently for the synthesis of enediynes fused to heteroindenes[14a] gave only reduced isocoumarin **9** in low yield (Table 4, entry 1). Similar results were obtained when the reaction was carried out in THF using Et_3N instead of DIPA-$(OH)_2$ (Table 4, entry 2). Switching to diisopropylamine as the base gave the desired cross-coupling product, but the yield was low (Table 4, entry 3).

Taking into account the fact that the cross-coupling of 4-iodoisocoumarins with various terminal acetylenes has previously been carried out successfully in the synthesis of a combinatorial library of isocoumarins,[12a] and that these reactions were carried out in the presence of a smaller amount of CuI (2 mol-%) as a cocatalyst, we decided to decrease the amount of CuI used. When we used less CuI, together with diisopropylamine as a base, the yield of target compound **10a** increased to 62 % (Table 4, entry 4). However, when the Sonogashira coupling was run with diisopropanolamine, a mixture of enediyne **10a** and reduced product **9** was again formed (Table 4, entry 5).

Table 4. Optimization of reaction conditions for the synthesis of isocoumarin-fused enediynes.



4a **9** **10a**

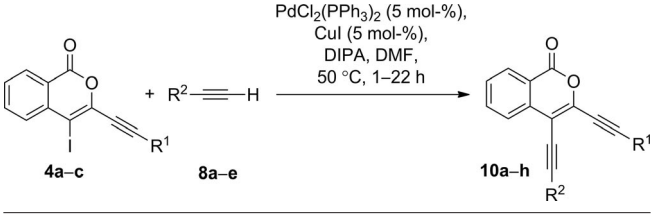
Entry	Acetylene, R	Base[a]	CuI, [mol-%[b]]	Product (isolated yield [%])
1	**8a**, Bu	DIPA-$(OH)_2$	15	**9** (27)
2	**8b**, CH_2OH	Et_3N	15	**9** (9)
3	**8b**, CH_2OH	DIPA	15	**10a** (17)
4	**8b**, CH_2OH	DIPA	5	**10a** (62)
5	**8b**, CH_2OH	DIPA-$(OH)_2$	5	**9** (22), **10a** (24)

[a] DIPA-$(OH)_2$ = diisopropanolamine; DIPA = diisopropylamine. [b] Other conditions: entries 1 and 3–5, (A): $PdCl_2(PPh_3)_2$ (5 mol-%), DMF, 50 °C, 1–5 h; entry 2, (B): $Pd(PPh_3)_4$ (5 mol-%), THF, 50 °C, 24 h.

These results show that both the amount of CuI and the nature of the base affect the reaction. Therefore, the best conditions (Table 4, entry 4) were used for the synthesis of other enediynes.

These optimized conditions allowed enediynes fused to an isocoumarin ring **10a**–**10h** to be obtained in yields from moderate to high (Table 5). Moreover, TMS, hydroxyalkyl, and alkoxyalkyl substituents, which are very important functional groups for the further transformation into macrocyclic enediynes, were introduced into the molecules in this step.

Table 5. Sonogashira coupling in the synthesis of enediynes fused to an isocoumarin core **10a**–**10h**.



4a–c **8a–e** **10a–h**

Entry	Substrate, R^1	Alkyne, R^2	Reaction time [h]	Product (isolated yield [%])
1	**4a**, Ph	**8b**, CH_2OH	1	**10a** (68)
2	**4a**, Ph	**8a**, Bu	20	**10b** (72)
3	**4a**, Ph	**8c**, TMS	2	**10c** (90)
4	**4b**, C_5H_{11}	**8d**, Ph	1	**10d** (90)
5	**4b**, C_5H_{11}	**8c**, TMS	3	**10e** (76)
6	**4b**, C_5H_{11}	**8e**, $(CH_2)_2OH$	22	**10f** (63)
7	**4c**, $(CH_2)_2OH$	**8d**, Ph	2	**10g** (68)
8	**4c**, $(CH_2)_2OH$	**8f**, CH_2OMe	22	**10h** (36)

The structure of enediynes **10b**–**10d** was verified by X-ray analysis (Figure 1).[23] The data obtained confirmed that the isocoumarin structures of the electrophilic cyclization products determined by NMR spectroscopy are correct. Moreover, these data gave values for bond angles (1 and 2) and *cd*-distances for the enediyne molecules (Table 6). These are important struc-

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tural parameters of enediynes in evaluating their ability to undergo Bergman cyclization (BC).[24]

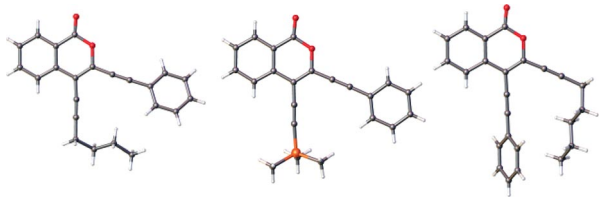
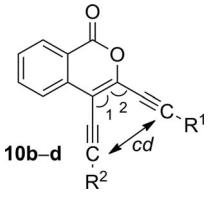


Figure 1. Molecular structures of isocoumarin-fused enediynes **10b** (left), **10c** (middle), and **10d** (right).

Table 6. Selected X-ray structural data of enediynes **10b**–**10d**.

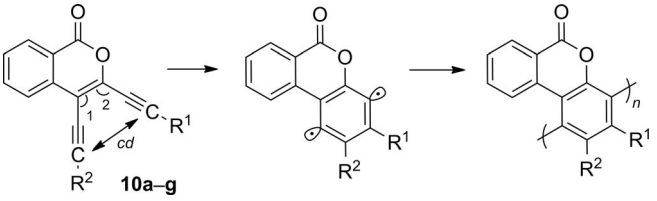


	R^1	R^2	1 [°]	2 [°]	*cd* [Å]
10b	Ph	Bu	120.8	125.8	4.35
10c	Ph	TMS	120.5	125.4	4.25
10d	C_5H_{11}	Ph	119.9	125.0	4.15

Finally the reactivity of enediynes **10a**–**10g** in Bergman cyclization was studied by differential scanning calorimetry (DSC), which is known to be an efficient, rapid method for this purpose.[25] Before running the DSC measurements, all the compounds were tested by thermogravimetric analysis (TGA). This showed significant loss of mass for enediynes **10b**–**10f** at temperatures around 200 °C, connected to vaporization of the sample before complete Bergman cyclization of all the sample volume had taken place.[26] Only two enediynes, **10a** and **10g**, bearing phenyl and hydroxyalkyl substituents at both ethynyl moieties, did not evaporate during the heating to 350 °C, and were therefore investigated by the conventional DSC technique using aluminium pans with pierced lids. Thus, the exothermic peaks observed in the thermograms (198 °C for **10a**, and 167 °C for **10g**, onset temperatures) obviously show that the Bergman cyclization of compounds **10a** and **10g** took place.[26] Additional evidence suggesting that irreversible Bergman cyclization followed by polymerization[27] occurred comes from the fact that neither endothermic nor exothermic features were observed when the thermolysed samples were scanned a second time.

To evaluate the ability of the other compounds to undergo Bergman cyclization, the DSC measurements were carried out in closed high-pressure steel pans (Table 7). It should be noted that under these conditions, the onset temperatures of the exothermic peaks for compounds **10a** and **10g** were found to be close to the temperatures obtained using aluminium pans with pierced lids (Table 7, entries 1 and 7). However, running the DSC measurements in closed pans led to a second exothermic effect at temperatures higher than those for the Bergman cyclization. The new exothermic effect observed could be due to oxidation of the sample by residual oxygen in the sealed pan.[26]

Table 7. Studying the reactivity of enediynes **10a**–**10g** in Bergman cyclization by DSC.[a]



Entry	Enediyne	R^1	R^2	T_{BC} [°C][b]
1	**10a**	Ph	CH_2OH	192 (198)
2	**10b**	Ph	Bu	164
3	**10c**	Ph	TMS	154
4	**10d**	C_5H_{11}	Ph	148
5	**10e**	C_5H_{11}	TMS	220
6	**10f**	C_5H_{11}	$(CH_2)_2OH$	164
7	**10g**	$(CH_2)_2OH$	Ph	162 (167)

[a] Polymeric structure of Bergman cyclization products obtained by heating of acyclic enediynes in a heating bath set at their peak DSC temperature has been reported.[27b] [b] Peak separation procedure for the obtained curves gave the values of the Bergman cyclization temperatures (T_{BC}). The onset temperatures of exothermic peaks from the experiments with closed high-pressure steel pans are given; onset temperatures from the DSC measurements in pans with pierced lids for enediynes **10a** and **10g** are given in parentheses.

As expected, the observed values of the Bergman cyclization temperatures (T_{BC}) for isocoumarin-fused enediynes (148–220 °C) are much lower than the T_{BC} for enediynes fused to heteroindenes (200–266 °C).[14a] This fact can be explained by the structural and electronic properties of the enediynes synthesized.

It has been shown that if the ring-strain energy does not influence the reactivity of endiynes,[28] then their ability to undergo Bergman cyclization strongly depends on the distance between the interacting C_{sp} atoms (*cd*-distance).[29] For the isocoumarin-fused enediynes, angles 1 and 2 were found to be smaller by 3–7° than the corresponding angles in acyclic enediynes fused to heteroindenes synthesized earlier (Table 6).[14a] As a result, the *cd*-distances in the isocoumarin-annulated enediynes became significantly smaller (4.1–4.3 Å) than the *cd*-distances in heteroindene-fused molecules (4.5–4.7 Å), and explains the increased reactivity of the isocoumarin-fused enediynes. Furthermore, for enediynes **10b**–**10d**, the values of the *cd*-distance obtained from the X-ray data (Table 6) are consistent with the values of T_{BC} (Table 7, entries 2–4). Thus, an increase in the *cd*-distance of 0.1 Å corresponds to in an increase in T_{BC} of 6–10 °C.

Regarding the electronic properties of the enediynes, it is known that annulation of an electron-deficient heterocycle[30] or a benzene ring with electron-withdrawing substituents[31] to an enediyne system results in a more reactive species in thermally induced cycloaromatization. Therefore, replacing the electron-rich heteroindene rings with an isocoumarin core in the heterocycle-fused enediynes might also result in a decrease in their T_{BC}.

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Conclusions

The electrophilic cyclization of methyl 2-(buta-1,3-diynyl)benzoates was found to proceed regioselectively as a 6-*endo*-*dig* cyclization to give 3-ethynyl-4-iodoisocoumarins. The Sonogashira coupling of the resulting iodoethynylisocoumarins with acetylenes led to enediynes fused to an isocoumarin core. We found that the amount of CuI used as cocatalyst and the nature of the base both strongly affected the results of the Sonogashira coupling and the formation of by-products due to the reduction of 4-iodoisocoumarins. Using this approach, asymmetrically substituted isocoumarin-fused enediynes were obtained in three synthetic steps. The results of DSC analysis demonstrated that the isocoumarin-fused enediynes were more reactive than acyclic enediynes fused to heteroindenes in Bergman cyclizations.

Experimental Section

General Remarks: Solvents, reagents, and chemicals [1,3-bis(trimethylsilyl)buta-1,3-diyne and terminal acetylenes **8a**–**8e**] were purchased from commercial suppliers, and were used without further purification. Catalysts $Pd(PPh_3)_4$, and $PdCl_2(PPh_3)_2$ were purchased from Sigma–Aldrich. Solvents were dried under standard conditions. Methyl *o*-iodobenzoate (**1**),[32] 2-methyl-6-phenylhexa-3,5-diyn-2-ol (**2a**),[14a] trimethyl(nona-1,3-diynyl)silane (**2c**),[33] 6-trimethylsilylhexa-3,5-diyn-1-ol (**2d**),[14a] and 3-methoxyprop-1-yne (**8f**)[34] were synthesized by known procedures without any modification. All reactions were carried out under Ar in flame-dried glassware. Evaporation of solvents and concentration of reaction mixtures were carried out under vacuum at 30–40 °C on a rotary evaporator. Thin-layer chromatography (TLC) was carried out on silica gel plates (silica gel 60, F254), with detection by UV light. Normal-phase silica gel (silica gel 60, 230–400 mesh) was used for preparative chromatography. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ (**3a–3d**, **4a**–**4c**, **10a**, **10c**–**10h**) or [D_6]DMSO (**10b**) without any internal standard. ^1H NMR spectroscopic data are reported as follows: chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad), coupling constants (*J*, given in Hz), and number of protons. ^{13}C NMR spectroscopic data are reported as follows: chemical shift (δ) and type of carbon (p, primary; s, secondary; t, tertiary; q, quaternary), as determined from DEPT experiments. Chemical shifts are reported as δ values (ppm), and were referenced to residual solvent signals [δ = 7.26 ($CHCl_3$) or 2.50 ([D_5]DMSO) ppm for ^1H; δ = 77.00 ($CDCl_3$) or 39.52 ([D_6]DMSO) ppm for ^{13}C]. High-resolution mass spectra (HRMS) were measured using the electrospray ionization (ESI) technique in positive-ion mode using time-of-flight (TOF) MS. Thermogravimetric analysis (TGA) for compounds **10a**–**10g** was carried out using a TG 209 F1 Libra thermogravimetric analyser (Netzsch). Samples (0.15–1.19 mg) were heated in aluminium pans under a flow of argon (90 cm^3/min) at a rate of 5 °C/min from 20 °C to 380 °C. Differential scanning calorimetry (DSC) for compounds **10a**–**10g** was carried out with a DSC 204 F1 Phoenix (Netzsch) calorimeter. The measurements for enediynes **10a** and **10g** were carried out in 40 μL aluminium crucibles with pierced lids. Then compounds **10a**–**10g** were analysed in closed high-pressure steel pans with a decomposition pressure of 100 bar. DSC samples (0.12–0.27 mg) were investigated at a heating rate of 10 °C/min under a flow of argon (70 mL/min). Samples precooled to 20 °C were heated to 400 °C, then cooled to 20 °C, and heated to 400 °C again. Peak separation was carried out using Netzsch Peak Separation software. X-ray analysis of single crystals of compounds **10b**–**10d** was carried out with a SuperNova, Dual, Cu at zero, Atlas diffractometer. A suitable crystal was kept at 100(2) K during data collection. Using Olex2,[35] the structure was solved with the Superflip structure-solution program[36] using charge flipping, and refined with the ShelXL refinement package[37] using least-squares minimization.

4-Phenylbuta-1,3-diyne (2a): Well-ground NaOH (12.1 mmol, 485 mg) was added to a solution of 2-methyl-6-phenylhexa-3,5-diyn-2-ol (4.02 mmol, 740 mg) in benzene (22.0 mL). The reaction mixture was stirred under Ar at 70 °C for 50 min. Then, the reaction mixture was cooled to room temperature, filtered, and washed with water until pH 7. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4, and evaporated to give a solution of 4-phenylbuta-1,3-diyne (**2a**) in a mixture of benzene and ethyl acetate (ca. 10 mL), which was used in the Sonogashira coupling without further purification.

Trimethylsilylbuta-1,3-diyne (2b): MeLi·LiBr complex (2.20 M solution in diethyl ether; 14.8 mmol, 6.7 mL) was added dropwise to a cooled (0 °C) stirred solution of 1,3-bis(trimethylsilyl)buta-1,3-diyne (6.0 mmol, 1.17 g) in absolute diethyl ether (60 mL). The reaction mixture was warmed to room temperature, and was stirred at room temperature for 6 h. Then, the reaction mixture was cooled to 0 °C, quenched with water (4.0 mL), and diluted with brine. The organic layer was separated, and the aqueous layer was acidified with HCl (10 % aq.), and extracted with Et_2O. The combined organic layers were washed with brine until pH 7, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure (not lower than 700 Torr). This gave a solution of trimethylsilyldiacetylene (**2b**) in Et_2O (ca. 6 mL), which was used in the Sonogashira coupling without further purification.

General Procedures for the Sonogashira Coupling of Methyl 2-Iodobenzoate 1 with Terminal Diacetylenes 2a and 2b, and TMS-Substituted Diacetylenes 2c and 2d

Method A: Methyl 2-iodobenzoate (**1**; 1.00 equiv.) was dissolved in triethylamine, and a solution of terminal diacetylene **2a** or **2b** (2–2.5 equiv.; see above) was added, followed by PPh_3 (10 mol-%) and $Pd(PPh_3)_4$ (5 mol-%). The resulting solution was evacuated and flushed with Ar several times. Then, CuI (15 mol-%) was added. The reaction mixture was evacuated and flushed with Ar once again, and then stirred at 40–45 °C. When TLC showed that the reaction was complete, the reaction mixture was poured into saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate. The organic phase was washed with saturated aqueous NH_4Cl, and brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

Method B: Methyl 2-iodobenzoate (**1**; 1 equiv.) was dissolved in DMF, and $Pd(PPh_3)_4$ (5 mol-%), DIPA-$(OH)_2$ (4 equiv.), CuI (15 mol-%), and KF (5 equiv.) were added. The reaction vial was evacuated and flushed with Ar several times, then it was sealed and MeOH (10 equiv.) was added, followed by TMS-substituted diacetylene **2c** or **2d** (1.0–1.5 equiv). The reaction mixture was stirred at 40 °C for 1–2 h (monitored by TLC). The reaction mixture was then allowed to cool, and worked up as described for method A.

Methyl 2-(Phenylbuta-1,3-diynyl)benzoate (3a): Compound **3a** was synthesized following method A in Et_3N (8 mL) from methyl 2-iodobenzoate (**1**; 1.64 mmol, 430 mg) and a solution of 4-phenylbuta-1,3-diyne (**2a**), obtained as described above from 2-methyl-6-

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phenylhexa-3,5-diyn-2-ol (4.02 mmol, 740 mg). Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) gave **3a** (320 mg, 75 %) as a white solid, m.p. 79–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, J = 7.8, J = 0.8 Hz, 1 H), 7.66 (dd, J = 7.6, J = 0.6 Hz, 1 H), 7.53–7.55 (m, 2 H), 7.48–7.51 (m, 1 H), 7.40–7.44 (m, 1 H), 7.32–7.38 (m, 3 H), 3.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2 (q), 135.3 (t), 132.8 (q), 132.7 (t), 132.0 (t), 130.7 (t), 129.4 (t), 128.8 (t), 128.6 (t), 122.8 (q), 121.9 (q), 83.4 (q), 79.9 (q), 79.0 (q), 74.3 (q), 52.7 (p) ppm. HRMS (ESI): calcd. for $C_{18}H_{13}O_2$ $[M + H]^+$ 261.0916; found 261.0902.

Methyl 2-[(Trimethylsilyl)buta-1,3-diynyl]benzoate (3b): Compound **3b** was synthesized following method A in Et_3N (9 mL) from methyl 2-iodobenzoate (**1**; 2.2 mmol, 590 mg) and a solution of trimethylsilylbuta-1,3-diyne (**2b**) in diethyl ether, obtained as described above from bis(trimethylsilyl)diacetylene (6.0 mmol, 1.17 g). Purification of the crude product by column chromatography on silica gel (petroleum ether, then petroleum ether/ethyl acetate, 90:1 then 70:1) gave **3b** (0.28 g, 48 %) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, J = 7.8, J = 1.0 Hz, 1 H), 7.62 (d, J = 7.6 Hz, 1 H), 7.45–7.49 (m, 1 H), 7.38–7.43 (m, 1 H), 3.94 (s, 3 H), 0.23 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (q), 135.6 (t), 133.0 (q), 132.0 (t), 130.7 (t), 128.9 (t), 122.4 (q), 92.6 (q), 88.0 (q), 79.1 (q), 74.9 (q), 52.5 (p), –0.26 (p) ppm. HRMS (ESI): calcd. for $C_{15}H_{17}O_2Si$ $[M + H]^+$ 257.0992; found 257.0994.

Methyl 2-(Nona-1,3-diynyl)benzoate (3c): Diacetylene **3c** was synthesized following method B from methyl 2-iodobenzoate (**1**; 2.0 mmol, 524 mg) and trimethyl(nona-1,3-diynyl)silane (**2c**; 3.0 mmol, 576 mg). Purification of the crude product by column chromatography (petroleum ether/ethyl acetate, 90:1 then 70:1) gave **3c** (420 mg, 84 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, J = 7.8, J = 1.1 Hz, 1 H), 7.60 (dd, J = 7.6, J = 1.3 Hz, 1 H), 7.43–7.47 (m, 1 H), 7.35–7.39 (m, 1 H), 3.94 (s, 3 H), 2.37 (t, J = 7.1 Hz, 2 H), 1.55–1.60 (m, 2 H), 1.29–1.43 (m, 4 H), 0.91 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (q), 135.3 (t), 132.9 (q), 131.8 (t), 130.6 (t), 123.1 (q), 86.9 (q), 79.6 (q), 73.0 (q), 65.4 (q), 52.4 (p), 31.2 (s), 28.0 (s), 22.3 (s), 19.8 (s), 14.0 (p) ppm. HRMS: calcd. for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1380; found 255.1381.

Methyl 2-(6-Hydroxyhexa-1,3-diynyl)benzoate (3d): Diacetylene **3d** was synthesized following method B from methyl 2-iodobenzoate (**1**; 2.0 mmol, 524 mg) and 6-(trimethylsilyl)hexa-3,5-diyn-1-ol (**2d**; 2.1 mmol, 349 mg) dissolved in DMF (2 mL). Purification of the crude product by column chromatography (petroleum ether/ethyl acetate, 3:1) gave **3d** (350 mg, 77 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.4 Hz, 1 H), 7.60 (d, J = 7.6 Hz, 1 H), 7.44–7.48 (m, 1 H), 7.37–7.41 (m, 1 H), 3.93 (s, 3 H), 3.78–3.82 (m, 2 H), 2.66 (t, J = 6.3 Hz, 2 H), 1.97 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2 (q), 135.4 (t), 132.9 (q), 131.9 (t), 130.7 (t), 128.7 (t), 122.8 (q), 83.0 (q), 79.1 (q), 73.7 (q), 67.2 (q), 60.9 (s), 52.5 (p), 24.3 (s) ppm. HRMS: calcd. for $C_{14}H_{13}O_3$ $[M + H]^+$ 229.0859; found 229.0759.

Optimization of Conditions for the Electrophilic Cyclization of Methyl 2-(Buta-1,3-diynyl)benzoate (3a): (Table 2, entry 1): A solution of iodine (0.550 mmol, 141 mg) in MeCN (2 mL) was added to an argon-flushed solution of methyl 2-(phenylbuta-1,3-diynyl)benzoate (**3a**; 0.550 mmol, 144 mg) in MeCN (7 mL). The reaction mixture was stirred at 40 °C for 2 d. Then, additional iodine (0.550 mmol, 144 mg) was added. The reaction mixture was heated at 40 °C for a further 24 h, then a third portion of iodine (0.550 mmol, 144 mg) was added. The resulting mixture was stirred at 40 °C for 2 d. Only the starting ester (i.e., **3a**) was detected in the reaction mixture by TLC analysis (hexane/ethyl acetate, 20:1). Then, the mixture was cooled to room temperature, diluted with $Na_2S_2O_3$ (5 % aq.), and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate, 20:1), followed by fine separation by preparative TLC (hexane/acetone, 3:1) to give iodoisocoumarin **4a** (70.0 mg, 34 %); MS (ESI): calcd. for $C_{17}H_{10}IO_2$ $[M + H]^+$ 372.97; found 372.97. Also isocoumarin with iodinated triple bond **5** (60 mg, 17 %); MS (ESI): calcd. for $C_{17}H_{10}I_3O_2$ $[M + H]^+$ 626.76; found 626.76. Also a mixture of iodoisocoumarin **4a** with diiodide **6** (or **7**) (20 mg); MS (ESI): calcd. for $C_{18}H_{12}I_2O_2K$ $[M + K]^+$ 552.86; found 552.86; ratio **4a**/**6** (or **7**) = 1:0.5. The identification of all the components allowed the composition of the crude mixture to be calculated from its ^{1}H NMR spectrum: **4a**/**5**/**6** (or **7**)/**3a** = 1:0.8:0.25:0.05.

General Procedure for the Electrophilic Cyclization of Methyl 2-(Buta-1,3-diynyl)benzoates: A solution of iodine (1.1–1.2 equiv.) in CH_2Cl_2 was added dropwise to an argon-flushed solution of methyl 2-(buta-1,3-diynyl)benzoate (**3**, 1 equiv.) in CH_2Cl_2. The reaction mixture was stirred under reflux until the reaction was complete (see Table 3). To monitor the reaction, an aliquot of the reaction mixture was passed through a layer of $Na_2S_2O_3$, evaporated to dryness, and analysed by ^{1}H NMR spectroscopy. When the reaction was complete, the mixture was cooled to room temperature, diluted with $Na_2S_2O_3$ (5 % aq.), and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

4-Iodo-3-(phenylethynyl)-1*H*-isochromen-1-one (4a): Compound **4a** was prepared following the general procedure from diyne (**3a**, 1.54 mmol, 400 mg) in CH_2Cl_2 (23 mL), and I_2 (1.85 mmol, 468 mg) in CH_2Cl_2 (30 mL). The reaction time was 20 h (Table 2, entry 1). Purification of the crude product by column chromatography on silica gel (petroleum ether/acetone, 3:1) gave pure isochromene **4a** (365 mg, 64 %), along with a mixture of **4a** and **3a** (71.0 mg); ratio **4a**/**3a** = 3:1 according to ^{1}H NMR spectroscopy. The total yield of **4a** was calculated to be 74 %. Data for **4a**: White solid, m.p. 138–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 7.9 Hz, 1 H), 7.78–7.82 (m, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.61–7.64 (m, 2 H), 7.55–7.59 (m, 1 H), 7.38–7.46 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (q), 140.7 (q), 137.6 (q), 135.9 (t), 132.2 (t), 131.5 (t), 130.14 (t), 130.09 (t), 129.9 (t), 128.7 (t), 121.2 (q), 121.0 (q), 97.6 (q), 84.9 (q), 83.6 (q) ppm. HRMS: calcd. for $C_{17}H_{10}IO_2$ $[M + H]^+$ 372.9725; found 372.9707.

3-(Hept-1-ynyl)-4-iodo-1*H*-isochromen-1-one (4b): Compound **4b** was synthesized following the general procedure from diyne **3c** (0.79 mmol, 200 mg) in CH_2Cl_2 (15 mL), and a solution of I_2 (0.87 mmol, 221 mg) in CH_2Cl_2 (17 mL). The reaction time was 21 h (Table 2, entry 3). Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 70:1) followed by recrystallization from petroleum ether gave **4b** (173 mg, 59 %) as a white solid, m.p. 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 7.9 Hz, 1 H), 7.73–7.77 (m, 1 H), 7.66 (d, J = 8 Hz, 1 H), 7.49–7.54 (m, 1 H), 2.52 (t, J = 6.9 Hz, 2 H), 1.62–1.68 (m, 2 H), 1.42–1.51 (m, 2 H), 1.32–1.39 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (q), 140.8 (q), 137.8 (q), 135.8 (t), 131.4 (t), 130.0 (t), 129.5 (t), 121.1 (q), 100.7 (q), 82.3 (q), 31.2 (s), 27.7 (s), 22.3 (s), 19.7 (s), 14.1 (p) [one C (q) signal overlaps with $CDCl_3$] ppm. HRMS: calcd. for $C_{16}H_{15}O_2INa$ $[M + Na]^+$ 389.0009; found 389.0024.

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3-(4-Hydroxybut-1-ynyl)-4-iodo-1*H*-isochromen-1-one (4c): Compound **4c** was prepared following the general procedure from diyne **3d** (0.70 mmol, 159 mg) in CH_2Cl_2 (9 mL), and I_2 (0.76 mmol, 194 mg) in CH_2Cl_2 (11 mL). The reaction time was 24 h (Table 2, entry 4). Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) gave a mixture of **4c** and starting material **3d** (120 mg); ratio **4c**/**3d** = 1:0.25 according to ^{1}H NMR spectroscopy. Recrystallization of the mixture from petroleum ether/CH_2Cl_2 (3:1) gave **4c** (95.0 mg, 40 %) as a white solid, m.p. 120–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 7.9 Hz, 1 H), 7.76–7.80 (m, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.53–7.57 (m, 1 H), 3.90 (t, J = 6.1 Hz, 2 H), 2.83 (t, J = 6.2 Hz, 2 H), 1.99 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (q), 140.4 (q), 137.5 (q), 135.9 (t), 131.5 (t), 130.1 (t), 129.9 (t), 121.3 (q), 96.8 (q), 83.2 (q), 78.3 (q), 60.6 (s), 24.2 (s) ppm. HRMS: calcd. for $C_{13}H_{10}O_3I$ $[M + H]^+$ 340.9669; found 340.9669.

3-(Phenylethynyl)-1*H*-isochromen-1-one (9): A stirred solution of 3-phenylethynyl-4-iodoisochromene (**4a**, 0.13 mmol, 48.4 mg), diisopropanolamine (0.54 mmol, 72.0 mg), $Pd(PPh_3)_4$ (0.007 mmol, 7.8 mg), and PPh_3 (0.013 mmol, 3.5 mg) in DMF (2 mL) was evacuated and flushed with Ar several times. Then CuI (0.020 mmol, 3.8 mg) was added, and the reaction mixture was evacuated and flushed with Ar once again. The vial was sealed, and warmed up to 50 °C. Hex-1-yne (**8a**; 0.27 mmol, 22.0 mg) was added to the reaction mixture, and the vial was heated with stirring for 5 h. After this time, the mixture was cooled, and the reaction mixture was worked up as described for compounds **3**. Purification of the crude product by column chromatography on silica gel (petroleum ether/acetone, 20:1) gave **9** (9.0 mg, 27 %) as a white solid, m.p. 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 7.9 Hz, 1 H), 7.70–7.75 (m, 1 H), 7.51–7.57 (m, 3 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.36–7.41 (m, 3 H), 6.82 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9 (q), 138.4 (q), 136.8 (q), 135.1 (t), 132.3 (t), 132.0 (t), 130.0 (t), 129.8 (t), 129.2 (t), 128.7 (t), 125.9 (t), 121.6 (q), 121.3 (q), 111.4 (t), 93.8 (q), 82.1 (q) ppm. HRMS: calcd. for $C_{17}H_{11}O_2$ $[M + H]^+$ 247.0759; found 247.0731.

General Method for the Synthesis of Isocoumarin-Fused Enediynes 10 by Sonogashira Coupling: A stirred solution of 3-ethynyl-4-iodo-1*H*-isochromen-1-one (**4**, 1 equiv.) and $PdCl_2(PPh_3)_2$ (5 mol-%) in DMF was evacuated and flushed with Ar several times. Then CuI (5 mol-%) was added, and the reaction mixture was evacuated and flushed with Ar once again. The reaction vial was sealed, and diisopropylamine (4 equiv.) was added. The reaction mixture was warmed up to 50 °C, and a terminal acetylene (4 equiv.) was added. The reaction mixture was heated with stirring for the appropriate time (Table 3). The mixture was then cooled, and worked up as described for compounds **3**.

4-(3-Hydroxyprop-1-ynyl)-3-(phenylethynyl)-1*H*-isochromen-1-one (10a): Compound **10a** was synthesized following the general method from isochromenone **4a** (0.13 mmol, 48.0 mg) and propargyl alcohol (**8b**; 0.52 mmol, 29.0 mg) in DMF (2 mL). The reaction time was 1 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1 then 1:1) gave **10a** (26.5 mg, 68 %) as a white solid, m.p. 188–189 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.20 (d, J = 7.9 Hz, 1 H), 7.96–7.99 (m, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.61–7.76 (m, 3 H), 7.44–7.60 (m, 3 H), 5.58 (t, J = 6.0 Hz, 1 H), 4.50 (d, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (q), 140.6 (q), 136.2 (t), 135.4 (q), 132.1 (t), 130.8 (t), 130.5 (t), 129.7 (t), 129.4 (t), 125.4 (t), 120.36 (q), 120.34 (q), 107.7 (q), 100.2 (q), 98.4 (q), 82.1 (q), 75.8 (q), 50.0 (s) ppm. HRMS: calcd. for $C_{20}H_{13}O_3$ $[M + H]^+$ 301.0859; found 301.0847.

4-(Hex-1-ynyl)-3-(phenylethynyl)-1*H*-isochromen-1-one (10b): Compound **10b** was synthesized following the general method from isochromenone **4a** (0.13 mmol, 48.0 mg) and hex-1-yne (**8a**; 0.52 mmol, 42.7 mg). The reaction time was 20 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/acetone, 60:1) gave **10b** (31.4 mg, 72 %) as a white solid, m.p. 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.9 Hz, 1 H), 7.87 (d, J = 7.8 Hz, 1 H), 7.77–7.82 (m, 1 H), 7.54–7.59 (m, 3 H), 7.36–7.44 (m, 3 H), 2.60 (t, J = 7.0 Hz, 2 H), 1.65–1.71 (m, 2 H), 1.53–1.61 (m, 2 H), 0.95 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (q), 141.0 (q), 136.6 (q), 135.2 (t), 132.2 (t), 129.83 (t), 129.81 (t), 129.3 (t), 128.7 (t), 125.6 (t), 121.6 (q), 120.8 (q), 108.4 (q), 100.9 (q), 97.9 (q), 82.4 (q), 72.7 (q), 30.9 (s), 22.2 (s), 19.7 (s), 13.7 (p) ppm. HRMS: calcd. for $C_{23}H_{19}O_2$ $[M + H]^+$ 327.1382; found 327.1380.

3-(Phenylethynyl)-4-[(trimethylsilyl)ethynyl]-1*H*-isochromen-1-one (10c): Compound **10c** was synthesized following the general method from isochromenone **4a** (0.13 mmol, 48.0 mg) and trimethylsilylacetylene (**8c**, 0.52 mmol, 51.1 mg). Reaction time was 2 h. Purification of the crude product by column chromatography on silica gel using petroleum ether/acetone (60:1) gave 40.0 mg (90 %) of **10c** as a white solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 7.8 Hz, 1 H), 7.87 (d, J = 7.4 Hz, 1 H), 7.80–7.84 (m, 1 H), 7.55–7.60 (m, 3 H), 7.37–7.45 (m, 3 H), 0.34 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5 (q), 142.2 (q), 135.9 (q), 135.3 (t), 132.1 (t), 130.0 (t), 129.9 (t), 129.5 (t), 128.7 (t), 125.5 (t), 121.4 (q), 120.6 (q), 107.7 (q), 105.4 (q), 98.7 (q), 96.5 (q), 82.2 (q), 0.1 (p) ppm. HRMS: calcd. for $C_{22}H_{19}O_2Si$ $[M + H]^+$ 343.1148; found 343.1149.

3-(Hept-1-ynyl)-4-(phenylethynyl)-1*H*-isochromen-1-one (10d): Compound **10d** was synthesized following the general method from isochromenone **4b** (0.14 mmol, 50.0 mg) and phenylacetylene (**8d**; 0.56 mmol, 57.2 mg). The reaction time was 1 h. Purification of the crude product by column chromatography on silica gel (light petroleum/acetone, 60:1) gave **10d** (43.0 mg, 90 %) as a white solid, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, J = 0.6, J = 7.9 Hz, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.79–7.83 (m, 1 H), 7.54–7.60 (m, 3 H), 7.38–7.40 (m, 3 H), 2.55 (t, J = 7.0 Hz, 2 H, CH_2), 1.63–1.70 (m, 2 H), 1.43–1.50 (m, 2 H), 1.30–1.37 (m, 2 H), 0.87 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (q), 141.7 (q), 136.2 (q), 135.2 (t), 131.8 (t), 129.9 (t), 129.2 (t), 129.0 (t), 128.6 (t), 125.3 (t), 122.9 (q), 120.6 (q), 106.8 (q), 101.8 (q), 98.1 (q), 81.6 (q), 74.1 (q), 31.1 (s), 27.9 (s), 22.3 (s), 19.9 (s), 14.0 (p) ppm. HRMS: calcd. for $C_{24}H_{21}O_2$ $[M + H]^+$ 341.1536; found 341.1541.

3-(Hept-1-ynyl)-4-[(trimethylsilyl)ethynyl]-1*H*-isochromen-1-one (10e): Compound **10e** was synthesized following the general method from isochromenone **4b** (0.14 mmol, 50.0 mg) and trimethylsilylacetylene (**8c**; 0.56 mmol, 54.9 mg). The reaction time was 3 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/acetone, 60:1) gave **10e** (36.0 mg, 76 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, J = 7.8 Hz, 1 H), 7.76–7.83 (m, 2 H), 7.55–7.51 (m, 1 H), 2.52 (t, J = 7.1 Hz, 2 H), 1.62–1.70 (m, 2 H), 1.43–1.50 (m, 2 H), 01.32–1.41 (m, 2 H), 0.93 (t, J = 7.2 Hz, 3 H), 0.31 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (q), 142.6 (q), 136.1 (q), 135.2 (t), 129.8 (t), 129.1 (t), 125.3 (t), 120.5 (q), 106.7 (q), 104.4 (q), 101.6 (q), 96.8 (q), 74.0 (q), 31.2 (s), 27.9 (s), 22.3 (s), 19.8 (s), 14.0 (p), 0.0 (p) ppm. HRMS: calcd. for $C_{21}H_{25}O_2Si$ $[M + H]^+$ 337.1618; found 337.1624.

3-(Hept-1-ynyl)-4-(4-hydroxybut-1-ynyl)-1*H*-isochromen-1-one (10f): Compound **10f** was synthesized following the general method from isochromenone **4b** (0.14 mmol, 50.0 mg) and but-3-yn-1-ol **8e** (0.56 mmol, 39.2 mg). The reaction time was 22 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) gave **10f** (27.0 mg, 63 %) as

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a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, J = 7.9 Hz, 1 H), 7.73–7.81 (m, 2 H), 7.50–7.53 (m, 1 H), 3.88 (t, J = 6.2 Hz, 2 H), 2.81 (t, J = 6.2 Hz, 2 H), 2.51 (t, J = 7.1 Hz, 2 H), 2.12 (br. s, 1 H), 1.63–1.68 (m, 2 H), 1.40–1.49 (m, 2 H), 1.31–1.40 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (q), 141.7 (q), 136.3 (q), 135.2 (t), 129.8 (t), 129.1 (t), 125.2 (t), 120.6 (q), 106.7 (q), 101.0 (q), 95.8 (q), 74.9 (q), 74.1 (q), 61.1 (s), 31.1 (s), 27.9 (s), 24.4 (s), 22.3 (s), 19.8 (s), 14.0 (p) ppm. HRMS: calcd. for $C_{20}H_{21}O_3$ $[M + H]^+$ 309.1485; found 309.1496.

3-(4-Hydroxybut-1-ynyl)-4-(phenylethynyl)-1*H*-isochromen-1-one (10g): Compound **10g** was synthesized following the general method from isochromenone **4c** (0.0880 mmol, 30.0 mg) and phenylacethylene **8d** (0.35 mmol, 36.0 mg). The reaction time was 2 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) gave **10g** (19.0 mg, 68 %) as a white solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 7.9 Hz, 1 H), 7.89 (d, J = 8.0 Hz, 1 H), 7.78–7.82 (m, 1 H), 7.54–7.60 (m, 3 H), 7.39–7.41 (m, 3 H), 3.88 (t, J = 6.2 Hz, 2 H), 2.82 (t, J = 6.2 Hz, 2 H), 1.98 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6 (q), 141.1 (q), 135.9 (q), 135.3 (t), 131.8 (t), 129.9 (t), 129.4 (t), 129.2 (t), 128.7 (t), 125.3 (t), 122.6 (q), 120.7 (q), 107.6 (q), 98.6 (q), 97.8 (q), 81.4 (q), 75.6 (q), 60.7 (s), 24.3 (s) ppm. HRMS: calcd. for $C_{21}H_{15}O_3$ $[M + H]^+$ 315.1016; found 315.1022.

3-(4-Hydroxybut-1-ynyl)-4-(3-methoxyprop-1-ynyl)-1*H*-isochromen-1-one (10h): Compound **10h** was synthesized following the general method from a mixture of isochromenone **4c** and ester **3d** (**4c**/**3d** = 1:0.25; 0.089 mmol of **4c**, 35.2 mg of the mixture) obtained after electrophilic cyclization, and 3-methoxyprop-1-yne (**8f**; 0.356 mmol, 24.9 mg). The reaction time was 22 h. Purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) gave **10h** (9.0 mg, 36 %) as a white solid, m.p. 44–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 7.9 Hz, 1 H), 7.76–7.82 (m, 2 H), 7.56 (ddd, J = 8.2, J = 6.4 Hz, J = 2.2 Hz, 1 H), 4.44 (s, 2 H), 3.87 (t, J = 6.0 Hz, 2 H), 3.51 (s, 3 H), 2.79 (t, J = 6.0 Hz, 2 H), 2.29 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4 (q), 141.8 (q), 135.8 (q), 135.3 (t), 129.9 (t), 129.5 (t), 125.2 (t), 120.6 (q), 106.8 (q), 97.9 (q), 94.2 (q), 78.7 (q), 75.4 (q), 60.7 (s), 60.6 (s), 58.1 (p), 24.4 (s) ppm. HRMS: calcd. for $C_{17}H_{15}O_4$ $[M + H]^+$ 283.0965; found 283.0968.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all compounds; copies of HMBC and COSY spectra for iodoisocoumarins **4**; structural elucidation of iodoisocoumarins **4** by 2D NMR spectroscopy; copies of DSC and TGA thermograms.

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