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Electrophilic Cyclization of Aryldiacetylenes in the Synthesis of Functionalized Enediynes Fused to a Heterocyclic Core

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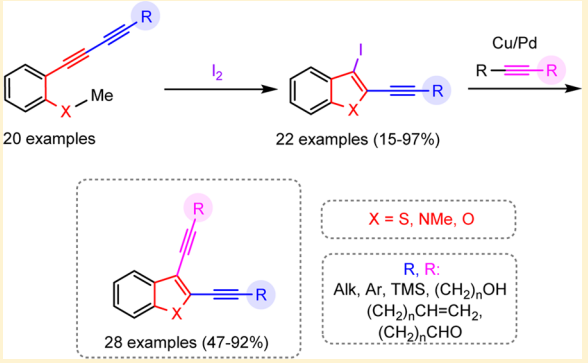
Supporting Information

ABSTRACT: An efficient strategy for the synthesis of asymmetrically substituted enediynes fused to benzothiophene, benzofuran, and indole was developed. The proposed approach is based on the electrophilic cyclization of diacetylenes and Sonogashira coupling. Thus, iodocyclization of readily available *ortho*-functionalized (buta-1,3-diynyl)arenes was used as a direct way for the synthesis of 2-ethynyl-3-iodoheteroindenes. These substrates and their modified derivatives were easily converted by Sonogashira coupling with acetylenes to a variety of asymmetrically substituted acyclic enediynes fused to heterocycles. The tolerance of the developed methodology to a variety of functional groups is a great advantage in the synthesis of macrocyclic enediyne systems fused to a heterocyclic core. Synthesis of indole-fused 12-membered macrocyclic dienediyne was achieved using ring-closing metathesis as a key step.



INTRODUCTION

Nowadays, the development of new, efficient anticancer drugs is one of the most important challenges for scientists around the world. A great variety of different classes of organic compounds with antitumor properties have been isolated from natural products.[1] Acetylene derivatives make a considerable contribution to this type of natural products.[2] Enediyne antibiotics, which first were isolated from different kinds of *Actinomyces* in the 1960s, represent an important family of naturally occurring acetylenic anticancer molecules.[3]

The key features of the enediynes structure are (*Z*)-hex-3-en-1,5-diyne or masked enyneallene moieties, which are able to undergo Bergman[4a] or Myers–Saito-type cyclizations,[4b,c] respectively, with the formation of highly reactive biradicals. These species abstract H atoms from the carbohydrate moiety in the DNA backbone that leads to DNA damage and cell death.[3a,4d−f]

Naturally occurring enediynes display the strongest antitumor activity among known antineoplastic agents.[2,3a] Nevertheless, despite the fact that many enediynes have been evaluated through phases I and II of clinical trials, only one drug based on neocarcinostatin (SMANCS) has been approved for patients with liver cancer in Japan.[3a] The second one, Mylotarg, was taken off the pharmaceutical market in 2010.[5] These problems are associated with the high instability, short half-life, high toxicity, allergenicity, and, therefore, narrow therapeutic window of naturally occurring enediynes. However, the remarkable potency of enediynes as anticancer agents provides a strong motivation to discover the next generation of these compounds. For this reason, the development of simple synthetic analogues of naturally occurring enediynes is a very important and attractive challenge for chemists and biologists.

During the last several decades, a large number of results in this field have been reported. The main trends of these investigations are summarized in several excellent reviews.[3b,f−k] From these data, two important trends can be identified. The first of these is the investigation of structure−activity relationships among different enediyne systems (Scheme 1, *a*−*d*).

It was found that in order for the Bergman cyclization (BC) to proceed at ambient temperature (≤37 °C) the *cd* distance should lie within 2.9−3.4 Å and the activation energy for the formation of biradical species should not exceed 22−24 kcal/mol.[3g,6] The majority of naturally occurring enediynes with an enediyne scaffold incorporated into a 9- or 10-membered ring match these conditions (Scheme 1, *a*). In these cases, macrocyclic systems on one hand are synthetically accessible and on the other are strained enough to undergo cycloaromatization at ambient temperatures. However, there is no predictive linear relationship between the *cd* distance and a value for the activation energy for BC, because the change of the strain energy in the transition and ground states was found to be the most important parameter.[7]

In addition, the nature of a substituents upon the enediyne scaffold influences the cyclization ability of the enediyne moieties: electron-withdrawing groups are favorable for the cyclization[3j,8]

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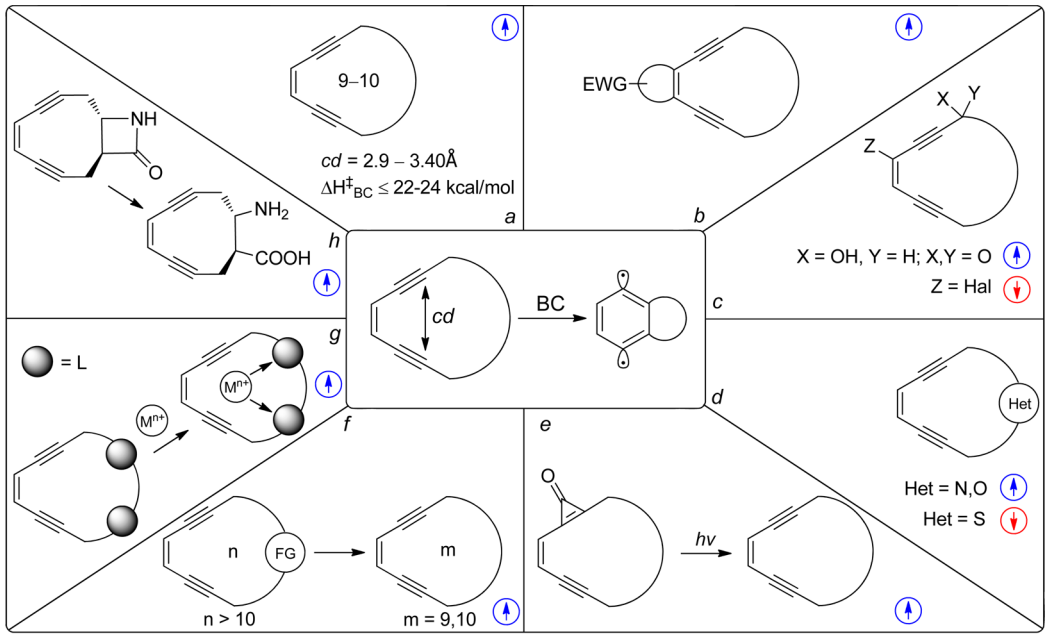
Scheme 1. Relationships between Structure of Enediynes and Their Activity in Bergman Cyclization



(Scheme 1, *b*); halogen atoms and other electron-withdrawing groups being attached at a vinyl position stabilizes the enediyne system against cyclization,[3j,9] whereas OH and C=O groups neighboring a triple bond carbon atom facilitate Bergman cyclization[10] (Scheme 1, *c*). Incorporation of oxygen[11a] and nitrogen atoms[11b,c] into enediyne macrocyclic system promotes the cyclization, whereas thiaenediynes are less active (Scheme 1, *d*).[12]

The second trend noted is the elaboration of highly reactive enediynes from their nonactive precursors or from molecules with a masked enediyne moiety (Scheme 1, *e*–*h*). The triggering process for such enediynes was achieved by light (Scheme 1, *e*),[3f,13] redox processes,[14] complexation with transition metal ions (Scheme 1, *g*),[3k,15] ring contraction under chemical[16a] and photochemical conditions,[16b,c] (Scheme 1, *f*) and by the reduction of strain energy in the transition state by cleavage of a four-membered lactam cycle fused to an enediyne scaffold (Scheme 1, *h*).[17]

Each approach obviously has its own advantages and limitations. Nevertheless, the ideal enediyne system has not yet been synthesized, and investigations in this area are still active.[18] From this point of view it should be noted that a heterocycle fused to an enediyne system may significantly influence the properties of the whole molecule. Moreover, it is known that molecules as small and flat as heterocycles impart intercalation ability to larger molecules.[19] This property is very promising in the case of enediyne systems because binding of enediyne molecules to DNA is necessary to promote DNA damage, and this binding can be achieved either by interaction with the DNA minor groove or by intercalation.[3a,20]

However, among hundreds of publications devoted to enediyne systems, there are only a few manuscripts that describe acyclic enediyne systems fused to a heterocyclic core.[8a,21] As a result, only four examples of a macrocyclic enediyne annelated with pyrimidine,[22] imidazole,[21d,e] furan,[14a] and cinnoline[8b] have been reported. This fact can be explained by the lack of efficient synthetic approaches toward heterocycle-fused enediyne systems. Known routes include double Sonogashira coupling of terminal acetylenes with dihalo- or halogen-triflate heterocycles,[8a,21a,b,d,e,g–i,22] rearrangement of bisvinylidenecarbene heterocycles to corresponding acetylene derivatives,[21c,k] Seyferth–Gilbert homologation,[21b,k] or even Negishi coupling.[21l] Undoubtedly, these approaches are not convenient for the synthesis of asymmetrically substituted enediyne systems, which are more useful substrates for generation of the corresponding macrocyclic enediynes.

The Richter-type cyclization of *ortho*-(alka-1,3-diynyl)-arenediazonium salt[23] was reported by us as a synthetic approach that allowed the construction of a cinnoline ring and introduction of an ethynyl moiety and a bromine atom to neighboring carbon atoms of the heterocycle formed in one step. Subsequent displacement of the halide by a second acetylene fragment gave asymmetrically substituted enediynes. This approach was used as a key step in the synthesis of 10-membered enediyne fused to a cinnoline ring[8b] and remains distinct from all methods described above. The limitation of this approach is its applicability to only one type of heterocycle, i.e., cinnoline.

Searching for a more general approach, we focused on the electrophilic cyclization of functionalized acetylenes, which was widely studied by Larock's group and others,[24] as a general method for the construction of a wide diversity of heterocycles[24a] as well as heterocycles with a halogen moiety.[24]

Switching to the iodocyclization of functionalized diynes without affecting one of the triple bonds opens access to a variety of heterocyclic systems containing both halogen and ethynyl moieties at neighboring carbon atoms. Recently, we reported briefly that electrophilic cyclization of diacetylenic derivatives of thioanisole, anisole, and *N*,*N*-dimethylaniline can be used in the synthesis of iodoethynylheteroindenes[25a] and as a key step in the preparation of a macrocyclic dienediyne system fused to a benzothiophene ring.[25b]

Herein, we report the full investigation of the scope and limitations of the approach proposed. Synthesis of *ortho*-functionalized aryldiacetylenes by Sonogashira coupling followed by their electrophilic cyclization and a second

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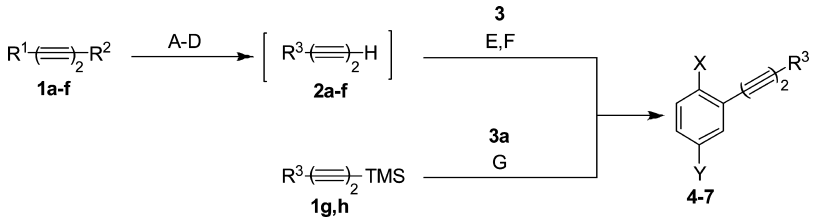
Sonogashira reaction of the corresponding iodoethynylheterocycles with monoacetylenes are discussed in detail. In this article, particular attention was given to the synthesis of heterocycle-fused enediyne systems with different functional groups at both ethynyl moieties. These functional groups are of crucial importance for further synthesis of macrocyclic enediynes, which can be obtained by a variety of different macrocyclization techniques.

Table 1. Synthesis of *Ortho*-Functionalized (Buta-1,3-diynyl)arenes 4–7



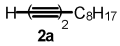
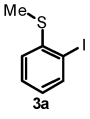
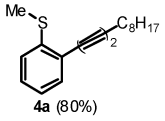
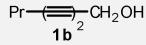
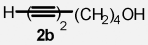
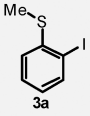
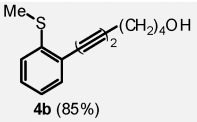
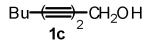
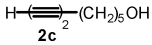
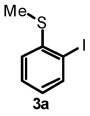
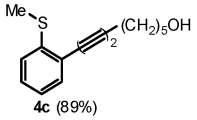
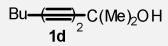
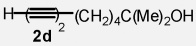
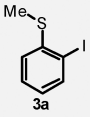
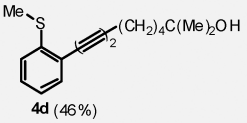
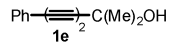
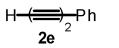
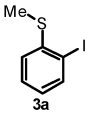
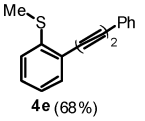
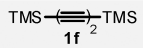
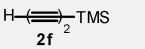
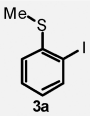
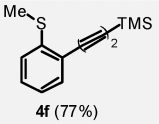
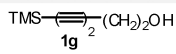
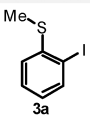
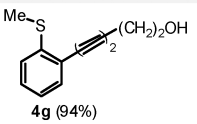
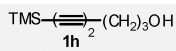
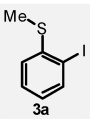
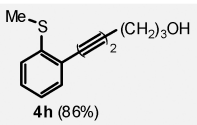
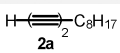
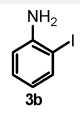
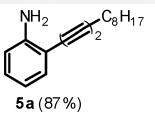
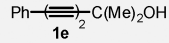
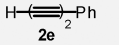
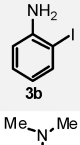
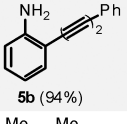
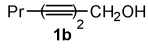
entry	internal diyne, **1**	method [a]	terminal diyne, **2**	iodoarene, **3**	method [b]	Product **4–7** (isolated yield, %)
1	 **1a**	A	 **2a**	 **3a**	D	 **4a** (80%)
2	 **1b**	A	 **2b**	 **3a**	E	 **4b** (85%)
3	 **1c**	A	 **2c**	 **3a**	E	 **4c** (89%)
4	 **1d**	A	 **2d**	 **3a**	E	 **4d** (46%)
5	 **1e**	B	 **2e**	 **3a**	D	 **4e** (68%)
6	 **1f**	C	 **2f**	 **3a**	D	 **4f** (77%)
7	 **1g**	-	-	 **3a**	F	 **4g** (94%)
8	 **1h**	-	-	 **3a**	F	 **4h** (86%)
9	 **1a**	A	 **2a**	 **3b**	D	 **5a** (87%)
10	 **1e**	B	 **2e**	 **3b**	D	 **5b** (94%)
11	 **1b**	A	**2b**	**3c**	E	**6a** (79%)

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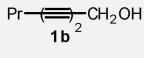
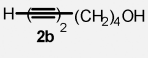
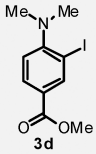
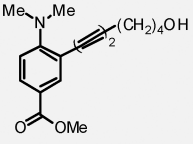
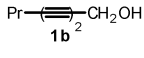
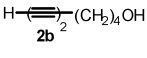
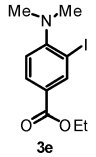
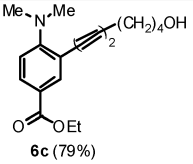
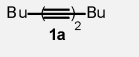
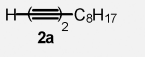
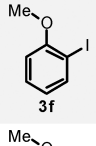
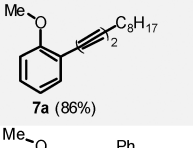
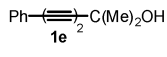
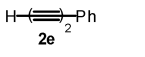
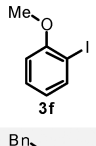
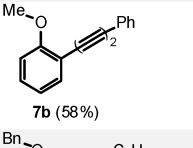
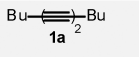
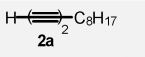
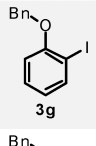
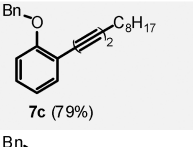
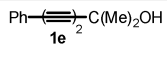
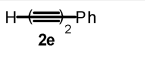
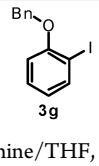
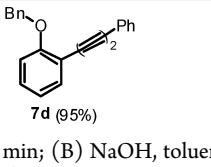
Table 1. continued

entry	internal diyne, **1**	method [a]	terminal diyne, **2**	iodoarene, **3**	method [b]	Product **4**–**7** (isolated yield, %)
12	 **1b**	A	 **2b**	 **3d**	E	 **6b** (82%)
13	 **1b**	A	 **2b**	 **3e**	E	 **6c** (79%)
14	 **1a**	A	 **2a**	 **3f**	D	 **7a** (86%)
15	 **1e**	B	 **2e**	 **3f**	D	 **7b** (58%)
16	 **1a**	A	 **2a**	 **3g**	D	 **7c** (79%)
17	 **1e**	B	 **2e**	 **3g**	D	 **7d** (95%)

[a]Conditions for the synthesis of terminal diacetylenes: (A) LAETA, ethylenediamine/THF, 15–20 °C, 10 min; (B) NaOH, toluene, 70 °C, 50 min; (C) MeLi/LiBr, Et_2O. [b]Conditions for the Sonogashira coupling: (D) $Pd(PPh_3)_4$/CuI, Et_3N; (E) $Pd(PPh_3)_2Cl_2$/CuI, diisopropanolamine (DIPA), DMF; (F) $Pd(PPh_3)_4$/CuI, K_2CO_3, MeOH, DMF.

RESULTS AND DISCUSSION

Synthesis of Starting Materials. Functionalized *ortho*-(buta-1,3-diynyl)arenes **4**–**7**, starting compounds for the electrophilic cyclization, were synthesized in several ways. The most efficient synthetic route to this type of compound is the Sonogashira coupling[26] of *ortho*-functionalized iodoarenes **3a**–**g** with terminal diacetylenes (Table 1). Terminal diacetylenes with alkyl (**2a**) and hydroxyalkyl substituents (**2b**–**d**) were easily obtained by treatment of corresponding internal diacetylene compounds **1a**–**d** with lithium 2-aminoethylamide (LAETA) (diacetylene zipper reaction)[27] (Table 1, Method A), which were then used without purification in Cu/Pd-catalyzed cross-coupling. This route was employed in the synthesis of the corresponding thioanisoles **4a**–**d** (Table 1, entries 1–4), anilines **5a** and **6a**–**c** (Table 1, entries 9, 11–13), and *O*-alkylated phenols **7a**,**c** (Table 1, entries 14, 16).

Phenyl- (**2e**) and TMS-substituted (**2f**) buta-1,3-diynes were synthesized according to known procedures (Table 1, Methods B, C)[28a,b] and were used subsequently in Sonogashira reactions without purification, providing the corresponding aryldiacetylenes **4e**,**f**, **5b**, and **7b**,**d** in good yields (Table 1, entries 5, 6, 10, 15, and 17).

In the case of compounds **4g**,**h**, the diacetylene zipper reaction of the corresponding internal diacetylenic alcohols is not easy to perform because it demands handling of gaseous acetylenes (propyne, 1-butyne) as starting materials for the preparation of corresponding internal diynes. Therefore, a special procedure for the synthesis of compounds **4g**,**h** based on one-pot TMS group removal and Sonogashira coupling starting from TMS-protected diacetylenes **1g**,**h** and *o*-iodothioanisole **3a** was developed (Table 1, entries 7, 8). In this case, a K_2CO_3/MeOH system was used as both a TMS-deprotection source and a base in the Sonogashira coupling. This route, which was used earlier with a Ag^I/Pd^0 system,[29] turned out to be very efficient in the synthesis of alcohols **4g**,**h** applying Cu^I/Pd^0 catalysts (Table 1, entries 7 and 8); moreover, it did not require an excess of the commonly used TMS-protected diacetylene, which is an important advantage of the developed procedure.

It was surprising that common conditions for the Sonogashira coupling (Pd/Cu, Et_3N, Table 1, Method D) that were efficient in the synthesis of compounds **4a**,**e**,**f** and **7a**–**d** (Table 1, entries 1, 5, 6, and 14–17) including *ortho*-(buta-1,3-diynyl)anilines **5a**,**b** (Table 1, entries 9, 10) as well as for the preparation of *ortho*-ethynyl-*N*,*N*-dimethylanilines[30] did not work for the Sonogashira coupling of *ortho*-iodo-*N*,*N*-dimethylanilines with terminal diacetylenes. Using DIPA as a base and DMF as a solvent was successful for the Sonogashira coupling of *ortho*-iodo-*N*,*N*-dimethylanilines with terminal diacetylenes and gave *ortho*-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines **6a**–**c** in good yields (Table 1, entries 11–13), whereas

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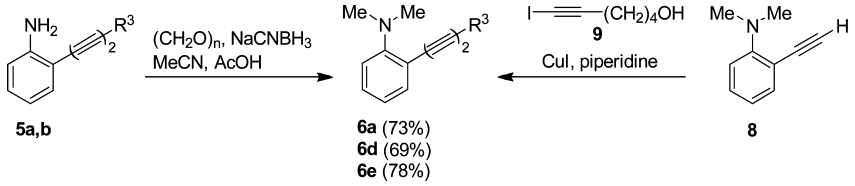
Scheme 2. Synthesis of Butadiynyl-*N*,*N*-dimethylanilines 6a,d,e via Alternative Methods[a]



[a]R^3 = C_8H_{17} (**5a**, **6d**), Ph (**5b**, **6e**), $(CH_2)_4OH$ (**6a**).

compounds **6d,e** were obtained by reductive methylation of corresponding anilines **5a,b**[31] (Scheme 2).

Optimized conditions for the coupling (Pd/Cu, DIPA, DMF, Table 1, Method E) were also the best for the synthesis of hydroxyalkylthioanisole derivatives (Table 1, entries 2–4).

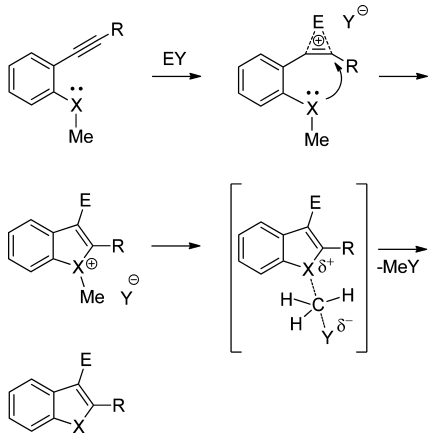
An alternative route to asymmetrically substituted buta-1,3-diynes is the Cadiot–Chodkiewicz coupling.[32] Taking into account that 2-ethynyl-*N*,*N*-dimethylaniline (**8**) can be easily synthesized,[30] we tested this widely used reaction in the synthesis of *o*-(buta-1,3-diynyl)-*N*,*N*-dimethylaniline **6a** (Scheme 2). Nevertheless, a lower overall yield and more expensive starting compounds, in comparison with that for the approaches discussed above, prompted us to reject this route in favor of the Sonogashira reaction of diacetylenes.

Thus, the Sonogashira coupling of terminal diacetylenes and their TMS derivatives with *ortho*-iodothioanisole, anisole, and *N*,*N*-dimethylanilines proved to be an efficient and convenient synthetic path to the corresponding *ortho*-*S*,*N*,*O*-functionalized aryldiacetylenes, which, in the next step, were used as substrates for the electrophilic cyclization.

Electrophilic Cyclization. During the past decade, an increasing number of S, N, O, Se, and Si cyclizations of acetylene derivatives in the presence of electrophiles have been reported as a general synthetic approach for the preparation of different heterocycles (heteroindenes, coumarins, chromones, quinolines, isoquinolines, oxazoles, thiazines, etc.) under relatively mild reaction conditions.[24]

The generally accepted mechanism of the electrophilic cyclization includes activation of the triple bond by an external electrophile followed by intramolecular nucleophilic attack of a heteroatom upon the activated triple bond. The reaction ends with the elimination of a leaving group via a S_N2 substitution reaction and the formation of the haloheterocycle (Scheme 3).[24b]

Scheme 3. Proposed Mechanism of the Electrophilic Cyclization of *Ortho*-Functionalized Arylacetylenes



Despite the fact that this reaction is well-studied among monoacetylenes, its mechanism has not been investigated in detail; thus, the rate-determining step is still unknown. It was shown that nucleophilicity of functional groups as well as electronic effects of substituents in aryl rings can either favor the cyclization or can be unfavorable for the formation of the heterocyclic product.[33] It was also noted that solubility of the onium salt intermediate in different solvents influences the reaction.[34] Nevertheless, there is no doubt that all transition states and intermediates in this process are partly or fully charged, so the polarity and solvation ability of the solvent employed will dramatically influence the reaction rate and yields. On the basis of this knowledge and our previous results, two solvents with different polarity (MeCN and DCM) were compared in order to choose the optimal conditions for the synthesis of ethynyliodoheterocycle-containing targets (Table 2).

Electrophilic cyclization of phenyl- (**4e**) (Table 2, entry 1), trimethylsilyl- (**4f**) (Table 2, entry 2), and hydroxyalkyl-substituted thioanisoles **4g,h** (Table 2, entries 3, 4) was faster in DCM than that in MeCN; moreover, using DCM as a solvent allowed us to obtain iodobenzothiophenes **10a,b,d,e** in almost quantitative yields (Table 2, entries 1–4). Increasing the reaction temperature to 40 °C notably decreased the reaction time that was used in the scale-up syntheses (5–15 mmol) of benzothiophene derivatives **10f–h** (Table 2, entries 5–7).

Iodocyclization of *N*,*N*-dimethylaniline derivatives **6a,d,e** in MeCN (Table 2, entries 8–10) proceeded slower than *S*-cyclization due to the decreased nucleophilicity of the nitrogen compared to that of the sulfur atom. These substrates demanded heating at 40 °C in MeCN over 5–20 h, whereas in DCM, the same reaction was accomplished within half of an hour with the formation of indole derivatives **11a–g** in satisfactory and good yields (Table 2, entries 8–14). Even electron-withdrawing groups in the arene ring did not hamper the formation of desired iodoethynylindoles **11e–g** in high yields (Table 2, entries 12–14). It was found that in the case of dimethylaniline derivatives with hydroxyalkyl substituents **6a–c** protection of the OH group with bulky silyl ethers was essential for the achievement of high yields of iodoindoles **11d,f,g** and to scaling-up the reaction up to 5–15 mmol (Table 2, entries 11, 13, and 14). The reaction with unprotected substrates **6a,c** ran only in the microscale range and was accompanied by the formation of byproducts with an iodinated triple bond. Although we were able to isolate unprotected indoles **11c,e** in rather good yields (Table 2, entries 10 and 12), fine chromatographic separation of the desired products from the byproducts was time- and resource-consuming.

One of the possible ways to modify the OH group is via substitution by halogen atoms. The substitution is usually carried out under Appel reaction conditions[36a] (halogen source, PPh_3). Thus, by using iodine, PPh_3, and imidazole, different alcohols can be easily converted to iodoalkanes.[36b,c] Because

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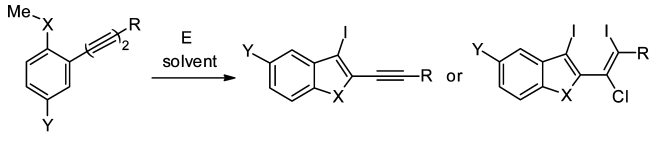
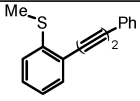
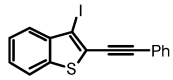
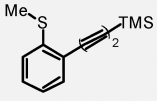
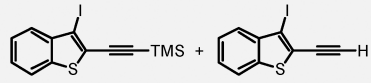
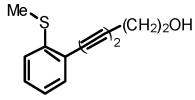
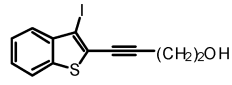
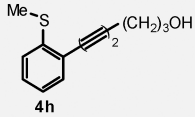
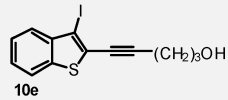
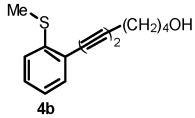
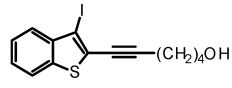
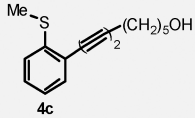
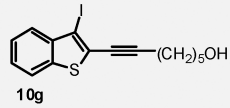
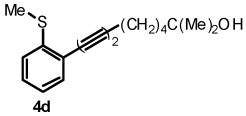
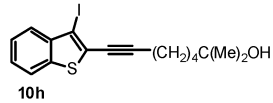
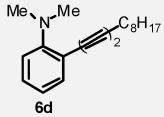
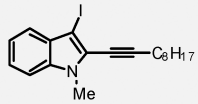
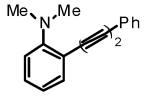
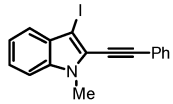
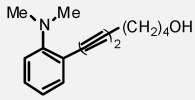
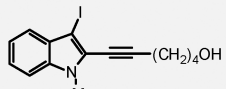
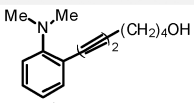
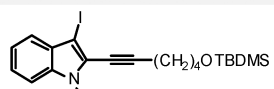
iodine is a suitable electrophile for the cyclization of *o*-functionalized aryldiacetylenes, we decided to combine these reactions in a one-pot synthesis in order to synthesize 3-iodo-2-iodoalkylethynylheteroindenes. It was found that the corresponding iodoethynylindole **11h** and iodobenzothiophene **10i** could be obtained in high yields (Scheme 4).

Table 2. Electrophilic Cyclization of *Ortho*-Functionalized (Buta-1,3-diynyl)arenes 4−7



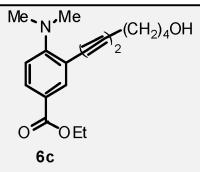
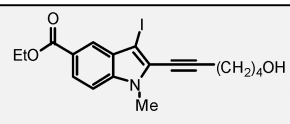
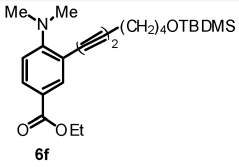
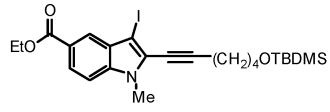
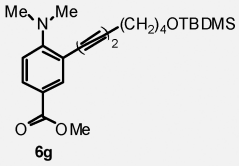
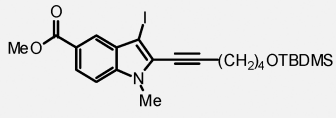
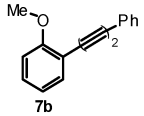
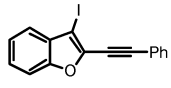
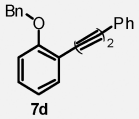
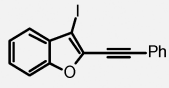
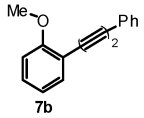
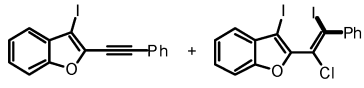
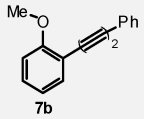
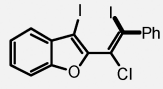
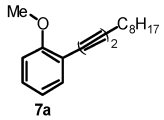
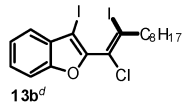
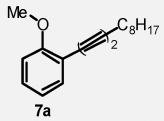
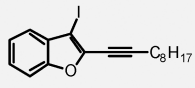
4-7 **10-12** **13**

E = I_2, ICl, IPy_2BF_4; solvent = MeCN, DCM

entry	substrate	conditions [a]	product	isolated yield, %
1	 **4e**	MeCN / rt / 3 h DCM / rt / 1.5 h	 **10a**	83 95
2	 **4f**	MeCN / rt / 3 h DCM / rt / 1.5 h	 **10b** **10c**	61:13 86:9
3	 **4g**	MeCN / rt / 3 h DCM / rt / 1.5 h	 **10d**	67 94
4	 **4h**	MeCN / rt / 5 h DCM / rt / 1.5 h	 **10e**	85 97
5	 **4b**	DCM / 40 °C / 0.5 h	 **10f**	93
6	 **4c**	DCM / 40 °C / 0.5 h	 **10g**	93
7	 **4d**	DCM / 40 °C / 0.5 h	 **10h**	83
8	 **6d**	MeCN / 40 °C / 5 h DCM / 40 °C / 0.5 h	 **11a**	89 55
9	 **6e**	MeCN / 40 °C / 5 h DCM / 40 °C / 0.5 h	 **11b**	75 65
10	 **6a**	MeCN / 40 °C / 20 h DCM / 40 °C / 0.5 h	 **11c**	72 75
11	 **6a**[b]	DCM / 40 °C / 0.5 h	 **11d**	77

dx.doi.org/10.1021/jo501396s | *J. Org. Chem.* 2014, 79, 9018−9045

Table 2. continued

entry	substrate	conditions [a]	product	isolated yield, %
12	 **6c**	DCM / 40 °C / 0.5 h	 **11e**	51
13	 **6f**	DCM / 40 °C / 0.5 h	 **11f**	76
14	 **6g**	DCM / 40 °C / 0.5 h	 **11g**	89
15	 **7b**	MeCN / 40 °C / overnight	 **12a**	16
16	 **7d**	ICl (1.5 equiv.) / MeCN / rt / overnight	 **12a**	49
17	 **7b**	ICl (1 equiv.) / DCM / rt / overnight	 **12a** **13a**	[c]
18	 **7b**	ICl (2 equiv.) / DCM / rt / overnight	 **13a**[d]	59
19	 **7a**	ICl (1.5 equiv.) / MeCN / rt / overnight	 **13b**[d]	38
20	 **7a**	Py_2IBF_4 (1.1 equiv.), $HBF_4{\cdot}Et_2O$ (1.1 equiv.) / DCM / rt to 30 °C / > 24 h	 **12b**	15

[a] I_2 (1.0 equiv) was used as the electrophile (entries 1−15). [b] Alcohol **6a** was converted to the corresponding TBDMS ether prior to the cyclization. [c] The mixture of **12a** and **13a** was detected by GC−MS monitoring. [d] The position of iodine and chlorine atoms in compounds **13a,b** was estimated by HMBC NMR experiments.[35]

Moreover, substitution of the OH group in the starting hydroxyalkyl aniline **6b** with iodine worked in the same way as that of *O*-TBDMS protection and afforded the formation of the corresponding iodoalkylethynyl indole **11h** without any byproducts.

In contrast to the results described above, the cyclization of diacetylenic derivatives of anisole proceeded with notable complications. Thus, iodocyclization of *ortho*-(4-phenylbuta-1,3-diynyl)anisole **7b** with 1 equiv of iodine in MeCN at 40 °C gave the desired product **12a** in an unsatisfactory yield due to poor conversion of the starting material (35%) (Table 2, entry 15). It was found that the use of iodine monochloride in MeCN is favorable for selective cyclization of *O*-benzylated derivative **7d**. In this case, 2-ethynylbenzofurane **12a** was isolated in 49% yield (Table 2, entry 16). The reaction of anisole **7b** with an equimolar amount of ICl in DCM led to the formation of a mixture of ethynylbenzofuran **12a** and byproduct **13a** with an iodochlorinated triple bond (Table 2, entry 17). Switching to a 2-fold excess of ICl accomplished the formation of benzofuran **13a** with an iodochlorinated triple bond (Table 2, entry 18) as a single reaction product.

Electrophilic cyclization of *ortho*-dodeca-1,3-diynylanisole **7a** mediated by iodine in MeCN as well as in DCM led to mixtures of reaction products **12b** and **13b** along with remaining

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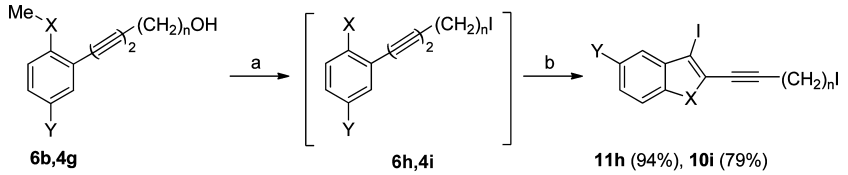
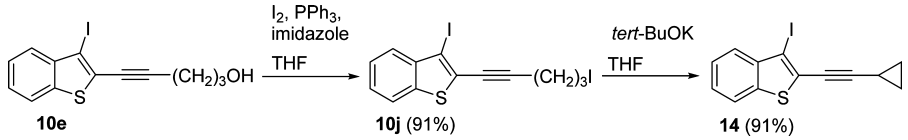
Scheme 4. One-Pot Synthesis of Diiodoheteroindenes[a]



[a]Reagents and conditions: (a) I_2, imidazole, PPh_3, −10 °C to rt, DCM; (b) I_2, 40 °C, DCM.

Scheme 5. Functional Group Modification in (Hydroxyalkylethynyl)benzothiophenes



starting material **7a** and starting compound **7a** with one iodinated triple bond. An attempt to use ICl in MeCN for the cyclization of anisole **7a** finished with the formation of 3-iodo-2-decynylbenzofurane with an iodochlorinated triple bond **13b** (Table 2, entry 19). Only the use of bis(pyridine)iodonium tetrafluoroborate allowed desired compound **12b** to be isolated, but the yield was low (Table 2, entry 20).

The low reactivity of alka-1,3-diynylanisole was expected, because similar results were observed in the case of electrophilic cyclization of *o*-(alk-1-ynyl)anisoles earlier. Thus, using iodine was absolutely ineffective in the synthesis of 2-alkyl-3-iodobenzofuran by electrophilic cyclization and led only to the iodination of the triple bond in the starting *o*-ethynylanisoles.[37] Evidently, this is because of the lower nucleophilicity of the alkoxy group in comparison with other nucleophilic groups and the higher reactivity of an alkyl-substituted triple bond toward electrophiles.

The empirical rank of reactivity of a single, activated triple bond toward different nucleophile functions is known to depend on electronic (relative nucleophilicity of the functional groups: SMe > COOMe > NMe_2 ≫ OMe > OBn; polarization of the carbon−carbon triple bond, and the cationic nature of the intermediate) and steric factors (hindrance and geometrical alignment of the functional groups).[33] The reactivity of diacetylene derivatives under electrophilic cyclization conditions observed herein is mostly in good accordance with the data established for monoacetylenes.

Moreover, the obtained data revealed that the use of less polar DCM for the electrophilic cyclization of *o*-methylsulfanyl- and *o*-dimethylaminoaryldiacetylenes is more efficient than carrying out these reactions in more polar acetonitrile. This observation could be explained by assuming that the last S_N2 dealkylation step is the limiting step of the overall process. The onium salt, which is the starting compound at this step, is more charged than the transition state and the reaction product (Scheme 3); therefore, the solvent with less polarity and solvation ability (DCM) would favor the reaction.

Synthesis and Properties of Enediynes. For the construction of the enediyne fragment fused to a heterocyclic core in the next step, the second ethynyl moiety was introduced into position 3 of the heterocycles obtained. At this stage, different types of substituents can be brought into enediyne systems easily along with the acetylene moiety: aryl and alkyl substituents and at least three different functional groups (OH−$(CH_2)_n$, TMS, terminal double bond), which are essential if macrocyclic enediyne systems are supposed to be target structures. These groups by themselves or after one or two steps might allow a lot of macrocyclization strategies to be applied that have been widely employed in the synthesis of enediynes (Nozaki−Hiyama−Kishi,[8b,13b,17,22,38a,e] pinacol coupling,[38b] McMurry reaction,[38c] intramolecular alkylation,[12,13a,16a,21d,e,38d,e] Mitsunobu reaction,[11c] ring-closing metathesis,[25b] and others).

Hydroxyalkyl groups can also be modified before the next Sonogashira coupling. Thus, in the case of hydroxyalkyl benzothiophene **10e**, a cyclopropyl moiety was easily introduced in two steps: the hydroxy group in **10e** was substituted by iodine, affording the diiodobenzothiophene **10j**. The last step involved the synthesis of cyclopropyl derivative **14** (Scheme 5).

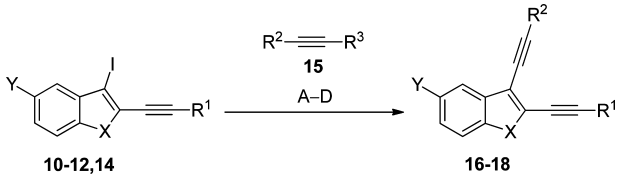
Iodoethynylheterocycles **10a,d−h**, **11a,d−g**, **12a**, and **14** were used as starting materials for a second Sonogashira reaction within the proposed approach (Table 3). Depending on the nature of the substituent at position 2 and the nature of the acetylene used in Sonogashira coupling, different reaction conditions were applied (Table 3).

In the case of TMS−acetylene, the highest yields of enediynes **16c−g**, **17b−d**, and **18b** were achieved by carrying out reactions at 50 °C (Table 3, entries 3−7, 22−24, and 28) in a 0.1 M concentration range of iodoheterocycle. To reach the full conversion for the Sonogashira coupling of hydroxyalkynyl derivatives **10d,e** with THP-protected acetylenic alcohols **16d,e**, higher temperature (up to 70 °C) and longer reaction time (36 h) (Table 3, entries 8−10) were required. In these cases, corresponding diols **16h−j** obtained after deprotection of the THPO group by Amberlyst-15 in methanol were isolated in good overall yields.

Despite the fact that the Sonogashira reaction is a commonly employed synthetic methodology and has been tested for a large number of different substrates,[26b] introduction of enyne fragments via Sonogashira coupling with one-pot deprotection of TMS-enynes is still unknown. Nevertheless, in our hands, this type of Sonogashira coupling of 3-iodo-2-substituted benzothiophene derivatives **10a,e** and **14** with TMS-protected enynes **15f,g** enabled us to introduce hex-5-en-1-yn-1-yl and pent-4-en-1-yn-1-yl fragments into position 3 of the benzothiophene ring (Table 3, entries 11−13). It should be pointed out that using of K_2CO_3 as a deprotection source and a base

dx.doi.org/10.1021/jo501396s | J. Org. Chem. 2014, 79, 9018−9045

Table 3. Synthesis of Enediyne Systems



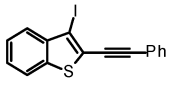
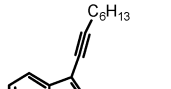
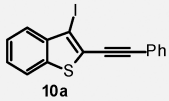
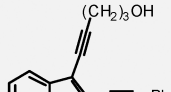
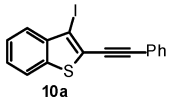
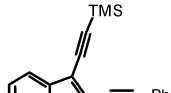
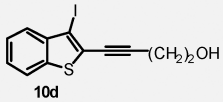
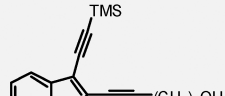
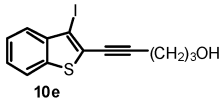
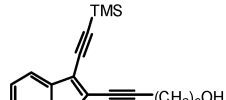
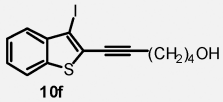
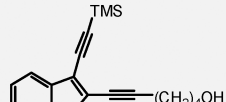
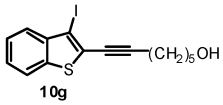
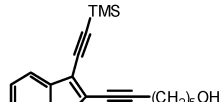
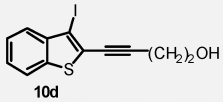
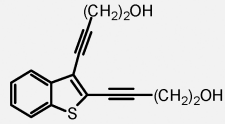
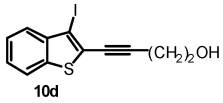
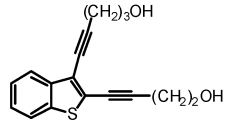
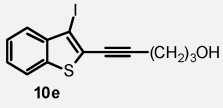
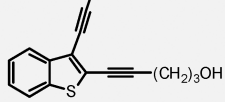
Entry	3-iodoheteroindene	acetylene	conditions[a]	product (isolated yield, %)
1	 **10a**	H—≡—C_6H_{13} **15a**	A	 **16a** (70%)
2	 **10a**	H—≡—$(CH_2)_3OH$ **15b**	A	 **16b** (72%)
3	 **10a**	H—≡—TMS **15c**	A	 **16c** (83%)
4	 **10d**	H—≡—TMS **15c**	A	 **16d** (63%)
5	 **10e**	H—≡—TMS **15c**	A	 **16e** (85%)
6	 **10f**	H—≡—TMS **15c**	B	 **16f** (83%)
7	 **10g**	H—≡—TMS **15c**	B	 **16g** (80%)
8	 **10d**	H—≡—$(CH_2)_2OTHP$ **15d**	A	 **16h** (71%)[b]
9	 **10d**	H—≡—$(CH_2)_3OTHP$ **15e**	A	 **16i** (66%)[b]
10	 **10e**	H—≡—$(CH_2)_3OTHP$ **15e**	A	 **16j** (83%)[b]

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Table 3. continued

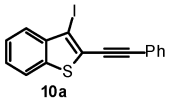
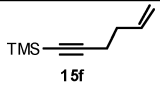
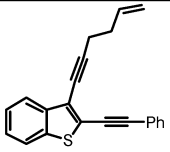
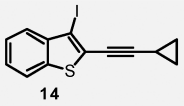
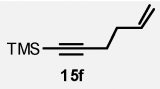
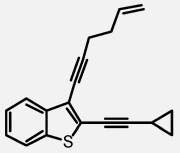
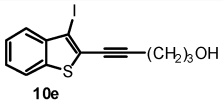
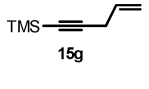
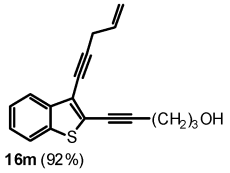
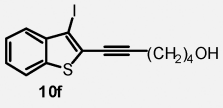
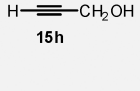
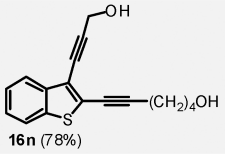
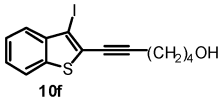
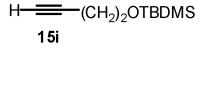
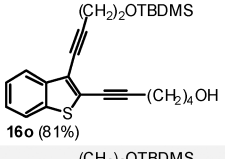
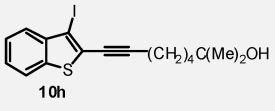
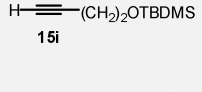
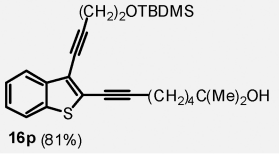
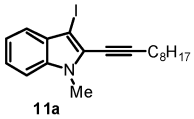
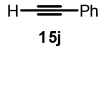
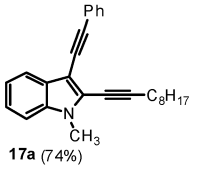
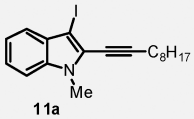
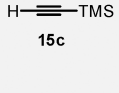
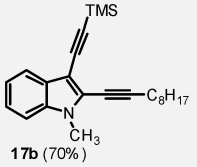
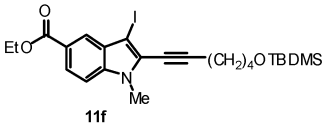
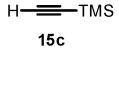
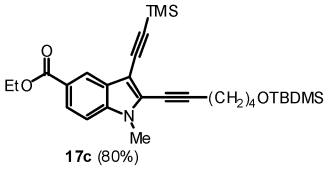
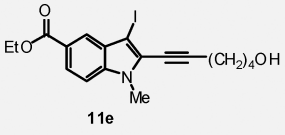
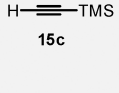
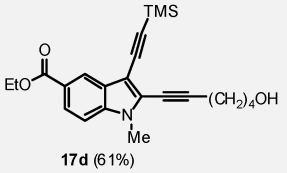
Entry	3-iodoheteroindene	acetylene	conditions[a]	product (isolated yield, %)
11	 **10a**	 **15f**	C	 **16k** (85%)
12	 **14**	 **15f**	D	 **16l** (85%)
13	 **10e**	 **15g**	D	 **16m** (92%)
18	 **10f**	 **15h**	B	 **16n** (78%)
19	 **10f**	 **15i**	B	 **16o** (81%)
20	 **10h**	 **15i**	B	 **16p** (81%)
21	 **11a**	 **15j**	A	 **17a** (74%)
22	 **11a**	 **15c**	A	 **17b** (70%)
23	 **11f**	 **15c**	B	 **17c** (80%)
24	 **11e**	 **15c**	B	 **17d** (61%)

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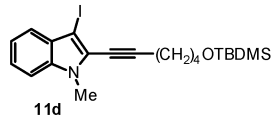
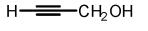
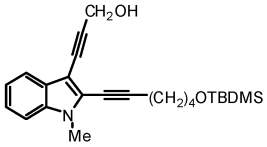
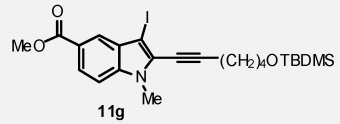
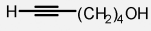
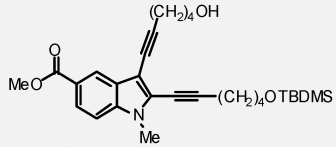
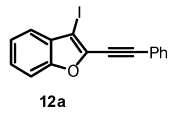
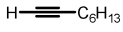
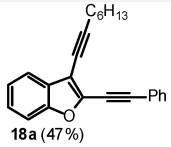
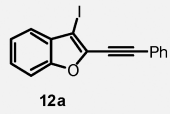
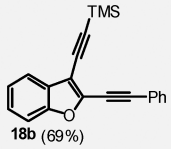
Table 3. continued

Entry	3-iodoheteroindene	acetylene	conditions[a]	product (isolated yield, %)
25	 **11d**	 **15h**	A	 **17e** (40%)
26	 **11g**	 **15k**	B	 **17f** (86%)
27	 **12a**	 **15a**	A	 **18a** (47%)
28	 **12a**	**15c**	A	 **18b** (69%)

[a]Conditions: (A) $Pd(PPh_3)_4$, CuI, PPh_3, DIPA, DMF, 40−70 °C; (B) $Pd(PPh_3)_2Cl_2$, CuI, PPh_3, DIPA, DMF, 40−70 °C; (C) $Pd(PPh_3)_4$, CuI, K_2CO_3, MeOH, DMF, 50 °C; (D) $Pd(PPh_3)_4$, CuI, KF, MeOH, DIPA, DMF, 40 °C. [b]Overall yields are given for two steps: Sonogashira coupling and deprotection of the OTHP group using Amberlyst 15 in MeOH at 45 °C over 3.5 h.

in the case of enyne **15g** afforded an inseparable mixture of products. The major product contained a double bond isomerized from the terminal to an internal position. To avoid double bond isomerization, KF was used as a TMS-deprotecting agent instead of K_2CO_3. This reaction, which can be defined as a type of *sila*-Sonogashira coupling,[39] allowed desired enediyne **16m** to be isolated with a terminal double bond in high yield (Table 3, entry 13).

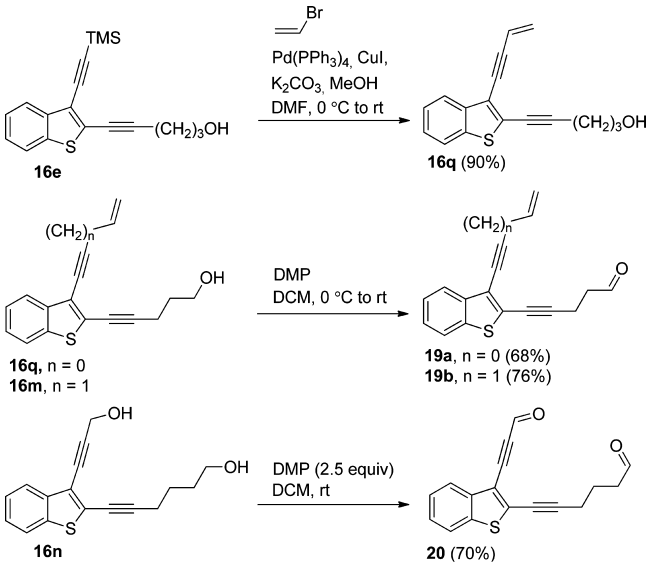
In order to illustrate some of the possibilities of functional group modification within synthesized enediynes, some additional reactions were carried out. Thus, the conjugated enyne system at position 3 of the benzothiophene ring was successfully constructed by one-pot TMS deprotection and Sonogashira coupling of TMS-protected enediyne **16e** with vinyl bromide (Scheme 6), employing K_2CO_3 as a deprotecting agent and a base. Dienediyne alcohols **16q,m** thus obtained were oxidized to corresponding aldehyde **19a,b** by Dess−Martin periodinane (DMP) in good yields (Scheme 6).

Double oxidation of an enediyne **16j** bearing two OH groups with DMP, which was recently used in the synthesis of symmetric enediyne dialdehyde,[25b] was also convenient for the synthesis of non-symmetrical dialdehyde **20** from the corresponding diol **16n** (Scheme 6).

Having in hand an efficient synthetic approach for constructing acyclic enediyne systems fused to S,N-heteroindenes with different functional groups at both ethynyl moieties, we decided to continue our previous investigation regarding the application of ring-closing metathesis (RCM) for the synthesis of a 12-membered dienediyne macrocycle fused to benzothiophene.[25b] An indole-containing dienediyne was chosen as a target structure.

As we described recently, synthesis of the benzothiophene-fused macrocycle was carried out using double oxidation of diol **16j** followed by double Wittig olefination and RCM.[25b]

Scheme 6. Modification of Benzothiophene-Fused Enediynes



However, the yield at the olefination step was only 61% and required an excess of a strong base such as NaHMDS.

For the synthesis of an indole ring-containing analogue, we decided to use an alternative approach. Therefore, double elimination was chosen as the key step for the synthesis of terminal diolefin **22**. Thus, diol **17g**, generated after deprotection of corresponding *O*-TBDMS ether **17f**, was easily converted to corresponding diiodide **21** using Appel iodination (Scheme 7).[36b,c]

The elimination step was supposed to run under usual conditions: by treating diiodide **21** with *tert*-BuOK.[40] However,

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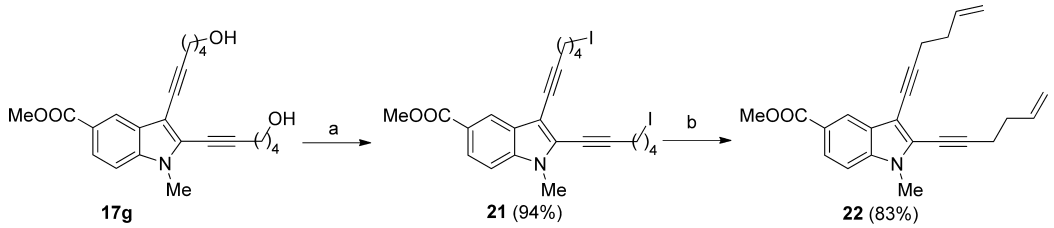
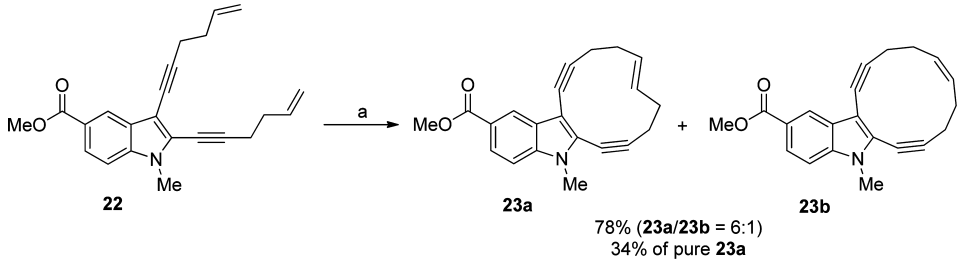
Scheme 7. Synthesis of Terminal Diolefin 22[a]



[a]Reagents and conditions: (a) I_2, PPh_3 imidazole, −20 °C to rt, THF; (b) TBAF, rt, DMSO.

Scheme 8. Synthesis of Indole-Fused 12-Membered Dienediyne Macrocycle[a]



[a]Reagents and conditions: (a) Grubbs II cat. (7 mol %), benzoquinone (21 mol %), reflux, DCM.

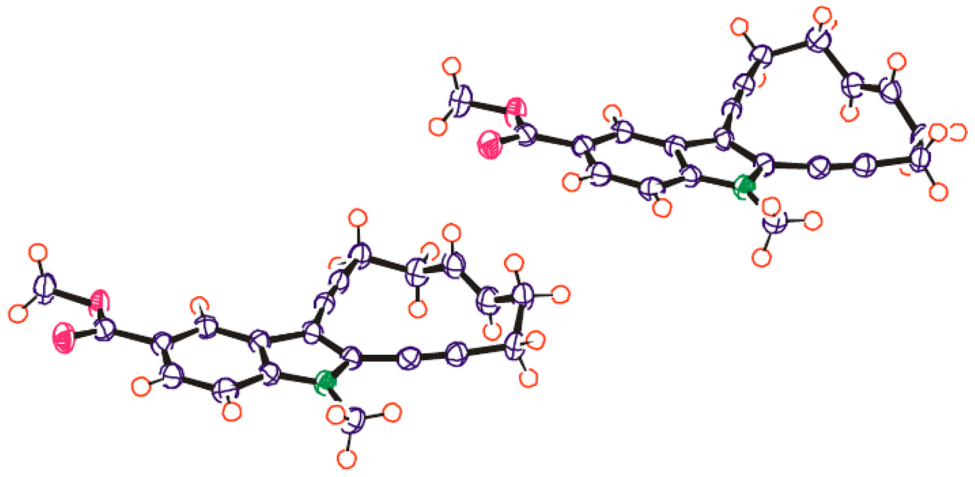


Figure 1. Molecular structure of dienediyne macrocycle **23a**.

this reaction occurred with low conversion and with the formation of a mixture of byproducts. Looking for efficient conditions for HI elimination, we paid attention to the dehydrohalogenation methodology using TBAF hydrate as a base in aprotic solvent (DMSO) reported earlier for the synthesis of terminal olefins.[41] This technique was extremely efficient in our case, allowing the one-step construction of both terminal double bonds and isolation of terminal diolefin **22** in high yield.

The RCM of terminal diolefin **22** was carried out under the same conditions as those for the synthesis of 12-membered benzothiophene-fused dienediyne.[25b] Thus, the employment of Grubbs II catalyst along with benzoquinone to prevent double bond migration[42] afforded a mixture of *E*- and *Z*-isomers **23a,b** (*E*/*Z* = 6:1) in 78% overall yield. A careful separation of this mixture by column chromatography allowed the isolation of the major *E*-isomer **23a** in 34% yield (Scheme 8).

The (*E*) configuration of the double bond formed in the major isomer **23a** was elucidated by ^{1}H NMR spectroscopy with selective decoupling from hydrogen atoms of both CH_2 groups next to the double bond that allowed the (H)C_{sp2}–(H)C_{sp2} spin–spin coupling constant to be measured. The value of the constant, ^3J = 15 Hz, fully corresponds to the (*E*) configuration of the double bond.

The structure of the major isomer **23a** was also confirmed by X-ray analysis (Figure 1).

Moreover X-ray studies revealed that dienediyne **23a**, as in the case of the benzothiophene-fused dienediyne,[25b] in the solid state presents a mixture of two enantiomers due to restricted switching of the double bond through the plane of the molecule. However, this chirality plane type, like that in cyclooctene[43a,b] and silacycloheptene[43c] derivatives, could not be fixed in a solution at room temperature due to a fast inversion process, which was confirmed by magnetic equivalence of H atoms of all methylene groups.

Thus, RCM, as a versatile synthetic method for the one-step formation of the double bond and ring closure, was found to be an efficient technique for the synthesis of *S,N*-heteroindene-fused dienediyne macrocycles.

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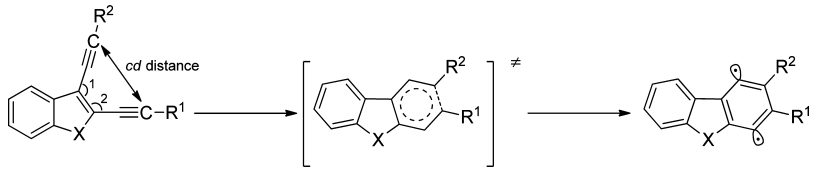
Table 4. Studying the Reactivity of Enediynes 16−18 in Bergman Cyclization by DSC and DFT Calculations[45]



Entry	no.	X	R^1	R^2	t_{BC} (°C)[a]	angle 1 (deg)	angle 2 (deg)	∑(1 + 2)	*cd* (Å)	$\Delta E^{\ddagger}$[b]
1	**17a**	NMe	C_8H_{17}	Ph	266	126.5	128.5	255.0	4.602	45.6
2	**16c**	S	Ph	TMS	258	124.0	127.8	251.8	4.511	48.0
3	**18b**	O	Ph	TMS	250	127.0	131.3	258.3	4.724	50.1
4	**18a**	O	Ph	C_6H_{13}	227	127.0	131.3	258.3	4.726	46.9
5	**16j**[c]	S	$(CH_2)_3OH$	$(CH_2)_3OH$	225	124.1	129.9	254.0	4.513	41.8
6	**16r**[d]	S	C_8H_{17}	C_6H_4-4-OMe	222	124.1	127.9	252.0	4.515	44.0
7	**16s**[d]	S	C_8H_{17}	Ph	220	124.0	128.0	252.0	4.518	43.8
8	**16t**[d]	S	$(CH_2)_2CHO$	$(CH_2)_2CHO$	200	124.0	127.8	251.8	4.500	41.6
9	**16u**[d]	S	$(CH_2)_2CH{=}CH_2$	$(CH_2)_2CH{=}CH_2$	203	124.0	127.9	251.9	4.508	41.4
10	**16v**	S	Me	Me	209[e]	124.1	127.9	252.0	4.514	42.4
11	**16w**[f]	S	H	H	137[e]	124.0	127.6	251.6	4.494	34.1

[a]Onset temperatures are reported. [b]$\Delta E^{\ddagger}$ = (*E* + ZPE), kcal/mol. [c]Data obtained for compound **16j** were not used in correlation. [d]The synthesis of enediynes **16r,s** and **16t,u** was described earlier.[25a,b] [e]t_{BC} values were calculated in accordance with the linear equation $y = -158.49 + 8.66x$. [f]Synthesis of polyphenylene from enediyne **16w** by thermolysis at 150 °C was reported.[21l]

Finally, the ability of some synthesized enediynes to undergo Bergman cyclization (BC) was studied by differential scanning calorimetry (DSC), which is known to be an efficient, express method for this purpose.[44] Enediynes (**16c,j,r−u**, **17a**, and **18a,b**) were picked for DSC studies (Table 4).

Thus, the exothermic peaks observed in the thermograms at 200−266 °C (onset temperatures) obviously illustrate that the BC of the corresponding compounds (**16c,j,r−u**, **17a**, and **18a,b**) took place. Additional evidence suggesting that irreversible BC occurred is the fact that neither endothermic nor exothermic features were observed during the scanning of the thermolyzed samples for the second time.[46] DSC measurement revealed that the nature of both the heterocycle and substituents at the ethynyl moieties influences the ability of enediynes to undergo BC.

The first inference comes from the comparison of onset Bergman cyclization temperatures (t_{BC}) of indole- (**17a**), furan- (**18a**), and benzothiophene (**16s**)-fused enediynes with similar substituents (Table 4, entries 1, 4, and 7). In this series of heteroindenes, a decrease of t_{BC} and therefore an increase of reactivity in BC was observed from indole to benzothiophene: N (266 °C), O (227 °C), and S (220 °C). As we have already discussed in the Introduction, the electron-withdrawing properties of substituents as well as a heterocycle fused to enediyne are known to facilitate BC.[3j,8] Because of the electron-donating ability of heteroindenes, which was found to change as benzofuran > indole > benzothiophene,[47] benzothiophene-fused enediyne is expected to be the most reactive within this rank. From another point of view, the sulfur's van der Waals atomic radius (1.85 Å), which is significantly larger than the radii of nitrogen (1.50 Å) and oxygen (1.40 Å),[48] evidently can reduce the values of bond angles 1 and 2 (Table 4) and therefore can lead to the decrease of the *cd* distance for benzothiophene-fused enediyne **16s**. In order to prove this assumption, DFT calculations[45] were carried out. As expected, calculated values of bond angles 1 and 2 as well as the *cd* distance are in inverse proportion with the van der Waals atomic radii of the heteroatoms. Thus, the *cd* distance decreases in as benzothiophene **16s** < indole **17a** < benzofuran **18a**, which fully coincides with the highest reactivity being observed for compound **16s**. It is interesting to note that the calculated activation energy $\Delta E^{\ddagger}$ for the BC changes in accordance with the electron properties of heterocycles and *cd* distance in enediynes **18a**, **17a**, and **16s**. However, from the DSC data, benzofuran **18a** was found to be more reactive than that of indole **17a**.

Regarding the nature of substituents, it is known that it also has an impact on the activity of enediynes in the cyclization. Thus, enediynes with bulky groups at ethynyl moieties (e.g., TMS) are less active in BC than unsubstituted ones.[7d,21a,49] This tendency is in a good accordance with high t_{BC} of TMS-substituted compounds **16c** and **18b** (258 and 250 °C) (Table 4, entries 2 and 3). The same conclusion came from the comparison of t_{BC} within benzothiophene derivatives **16j,r−u** (Table 4, entries 5−9). Thus, introduction of terminal C=C or C=O double bonds into the substituents at both ethynyl moieties lowered the t_{BC} from the average value of 220 °C (**16j,r,s**) (Table 4, entries 5−7) to ∼200 °C (**16t,u**) (Table 4, entries 8 and 9). However, all calculated values of *cd* distance (4.50−4.52 Å) and bond angles (the sum of both angles ∼252°) were found to be almost the same within the benzothiophene series, including TMS-substituted enediyne **16c**, and do not depend on the nature of substituents. This fact could be attributed to reduced steric interaction between both substituents with terminal double bonds in the transition state in comparison with that of TMS-, Ar-, and Alk-substituted enediynes, which might lead to the reduction of activation energy of BC for enediynes **16t,u**.

It is known that the ability of enediynes to undergo Bergman cyclization correlates accurately with the values of activation energy barriers.[7] We found that calculated activation barriers $\Delta E^{\ddagger}$ and t_{BC} obtained from DSC measurements are in good agreement. Moreover, there is a quite good correlation (R = 0.992) between $\Delta E^{\ddagger}$ and t_{BC} within the benzothiophene-fused enediyne series, which could be used for the prediction of reactivity.[50] For example, values of t_{BC} for dimethylenediyne **16v** and unsubstituted 2,3-bisethynylbenzithiophene **16w** are supposed to be 209 and 137 °C (Table 4).

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However, for indole derivative **17a** and benzothiophene-fused enediyne with OH groups **16j**, the calculated values of activation energy do not match the observed t_{BC}. This misfit could probably be caused by the proton-acceptor and -donor capability of compounds **17a** and **16j**, respectively, which can affect the mechanism of BC.

In order to illustrate the influence of a fused heterocycle on the reactivity of a macrocyclic enediyne system in the cycloaromatization process, DSC measurements for indole-containing dienediyne **23a** were carried out. It was found that the onset temperature of the exothermic peak observed upon the first heating of compound **23a** is 239 °C,[46] which is significantly higher than the temperature estimated earlier for the benzothiophene-fused dienediyne (201 °C).[25b,51] This difference is the result of both the electron properties of heteroindenes and the atomic radii of heteroatoms discussed above and fully corresponds with the structure−reactivity relationships for the series of acyclic enediynes. From this point of view, benzothiophene-fused macrocyclic enediynes are supposed to be more promising in the search for bioactive molecules.

On the other hand, it is obviously clear that even the incorporation of an additional double bond into the enediyne system does not increase the reactivity of 12-membered enediynes in thermal-induced cycloaromatization. Therefore, smaller macrocyclic enediynes fused to heterocycles are challenging synthetic targets and are the topic of on going investigations in our research group.

CONCLUSIONS

A convenient and efficient approach toward enediyne systems fused to a heterocyclic core based on electrophilic cyclization and Sonogashira coupling was elaborated. The innovation of this synthetic route is the iodocyclization of readily available *ortho*-functionalized aryldiacetylenes that allowed the construction of heterocycles bearing the ethynyl moiety along with iodine functionality at neighbor positions in a single step. The effect of solvent polarity on the cyclization was revealed, and dichloromethane was found to be better than acetonitrile for the synthesis of benzothiophenes and indoles. The lower nucleophilicity of alkoxy groups in comparison with that of S- and N-containing groups required electrophilic reagents stronger than iodine for the cyclization to proceed and led to lower yields of 2-ethynyl-3-iodobenzofurans. Subsequent Sonogashira coupling of the heterocycles obtained with acetylenes afforded asymmetrically substituted enediyne systems fused to *S,N,O*-heteroindenes with various functional groups at both ethynyl fragments. In this way, a diversity of asymmetrically substituted acyclic enediyne systems fused to benzothiophene, benzofuran, and indole was synthesized with complete regiocontrol. Because of both the tolerance of this methodology to the nature of functional groups attached to ethynyl moieties and the opportunity for further functional group transformation, the approach developed can be used in the synthesis of heterocycle-fused macrocyclic enediyne systems. Ring-closing metathesis was found to be an efficient technique for the synthesis of *S,N*-heteroindene-fused macrocycles as the method for the one-step formation of the double bond and closing of 12-membered dienediene macrocycles. It was estimated that the nature of the heteroatom does not influence the general structural properties of 12-membered dienediynes. However, the nature of the heterocycle fused to both cyclic and acyclic enediyne systems significantly influences their ability to undergo thermal-induced cycloaromatization. Other macrocyclization approaches for the synthesis of macrocyclic enediynes within the methodology developed are under investigation.

EXPERIMENTAL SECTION

General Information and Methods. Solvents, reagents, and chemicals (**1f**, **3a,b,f**, **15a−c,h,j,k**) used for reactions were purchased from commercial suppliers. Catalysts $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and Grubbs II catalyst were purchased in Sigma-Aldrich. Solvents were dried under standard conditions; chemicals were used without further purification. Compounds **3c**,[52a] **3d**,[31] **3e**,[31] **3g**,[52b] **8**,[30] **9**,[52c] **15d,e**,[52d] **15g**,[52e] **15i**,[52f] and enediynes **16t,u**[25b] 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 performed in vacuo 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 or staining with a basic aqueous solution of $KMnO_4$. Normal-phase silica gel (Silica gel 60, 230−400 mesh) was used for preparative chromatography. Melting points (mp) determined are uncorrected. Differential scanning calorimetry (DSC) experiments were carried out with 0.4−1.4 mg of samples using crucibles with pierced caps under an argon (for **23a**) or a nitrogen (for all other compounds) atmosphere at a heating/cooling rate of 20 °C min^{-1} from a temperature of 20 °C up to 395 °C, followed by cooling to 20 °C and heating to 395 °C for the second time. IR spectra were recorded for thin films on KBr or using ATR technique. Absorption is reported as values in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz (for **1a,b,d**, **6a,c**, **7a**, and **17b**) or at 400 and 100 MHz (for all other compounds) in $CDCl_3$ with TMS as the internal standard (for compounds **4b−c**, **6c,f,g**, **10f−g**, **11c,e,f**, **16f−g**, and **17c−d**) or in $CDCl_3$ without the internal standard (for all other compounds). The homonuclear decoupling experiment for dienediyne **23a** was carried out at a proton frequency of 300.13 MHz. The ^1H NMR data are reported as the 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. The ^{13}C NMR data are reported as the chemical shift (δ) and type of carbon, determined from DEPT 135 experiments (only quaternary atoms are marked as C_q). Chemical shifts are reported as δ values (ppm) and referenced to residual solvent (δ = 7.26 ppm for ^1H; δ = 77.00 ppm for ^{13}C). Low-resolution mass spectra (MS) were obtained using electron-impact ionization (EI), 70 eV, or fast atom bombardment (FAB) ionization with 3-nitrobenzyl alcohol (3-NBA) matrix. High-resolution mass spectra (HRMS) were measured using EI, FAB, or electrospray ionization (ESI) in the mode of positive ion registration using time-of-flight (TOF) MS. Elemental analysis was performed on automatic CHNS analyzer. GC−MS experiments were carried out at a heating rate of 15 °C min^{-1} from a temperature of 60 °C up to 150 °C. The single-crystal X-ray diffraction studies were carried out at 100.0 K using Cu Kα radiation (λ = 1.54184 Å). For further information, see the Experimental Section and Supporting Information.

Synthesis of 1-Bromoalk-1-ynes. 1-Bromo-2-phenylacethylene, 1-bromopent-1-yne, and 1-bromohex-1-yne were synthesized by a partly modified Straus reaction.[53] Bromine (0.260 mol, 41.6 g, 13.2 mL) was added dropwise to a solution of KOH (0.821 mol, 46.0 g) in water (200 mL) at −15 °C. It is essential to keep the temperature below −15 °C in order to avoid the formation of $KBrO_3$. After the addition of Br_2, the cooling bath was removed, and the reaction mixture was stirred for 20 min. Then, alkyne (0.100 mol) was added dropwise, and the reaction mixture was vigorously stirred overnight. The next day, the 1-bromoalk-1-yne formed as a colorless lower layer was separated, dried over anhydrous Na_2SO_4, and used in the next step (Cadio−Chodkiewiz coupling) without further purification.

Dodeca-5,7-diyne (1a). A partly modified Glaser−Hay oxidative coupling procedure was used.[54a] Freshly prepared CuCl (20.0 mmol, 1.98 g) was added to a solution of TMEDA (20.0 mol, 2.32 g, 3.21 mL) in acetone (20.0 mL) in a three-necked round-bottomed

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flask equipped with thermometer, condenser, and gas inlet tube, affording a deep blue solution. Hex-1-yne (0.200 mol, 16.4 g, 22.9 mL) was added in portions, and the reaction mixture became yellow due to the formation of Cu acetylenide. Then, O_2 was bubbled through the reaction mixture at such a rate so as to avoid boiling acetone. After the reaction finished, which was detected by a stable deep blue color of the reaction mixture, it was poured into a 10% solution of HCl (50 mL), the organic layer was separated, and the aqueous was extracted with diethyl ether. The combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure (not lower than 500 Torr), and the residue was purified by distillation. Yield, 13.8 g (85%). Colorless liquid, bp 99−100 °C/4 Torr (lit.[54b] bp 78−79 °C/1 Torr). ^{1}H NMR (300 MHz $CDCl_3$, δ): 0.87 (t, J = 7.1 Hz, 6H), 1.32−1.52 (m, 8H), 2.22 (t, J = 6.6 Hz, 4H).

Synthesis of Diacetylenic Alcohols 1b−e. A partly modified Cadio−Chodkiewiz coupling procedure was used.[55a] To an Ar flushed solution of *n*-$BuNH_2$ (0.200 mol, 14.6 g, 19.7 mL) in EtOH (30.0 mL) was added freshly prepared CuCl (5.00 mmol, 495 mg), and the suspension formed was stirred under Ar for 20 min. Then, NH_2OH·HCl (50.0 mmol, 3.48 g,) was added, and the resulting mixture was stirred under Ar for 20 min. A solution of alkyne (0.300 mol) in EtOH (45.0 mL) was added to the reaction mixture. The yellow solution obtained was stirred under Ar for 20 min, and then a solution of 1-bromalkyne (0.100 mol) in EtOH (15.0 mL) was added dropwise. The reaction mixture was stirred under Ar overnight, poured into a saturated solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with H_2O and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel or by distillation.

Octa-2,4-diyn-1-ol (1b).[55b] Compound **1b** was obtained from 1-bromopent-1-yne (0.340 mol, 50 g) and propargyl alcohol (1.02 mol, 57.2 g, 59.4 mL). Yield, 25.3 g (61%). Colorless oil, bp 87−89 °C/2 Torr (lit.[55c] bp 118−129 °C/15 Torr). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.99 (t, J = 7.4 Hz, 3H), 1.50−1.59 (m, 2H), 1.80 (br s, 1H), 2.26 (t, J = 7.0 Hz, 2H), 4.31 (s, 2H).

Nona-2,4-diyn-1-ol (1c).[55b] Compound **1c** was obtained from 1-bromohex-1-yne (17.5 g) and propargyl alcohol (18.5 g, 0.330 mol, 19.2 mL). Yield, 8.53 g (57%). Colorless oil, bp 100−103 °C/2 Torr (lit.[55d] bp 103−105 °C/2 Torr). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.89 (t, J = 7.8 Hz, 3H), 1.36−1.53 (m, 4H), 2.23−2.29 (m, 3H), 4.30 (d, J = 2.8 Hz, 2H).

2-Methyldeca-3,5-diyn-2-ol (1d). Compound **1d** was obtained from 1-bromohex-1-yne (34.0 mmol, 5.47 g) and 2-methyl-but-3-yn-2-ol (0.100 mol, 8.41 g, 9.67 mL). Yield, 3.72 g (67%). Colorless oil, bp 100−102 °C/1 Torr (lit.[55e] bp 109 °C/2 Torr). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.90 (t, J = 7.1 Hz, 3H), 1.30−1.60 (m, 11H), 2.27 (t, J = 6.8 Hz, 2H).

2-Methyl-6-phenylhexa-3,5-diyn-2-ol (1e). Compound **1e** was obtained from 1-bromphenylacetylene (20.0 mmol 3.62 g) and 2-methyl-but-3-yn-2-ol (60.0 mmol, 5.05 g, 5.82 mL). Purification of the crude product by column chromatography using petroleum ether/ethyl acetate (20:1 → 5:1) as the eluent gave 2.43 g (66%) of **1e** as a white solid. mp 58−60 °C (lit.[55f] mp 57−58 °C). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.58 (s, 6H), 2.12 (br s, 1H), 7.30−7.38 (m, 3H), 7.48 (d, J = 6.9 Hz, 2H).

6-Trimethylsilylhexa-3,5-diyn-1-ol (1g).[56] Compound **1g** was synthesized from of 4-iodobut-3-yn-1-ol (25.3 mmol, 4.96 g) and trimethylsilylacetylene (69.7 mmol, 6.85 g, 9.86 mL) according to the procedures described[25b] for the synthesis of alcohol **1h**. 4-Iodobut-3-yn-1-ol was synthesized from but-3-yn-1-ol in a manner similar to the synthesis of 5-iodopent-4-yn-1-ol.[25b] Yield of **1g**, 3.49 g (83%). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.19 (s, 9H), 1.76 (t, J = 6.0, 1H), 2.55 (t, J = 6.2 Hz, 2H), 3.75−3.77 (m, 2H).

7-Trimethylsilylhepta-4,6-diyn-1-ol (1h). Compound **1h** was synthesized from 5-iodopent-4-yn-1-ol (12.0 mmol, 2.52 g) and trimethylsilylacetylene (33.0 mmol, 3.24 g, 4.66 mL) as described earlier.[25b] Yield, 1.76 g (81%). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.18 (s, 9H), 1.52 (br s, 1H), 1.74−1.81 (m, 2H), 2.41 (t, J = 7.0 Hz, 2H), 3.74 (t, J = 6.1 Hz, 2H).

Synthesis of Terminal Diacetylenes (see Table 1), Methods A−C. Method A: Diacetylene Zipper Reaction. *Conditions for Unfunctionalized Diacetylene* ***2a****.* Conditions described earlier[27a] were partly modified. To a stirred solution of absolute ethylenediamine (EDA) (37.0 mmol, 2.22 g, 2.47 mL) in anhydrous THF (8.80 mL) lithium (37.0 mmol, 257 mg) was placed in portions in a stream of Ar. The reaction mixture was stirred under Ar at 40 °C until the formation of lithium 2-aminoethylamide (LAETA) was complete, which was indicated by a color change from deep blue to gray. The reaction mixture was cooled to room temperature, and anhydrous *n*-hexane (8.80 mL) followed by anhydrous toluene (8.80 mL) was added. Then, the reaction mixture was cooled to 15 °C, and dodeca-5,7-diyne (**1a**) (12.3 mmol, 2.00 g) was added in one portion. The reaction mixture was stirred at 15−18 °C for 15 min, poured into ice, and extracted with Et_2O, and the organic layer was washed with a saturated solution of NH_4Cl (until pH 7), water, and brine and dried over anhydrous Na_2SO_4. Et_2O was evaporated on rotary evaporator at 35 °C and pressure not lower than 400 Torr. To the resulting solution was added the required amount of absolute hexane that gave a 1.00 M solution of crude dodeca-1,3-diyne (12.3 mL). This solution was used in Sonogashira coupling without further purification.

Synthesis of Diacetylenic Alcohols ***2b−d****.* Conditions described earlier[27b] were used without any modification. Diacetylenic alcohols **2b−d** obtained were used in the next step without further purification assuming that the yield is quantitative.

Method B: Synthesis of 4-Phenylbuta-1,3-diyne (2e). Conditions described earlier[28a] were partly modified. To the solution of 2-methyl-6-phenylhexa-3,5-diyn-2-ol (**1e**) (2.00 mmol, 368 mg) in toluene (10.0 mL) was added well-ground NaOH (6.00 mmol, 240 mg). The reaction mixture was stirred under Ar at 70 °C for 50 min. Then, the reaction mixture was cooled to room temperature, filtered, and the toluene solution of 4-phenylbuta-1,3-diyne (**2e**) obtained was used in Sonogashira coupling without further purification.

Method C: Synthesis of Trimethylsilylbuta-1,3-diyne (2f). Conditions described earlier[28b] were partly modified. To a cooled (0 °C) stirred solution of bis(trimethylsilyl)diacetylene (**1f**) (15.0 mmol, 2.92 g) in diethyl ether (150 mL) was added a 2.20 M solution of MeLi·LiBr complexes in diethyl ether (37.0 mmol, 16.8 mL) dropwise. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 6 h. Then, the reaction mixture was cooled to 0 °C, quenched with water (8.00 mL), and diluted with brine. The organic layer was separated, and the aqueous layer was acidified with 10% HCl and extracted with Et_2O. Combined organic layers were washed with brine until pH 7, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure (not lower than 700 Torr) to give the solution of trimethylsilyldiacetylene in Et_2O (∼10 mL), which was used in Sonogashira coupling without further purification.

Synthesis of (Buta-1,3-diynyl) Arenes by Sonogashira Coupling (See Table 1), Methods D−F. Method D. To the solution of iodoarene (1.00 equiv) in triethylamine were added terminal diacetylene **2** (1.50−3.00 equiv), 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, and the reaction mixture was evacuated and flushed with Ar once again and allowed to stir at 40 °C. After completion of the reaction (overnight if not otherwise mentioned, TLC control), the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, extracted with ethyl acetate, washed with saturated solution of NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

Method E. To an Ar flushed 0.05 M solution of iodoarene (1.00 equiv) in DMF were added $Pd(PPh_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), DIPA (4.00 equiv). Diacetylene (4.00 equiv) was then added, and reaction mixture was stirred at room temperature under Ar for 30 min. Then, CuI (15 mol %) was added, and the reaction mixture was stirred at 40 °C until completion of the reaction (TLC monitoring), cooled, and worked up as described for Method D.

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Method F. To a degassed solution of *o*-iodothioanisole **3a** (1.00 equiv) in anhydrous DMF were added $Pd(PPh_3)_4$ (5 mol %), CuI (15 mol %) and anhydrous K_2CO_3 (8.00 equiv). The reaction mixture was evacuated and flushed with Ar several times and stirred under Ar for 5 min; then, MeOH (8.00 equiv) followed by a solution of TMS-protected diacetylenic alcohol **1g**,**h** (1.00 equiv) in anhydrous degassed DMF was added. The reaction mixture was stirred at 40 °C until completion (TLC control), which took around 12 h, cooled, and worked up as described for Method D.

1-(Dodeca-1,3-diyn-1-yl)-2-methylsulfanylbenzene (4a). Diacetylene **4a** was synthesized in accordance with Method D from *o*-iodothianisole **3a** (0.84 mmol, 210 mg) and a 1.00 M solution of dodeca-1,3-diyne (**1a**) in hexane (1.68 mmol, 272 mg, 1.68 mL) in triethylamine (7 mL). Purification of the crude product by column chromatography using cyclohexane as the eluent gave 192 mg (80%) of **4a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.7, 3H), 1.26−1.33 (m, 8H), 1.38−1.45 (m, 2H), 1.54−1.59 (m, 2H) overlaps with water signal, 2.37 (t, J = 7.1, 2H), 2.49 (s, 3H), 7.06−7.08 (m, 1H), 7.14 (d, J = 8.0, 1H), 7.27−7.31 (m, 1H), 7.43 (dd, J = 7.6, J = 1.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 15.2, 19.7, 22.6, 28.2, 28.9, 29.1, 29.1, 31.8, 64.9 (C_q), 72.0 (C_q), 80.6 (C_q), 86.9 (C_q), 120.4 (C_q), 124.3, 124.3, 129.1, 133.5, 143.0 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 2925, 2855, 2237 (C≡C), 1581, 1464, 1434, 1383, 1300, 1275, 1251, 1198, 1164, 1117, 1064, 1039, 968, 749, 720, 696. HRMS (m/z): calcd for $C_{19}H_{24}S$ $[M]^+$, 284.1599; found, 284.1602.

8-[2-(Methylsulfanyl)phenyl]octa-5,7-diyn-1-ol (4b).[27b] Compound **4b** was synthesized in accordance with Method E in DMF (280 mL) from *o*-iodothioanisole **3a** (14.0 mmol, 3.50 g) and octa-5,7-diyn-1-ol (**2b**), obtained by Method A from alcohol **1b** (56.0 mmol, 6.83 g). Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 2.90 g (85%) of **4b** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.46 (br s, 1H), 1.63−1.75 (m, 4H), 2.43 (t, J = 6.5 Hz, 2H), 2.48 (s, 3H), 3.68 (t, J = 5.6 Hz, 2H), 7.04−7.08 (m, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.27−7.31 (m, 1H), 7.42 (d, J = 7.6 Hz, 1H).

9-[2-(Methylsulfanyl)phenyl]nona-6,8-diyn-1-ol (4c).[27b] Compound **4c** was synthesized in accordance with Method E in DMF (280 mL) from *o*-iodothioanisole **3a** (14.0 mmol, 3.50 g) and nona-6,8-diyn-1-ol (**2c**), obtained by Method A from alcohol **1c** (56.0 mmol, 7.50 g). Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 3.20 g (89%) of **4c** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.35 (br s, 1H), 1.46−1.55 (m, 2H), 1.57−1.66 (m, 4H) overlaps with water signal, 2.40 (t, J = 6.7 Hz, 2H), 2.48 (s, 3H), 3.67 (t, J = 6.1 Hz, 2H), 7.04−7.08 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.04−7.08 (m, 1H), 7.42 (d, J = 7.6 Hz, 1H).

2-Methyl-10-[2-(methylsulfanyl)phenyl]deca-7,9-diyn-2-ol (4d).[27b] Compound **4d** was synthesized in accordance with Method E in DMF (54.0 mL) from *o*-iodothioanisole **3a** (2.68 mmol, 670 mg) and compound **2d**, obtained by Method A from alcohol **1d** (10.7 mmol, 1.76 g). Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 350 mg (46%) of **4d** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.19 (s, 6H), 1.43−1.47 (m, 2H), 1.53−1.61 (m, 2H), 2.37 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 7.01−7.05 (m, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.24−7.28 (m, 1H), 7.42 (d, J = 7.7 Hz, 1H).

1-[2-(Methylsulfanyl)phenyl]-4-phenylbuta-1,3-diyne (4e). Compound **4e** was synthesized in accordance with Method D in triethylamine (10.0 mL) from *o*-iodothianisole **3a** (1.00 mmol, 250 mg) and phenyldiacetylene **2e**, obtained by Method B from diacetylene **1e** (3.00 mmol, 552 mg). Purification of the crude product by column chromatography using cyclohexane and then hexane/ethyl acetate (70:1) as the eluent gave 170 mg (68%) of **4e** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.52 (s, 3H), 7.08−7.12 (m, 1H), 7.18 (d, J = 7.7, 1H), 7.31−7.38 (m, 4H), 7.48−7.55 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 15.2, 73.8 (C_q), 78.8 (C_q), 80.0 (C_q), 83.4 (C_q), 120.1 (C_q), 121.8 (C_q), 124.4, 124.5 128.4, 129.2, 129.5, 132.5, 133.5, 143.2 (C_q). IR (neat) ν_{max} (cm^{-1}): 2919, 2207 (C≡C), 2142 (C≡C), 1578, 1487, 1460, 1428, 1275, 1255, 1160, 1128, 1071, 1039, 1025, 962, 952, 909, 859, 800, 747, 717, 683. MS (EI, 70 eV), m/z (%): 248.1 (100, M^+), 247.1 (97, $M^+ - H$). HRMS (m/z): calcd for $C_{17}H_{12}S$ $[M]^+$, 248.0660; found, 248.0663.

Trimethyl{[2-(methylsulfanyl)phenyl]buta-1,3-diyn-1-yl}-silane (4f). Diacetylene **4f** was synthesized in accordance with Method D in Et_3N (30.0 mL) from *o*-iodothioanisole **3a** (7.00 mmol, 1.75 g) and 4-(trimethylsilyl)buta-1,3-diyne **2f**, obtained by Method C from bis(trimethylsilyl)diacetylene (15.0 mmol, 2.92 g). The last degassing of the reaction mixture was done before adding buta-1,3-diyne **2f**, and CuI was added to the reaction mixture in the stream of Ar. Reaction time was 2.5 h. Purification of the crude product by column chromatography using pentane as the eluent gave 1.31 g (77%) of **4f**. Compound **4f** became dark brown after the removal of pentane until dryness; however, it did not affect the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.23 (s, 9H), 2.49 (s, 3H), 7.05−7.09 (m, 1H), 7.15 (d, J = 8.0, 1H), 7.29−7.33 (m, 1H), 7.44 (d, J = 7.7, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −0.4, 15.2, 73.9 (C_q), 80.2 (C_q), 87.6 (C_q), 92.5 (C_q), 119.6 (C_q), 124.3, 124.4, 129.6, 133.8, 143.5 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3061, 2960, 2922, 2200 (C≡C), 2101 (C≡C), 1582, 1462, 1250 (C−Si), 1131, 1079, 1039, 1011, 962, 846, 750. MS (FAB), m/z: 245 (51, M + H^+), 244 (73, M^+), 229 (100, $M^+ - CH_3$). HRMS (FAB) (m/z): calcd for $C_{14}H_{16}SiS$ $[M]^+$, 244.0742; found, 244.0737.

6-[2-(Methylsulfanyl)phenyl]hexa-3,5-diyn-1-ol (4g). Diacetylene **4g** was synthesized in accordance with Method F from *o*-iodothioanisole **3a** (8.00 mmol, 2.00 g) in anhydrous DMF (15.0 mL) and 1-trimethylsilylhexa-1,3-diyn-6-ol (**1g**) (8.00 mmol, 1.33 g) in anhydrous degassed DMF (10.0 mL). Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (5:1) as the eluent gave 1.63 g (94%) of **4g** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.86 (t, J = 6.2, 1H), 2.49 (s, 3H), 2.66 (t, J = 6.2 Hz, 2H), 3.78−3.82 (m, 2H), 7.05−7.09 (m, 1H), 7.15 (d, J = 7.9, 1H), 7.28−7.33 (m, 1H), 7.43 (dd, J = 7.6, J = 1.2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 15.2, 24.1, 60.7, 66.8 (C_q), 72.7 (C_q), 80.02 (C_q), 82.9 (C_q), 120.0 (C_q), 124.32, 124.38, 129.4, 133.6, 143.2 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3357 (OH), 3059, 2921, 2887, 2236(C≡C), 2156(C≡C), 1580, 1463, 1433, 1384, 1336, 1300, 1275, 1251, 1164, 1111, 1040, 953, 844, 750. MS (EI, 70 eV), m/z (%): 216 (11, M^+), 197 (5, $M^+ - H_2O$), 185 (59, $M^+ - CH_2OH$) 184 (78, $M^+ - CH_3OH$), 171 (42, $M^+ - CH_2CH_2OH$). HRMS (m/z): calcd for $C_{13}H_{12}OS$ $[M]^+$, 216.0609; found, 216.0612. Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82. Found: C, 72.38; H, 5.64; S, 14.72.

7-[2-(Methylsulfanyl)phenyl]hepta-4,6-diyn-1-ol (4h).[25b] The diacetylene **4h** was synthesized in accordance with Method F from *o*-iodothioanisole **3a** (8.00 mmol, 2.00 g) in anhydrous DMF (15.0 mL) and 1-trimethylsilylhepta-1,3-diyn-6-ol (**1h**) (8.00 mmol, 1.44 g) in anhydrous degassed DMF (10.0 mL). Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 1.59 g (86%) of **4h** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.54 (br s, 1H), 1.80−1.87 (m, 2H), 2.48 (s, 3H), 2.52 (t, J = 7.0 Hz, 2H), 3.78 (t, J = 6.1 Hz, 2H), 7.04−7.08 (m, 1H), 7.14 (d, J = 7.7, 1H), 7.27−7.31 (m, 1H), 7.43 (dd, J_1 = 7.7, J_2 =1.3, 1H).

2-(Dodeca-1,3-diyn-1-yl)aniline (5a).[27a] Diacetylene **5a** was synthesized in accordance with Method D from *o*-iodoaniline (**3b**) (1.00 mmol, 219 mg) and a 1.00 M solution of dodeca-1,3-diyne in hexane (1.50 mmol, 243 mg, 1.50 mL) in a mixture of triethylamine (7.00 mL) and acetonitrile (3.00 mL). Reaction time was 7 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (20:1) as the eluent gave 220 mg (87%) of **5a** as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.7, 3H), 1.28−1.48 (m, 10H), 1.54−1.63 (m, 2H) overlaps with water signal, 2.37 (t, J = 7.0, 2H), 4.35 (br s, 2H), 6.62−6.68 (m, 2H), 7.09−7.15 (m, 1H), 7.30 (d, J = 8.1, 1H).

2-(Phenylbuta-1,3-diyn-1-yl)aniline (5b). Diacetylene **5b** was synthesized in accordance with Method D from *o*-iodoaniline (**3b**) (1.00 mmol, 219 mg) and phenyldiacetylene **2e**, obtained by Method B from diacetylene **1e** (2.00 mmol, 368 mg) in triethylamine (10.0 mL). Purification of the crude product by column chromatography using

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cyclohexane and then cyclohexane/ethyl acetate (20:1) as the eluent gave 205 mg (94%) of **5b** as a yellowish solid. mp 73−74 °C (lit.[57] mp 73−75 °C). ^{1}H NMR (250 MHz, $CDCl_3$, δ): 4.33 (br s, 2H), 6.69−6.72 (m, 2H), 7.13−7.20 (m, 1H), 7.31−7.39 (m, 4H), 7.52−7.56 (m, 2H).

8-[2-(Dimethylamino)phenyl]octa-5,7-diyn-1-ol (6a). Compound **6a** was obtained using Method E from dimethylaniline **3c** (6.27 mmol, 1.55 g) dissolved in DMF (125 mL) and a solution of octa-5,7-diyn-1-ol (**2b**) in Et_2O (5.00 mL), obtained by Method A from alcohol **1b** (25.08 mmol, 3.06 g) at 40 °C. Reaction time was overnight. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 1.20 g (79%) of **6a** as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (br s, 1H), 1.63−1.77 (m, 4H), 2.41−2.45 (t, J = 6.6 Hz, 2H), 2.94 (s, 6H), 3.69 (t, J = 5.8 Hz, 2H), 6.80−6.89 (m, 2H), 7.21−7.26 (m, 1H), 7.41−7.44 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 19.5, 24.6, 31.8, 43.5, 62.3, 65.9 (C_q), 74.1 (C_q), 79.3 (C_q), 85.2 (C_q), 113.6 (C_q), 116.8, 120.3, 129.7, 135.4, 156.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3357 (OH), 3061, 2941, 2865, 2837, 2789, 2233 (C≡C), 2141 (C≡C), 1592, 1562, 1492, 1453, 1430, 1384, 1339, 1315, 1273, 1195, 1159, 1143, 1122, 1057, 977, 948, 753. EIMS (70 eV), m/z: 241 (9, M$^+$), 240 (17, M$^+$−H), 227 (31), 189 (36), 158 (27), 153.0 (65), 149 (43), 136 (37), 107.0 (39), 43.0 (100). HRMS (m/z): calcd for $C_{16}H_{19}NO$ [M]$^+$, 241.1467; found, 241.1466.

Synthesis of Diyne 6a by Cadiot−Chodkiewicz Coupling. A well-degassed stirred solution of 2-ethynyl-*N*,*N*-dimethylaniline (**8**)[52a] (1.23 mmol, 179 mg) and 6-iodohex-5-yn-1-ol (**9**)[52c] (0.820 mmol, 184 mg) in pyrrolidine (3.00 mL) was cooled to −5 °C, and CuI (10 mol %, 16.0 mg) was added in one portion to the reaction mixture. The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 6 h, quenched with saturated solution of NH_4Cl (15.0 mL), extracted with ethyl acetate, washed with a saturated solution of NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using hexane/ethyl acetate (2:1) as the eluent to give 143 mg (73%) of **6a** as an orange oil.

Methyl 4-(Dimethylamino)-3-(8-hydroxyocta-1,3-diyn-1-yl)-benzoate (6b). Compound **6b** was obtained using Method E from dimethylaniline **3d** (11.0 mmol, 3.36 g) dissolved in DMF (220 mL) and solution of octa-5,7-diyn-1-ol **2b** in Et_2O (5.00 mL), obtained by Method A from diacetylenic alcohol **1b** (44.0 mmol, 5.37 g) at 40 °C. Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 2.70 g (82%) of **6b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.51 (br s, 1H), 1.61−1.78 (m, 4H), 2.42 (t, J = 6.5 Hz, 2H), 3.08 (s, 6H), 3.68 (t, J = 5.8 Hz, 2H), 3.84 (s, 3H), 6.75 (d, J = 8.8 Hz, 1H), 7.82 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.08 (d, J = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.5, 24.6, 31.7, 42.8, 51.8, 62.2, 65.6 (C_q), 73.7 (C_q), 79.4 (C_q), 85.5 (C_q), 110.0, 115.1, 120.1, 131.1, 138.0, 158.0, 166.3. HRMS (FAB) (m/z): calcd for $C_{18}H_{22}NO_3$ [M + H]$^+$, 300.1600; found, 300.1598. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.53; H, 7.12; N, 4.39.

Ethyl 4-(Dimethylamino)-3-(8-hydroxyocta-1,3-diyn-1-yl)-benzoate (6c).[27b] Compound **6c** was synthesized in accordance with Method E in DMF (360 mL) from dimethylaniline **3e** (18.0 mmol, 5.74 g) and compound **2b**, obtained by Method A from diacetylenic alcohol **1b** (63.0 mmol, 7.69 g). Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 4.43 g (79%) of **6c** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.36 (t, J = 7.1 Hz, 3H), 1.62−1.74 (m, 5H), 2.43 (t, J = 6.6 Hz, 2H), 3.09 (s, 6H), 3.70 (t, J = 6.1 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 6.77 (d, J = 8.8 Hz, 1H),7.85 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H).

2-(Dodeca-1,3-diyn-1-yl)-*N*,*N*-dimethylaniline (6d). Compound **6d** was synthesized as described earlier[31] from *o*-(buta-1,3-diynyl)aniline **5a** (0.780 mmol, 198 mg) by reductive methylation. Yield, 150 mg (69%). Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.4 Hz, 3H), 1.28−1.37 (m, 10H), 1.38−1.43 (m, 2H), 1.53−1.60 (m, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.94 (s, 6H), 6.81−6.88 (m, 1H), 7.21−7.26 (m, 1H), 7.42 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 19.7, 22.6, 28.3, 28.9, 29.06, 29.14, 31.8, 43.5, 65.4 (C_q), 73.9 (C_q), 79.5 (C_q), 85.9 (C_q), 113.7 (C_q), 116.8, 120.3, 129.7, 135.4, 156.1 (C_q).

***N*,*N*-Dimethyl-2-(phenylbuta-1,3-diyn-1-yl)aniline (6e).** Compound **6e** was synthesized as described earlier[31] from *o*-(buta-1,3-diynyl)aniline **5b** (0.370 mmol, 80.0 mg) by reductive methylation. Yield, 70.8 mg (78%). Yellowish solid. mp 64−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.99 (s, 6H), 6.84−6.91 (m, 2H), 7.25−7.29 (m, 2H), 7.32−7.36 (m, 3H), 7.47−7.49 (m, 1H), 7.51−7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 43.6, 74.4 (C_q), 78.9 (C_q), 81.0 (C_q), 82.6 (C_q), 113.1 (C_q), 116.8, 120.2, 122.1 (C_q), 128.4, 129.0, 130.1, 132.4, 135.4, 156.2 (C_q).

1-(Dodeca-1,3-diyn-1-yl)-2-methoxybenzene (7a). Diacetylene **7a** was synthesized in accordance with Method D from *o*-iodoanisole **3f** (0.800 mmol, 187 mg) and a 1.00 M solution of dodeca-1,3-diyne in hexane (1.20 mmol, 195 mg, 1.20 mL) in triethylamine (7.00 mL). Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (200:1) as the eluent gave 185 mg (86%) of **7a** as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.88 (t, J = 6.7, 3H), 1.28−1.55 (m, 10H), 1.62−1.66 (m, 2H), 2.36 (t, J = 7.1, 2H), 3.88 (s, 3H), 6.84−6.91 (m, 2H), 7.26−7.33 (m, 1H), 7.44 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.5, 20.1, 23.1, 28.7, 29.3, 29.50, 29.58, 32.3, 56.2, 65.7 (C_q), 71.5 (C_q), 78.6 (C_q), 85.9 (C_q), 111.0, 111.8 (C_q), 120.8, 130.6, 134.9, 161.8 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 2929, 2855, 2241 (C≡C), 2147 (C≡C), 1594, 1573, 1492, 1463, 1434, 1383, 1275, 1246, 1181, 1162, 1128, 1092, 1046, 1024, 751. MS (EI, 70 eV), m/z (%): 268.2 (100, M$^+$), 225 (17, M$^+$ − $(CH_2)_2CH_3$), 211 (25, M$^+$ − $(CH_2)_3CH_3$), 197.1 (15, M$^+$ − $(CH_2)_4CH_3$), 181 (19), 153 (19), 141 (18), 139 (17), 115 (35). HRMS (m/z): calcd for $C_{19}H_{24}O$ [M]$^+$, 268.1827; found, 268.1825.

1-Methoxy-2-(phenylbuta-1,3-diyn-1-yl)benzene (7b). Diacetylene **7b** was synthesized in accordance with Method D from *o*-iodoanisole **3f** (1.00 mmol, 234 mg) and phenyldiacetylene **2e**, obtained by Method B from diacetylene **1e** (2.00 mmol, 368 mg) in triethylamine (10.0 mL). Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (40:1) as the eluent gave 135 mg (58%) of **7b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 3.91 (s, 3H), 6.88−6.94 (m, 2H), 7.35−7.38 (m, 4H), 7.48−7.54 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 55.9, 74.2 (C_q), 77.6 (C_q), 78.1 (C_q), 82.1 (C_q), 110.7, 111.1 (C_q), 120.5, 122.0 (C_q), 128.4, 129.1, 130.7, 132.4, 134.4, 161.4 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 2938, 2836, 2214 (C≡C), 2139 (C≡C), 1594, 1573, 1487, 1462, 1433, 1384, 1278, 1251, 1178, 1162, 1117, 1069, 1048, 1023, 916, 805, 751, 688. MS (EI, 70 eV), m/z (%): 232 (100, M$^+$), 231 (80, M$^+$ − H), 202 (32, M$^+$ − CH_2O), 189 (32). HRMS (m/z): calcd for $C_{17}H_{12}O$ [M]$^+$, 232.0888; found, 232.0885.

1-(Benzyloxy)-2-(dodeca-1,3-diyn-1-yl)benzene (7c). Diacetylene **7c** was synthesized in accordance with Method D from 2-benzyloxyiodobenzene **3g**[52b] (0.800 mmol, 248 mg) and a 1.00 M solution of dodeca-1,3-diyne in hexane (1.20 mmol, 194 mg, 1.20 mL) in triethylamine (7.00 mL). Purification of the crude product by column chromatography using cyclohexane as the eluent gave 218 mg (79%) of **7c** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.7, 3H), 1.29−1.47 (m, 10H), 1.55−1.61 (m, 2H) overlaps with water signal, 2.37 (t, J = 7.1, 2H), 5.19 (s, 2H), 6.85−6.92 (m, 2H), 7.21−7.25 (m, 1H), 7.29−7.48 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.1, 19.7, 22.7, 28.3, 28.9, 29.10, 29.17, 31.9, 65.4 (C_q), 70.4, 71.2 (C_q), 78.4 (C_q), 85.3 (C_q), 112.3 (C_q), 112.9, 120.9, 126.9, 127.8, 128.5, 130.0, 134.5, 136.9 (C_q), 160.5 (C_q). HRMS (ESI) (m/z): calcd for $C_{25}H_{29}O$ [M + H]$^+$, 345.2218; found, 345.2215.

1-(Benzyloxy)-2-(phenylbuta-1,3-diyn-1-yl)benzene (7d). Diacetylene **7d** was synthesized in accordance with Method D from 2-benzyloxyiodobenzene **3g**[52b] (1.00 mmol, 310 mg) and phenyldiacetylene **2e**, obtained by Method B from diacetylene **1e** (3.00 mmol, 552 mg) in triethylamine (10.0 mL). Purification of the crude product by column chromatography using cyclohexane as the eluent gave 292 mg (95%) of **7d** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.22 (s, 2H), 6.90−6.95 (m, 2H), 7.26−7.42 (m, 7H), 7.48−7.55 (m, 5H).

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^{13}C NMR (75 MHz, $CDCl_3$, δ): 70.5, 74.3 (C_q), 77.8 (C_q), 78.2 (C_q), 82.0 (C_q), 111.9 (C_q), 112.8, 120.9, 122.0 (C_q), 126.9, 127.8, 128.4, 128.6, 129.0, 130.5, 132.4, 134.5, 136.7 (C_q), 160.5 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3063, 3032, 2927, 2215 (C≡C), 2144 (C≡C), 1594, 1572, 1485, 1445, 1381, 1281, 1247, 1162, 1117, 1048, 1022, 915, 848, 751. MS (EI, 70 eV), m/z (%): 308 (81, M^+), 307 (76, $M^+ - H$), 231 (49, $M^+ - C_6H_5$), 189 (35), 91 (100, $CH_2C_6H_5$). HRMS (m/z): calcd for $C_{23}H_{16}O$ $[M]^+$, 308.1201; found, 308.1198.

Ethyl 3-[8-(*tert*-Butyldimethylsilyloxy)octa-1,3-diynyl]-4-(dimethylamino)benzoate (6f). Compound **6f** was obtained by a method reported earlier[58] from *o*-(buta-1,3-diynyl)-*N*,*N*-dimethylaniline (**6c**) (1.60 mmol, 500 mg) and *tert*-butyldimethylsilyl chloride (1.76 mmol, 265 mg) in DCM (3.00 mL). Reaction time was overnight. Purification of the crude product by column chromatography using hexane/ethyl acetate (30:1) as the eluent gave 600 mg (87%) of **6f** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.06 (s, 6H), 0.90 (s, 9H), 1.36 (t, J = 7.1 Hz, 3H), 1.63−1.66 (m, 4H), 2.37−2.42 (m, 2H), 3.09 (s, 6H), 3.61−3.69 (m, 2H), 4.32 (q, J = 7.1 Hz, 2H), 6.77 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 14.4, 18.3 (C_q), 19.5, 24.9, 26.0, 31.9, 42.8, 60.5, 62.5, 65.5 (C_q), 73.7 (C_q), 79.5 (C_q), 85.8 (C_q), 110.2 (C_q), 115.2, 120.7 (C_q), 131.1, 138.0, 158.0 (C_q), 165.8. HRMS (ESI) (m/z): calcd for $C_{25}H_{38}NO_3Si$ $[M + H]^+$, 428.2621; found, 428.2620.

Methyl 3-[8-(*tert*-Butyldimethylsilyloxy)octa-1,3-diynyl]-4-(dimethylamino)benzoate (6g). Compound **6g** was obtained by a method reported earlier[58] from *o*-(buta-1,3-diynyl)-*N*,*N*-dimethylaniline (**6b**) (8.72 mmol, 2.66 g) and TBDMSCl (9.60 mmol, 1.45 g) in DCM (15.0 mL). Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (30:1) as the eluent gave 3.39 g (94%) of **6g** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.05 (s, 6H), 0.89 (s, 9H), 1.59−1.67 (m, 4H) overlaps with water signal, 2.38−2.42 (m, 2H), 3.09 (s, 6H), 3.64 (t, J = 5.8 Hz, 2H), 3.85 (s, 3H), 6.76 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.09 (d, J = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3(C_q), 19.5, 24.8, 26.0, 31.8, 42.8, 51.8, 62.5, 65.4 (C_q), 73.5 (C_q), 79.5 (C_q), 85.8 (C_q), 100.2 (C_q), 115.1, 120.2 (C_q), 131.1, 138.0, 158.0 (C_q), 166.3. HRMS (FAB) (m/z): calcd for $C_{24}H_{36}NO_3Si$ $[M + H]^+$, 414.2464; found, 414.2463. Anal. Calcd for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.50; H, 8.47; N, 3.23.

Standard Procedure for the Iodocyclization of *o*-Functionalized (Buta-1,3-diynyl)arenes (See Table 2). To an Ar flushed solution of corresponding (buta-1,3-diynyl)arene **4**−**7** (1.00 equiv) in MeCN or DCM (see Table 2) was added a solution of iodine (1.00 equiv) in MeCN or DCM dropwise. The reaction mixture was stirred at corresponding temperature until the reaction has completed according to TLC. Then, the reaction mixture was diluted with a 5% aqueous solution of $Na_2S_2O_3$. In the case of MeCN, the reaction mixture was extracted with DCM; in the case of DCM, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

3-Iodo-2-(phenylethynyl)benzo[*b*]thiophene (10a). (A) Compound **10a** was obtained from thioanisole **4e** (0.200 mmol, 50.0 mg) in CH_3CN (4.00 mL) and a solution of iodine (0.200 mmol, 51.0 mg) in MeCN (1.00 mL) at room temperature. Reaction time was 3 h. Purification of the crude product by column chromatography using cyclohexane as the eluent gave 60.0 mg (83%) of **10a** as a white solid. mp 106−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.39−7.48 (m, 5H), 7.63−7.65 (m, 2H), 7.72−7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 84.0 (C_q), 88.0 (C_q), 98.6 (C_q), 122.1, 122.3 (C_q), 124.9 (C_q), 125.7, 126.1, 126.5, 128.5, 129.1, 131.7, 139.0 (C_q), 140.5 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3013, 2203 (C≡C), 1596, 1513, 1475, 1452, 1440, 1429, 1317, 1245, 1168, 1095, 1068, 1018, 912, 843, 804, 744, 721, 708, 685. MS (EI, 70 eV), m/z (%): 360.0 (100, M^+), 291 (33) 289 (35), 234 (14), 232 (17), 229 (14), 189 (21), 153 (21). HRMS (m/z): calcd for $C_{16}H_9SI$ $[M]^+$, 359.9470; found, 359.9468. Anal. Calcd for $C_{16}H_9IS$: C, 53.35; H, 2.52; S, 8.90. Found: C, 53.21; H, 2.53; S, 8.76.

(B) Compound **10a** was obtained from thioanisole **4e** (0.200 mmol, 50.0 mg) in DCM (4.00 mL) and a solution of iodine (0.2 mmol, 51.0 mg) in DCM (1.00 mL). Reaction time was 1.5 h. Purification of the crude product by column chromatography using cyclohexane as the eluent gave 68.0 mg (94%) of **10a.**

[(3-Iodobenzo[*b*]thiophen-2-yl)ethynyl]trimethylsilane (10b). (A) Compound **10b** was obtained from thioanisole **4f** (0.503 mmol, 123 mg) in MeCN (5.00 mL) and a solution of iodine (0.503 mmol, 127 mg) MeCN (2.00 mL) at room temperature. Reaction time was 3 h. Purification of the crude product by column chromatography using pentane as the eluent gave 54.0 mg (30%) of TMS-benzothiophene **10b** as colorless oil and 74.0 mg of the mixture of **10b** and **10c** in molar ratio (2.3:1) according to ^{1}H NMR. Calculated overall yield of **10b** was 109 mg (61%), and that of **10c** was 19.0 mg (13%). Analytic data for **10b**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.32 (s, 9H), 7.37−7.48 (m, 2H), 7.69−7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −0.2, 88.7 (C_q), 98.3 (C_q), 105.5 (C_q), 122.1, 124.8 (C_q), 125.7, 126.3, 126.6, 138.8 (C_q), 140.3 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3059, 2959, 2898, 2149 (C≡C), 1590, 1552, 1494, 1452, 1429, 1318, 1298, 1248 (Si−CH_3), 1202, 1149, 1123, 1067, 1019, 972, 916, 845 (Si−CH_3), 790, 750, 724, 701, 682. MS (FAB), m/z: 357 (80, M + H $^+$) 356 (90, M^+), 341 (100, $M^+ - CH_2$). HRMS (FAB) (m/z): calcd for $C_{13}H_{13}ISSi$ $[M]^+$, 355.9552; found, 355.9556. Anal. Calcd for $C_{13}H_{13}ISSi$: C, 43.82; H, 3.68; S, 9.00. Found: C, 44.05; H, 3.68; S, 9.00.

(B) To an Ar flushed solution of thioanisole **4f** (5.33 mmol, 1.30 g) in dry DCM (50.0 mL) was added a solution of iodine (5.33 mmol, 1.35 g) in dry DCM (50.0 mL) dropwise (~15 min) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, anhydrous powder of $Na_2S_2O_3$ was added to the reaction mixture, and the suspension obtained was stirred for 15 min and filtered; DCM was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using pentane as the eluent to give 1.77 g of the mixture of **10b** and **10c** in molar ratio (10.8:1) according to ^{1}H NMR. Calculated overall yield of **10b** was 1.65 g (86%), and that of **10c** was 120 mg (9%).

2-Ethynyl-3-iodobenzo[*b*]thiophene (10c). To an Ar flash-cooled (0 °C) solution of the mixture of **10b** (2.30 mmol, 820 mg) and **10c** (0.23 mmol, 65.0 mg) in absolute THF was added a 1.00 M solution of TBAF (4.60 mmol, 4.60 mL) dropwise (~15 min). The resulting dark reaction mixture was stirred under Ar at 0 °C for 2 h, quenched with water (40.0 mL), extracted with diethyl ether, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel using pentane as the eluent to give 590 mg (81%) of **10c** as a light orange solid becoming brown upon drying. mp 55−56 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.74 (s, 1H), 7.41−7.48 (m, 2H), 7.70−7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 77.9 (C_q), 86.6, 88.6 (C_q), 122.1, 123.8 (C_q), 125.8, 126.4, 126.8, 138.9 (C_q), 140.2 (C_q). IR (neat) ν_{max} (cm^{-1}): 3277, 2100 (C≡C), 1450, 1424,1315, 1293, 1242, 905, 778, 741, 718, 673, 649, 611, 588, 471, 438. MS (EI, 70 eV), m/z (%): 284 (100, M^+), 157 (27, M^+−I), 113 (27). HRMS (m/z): calcd for $C_{10}H_5SI$ $[M]^+$, 283.9157; found, 283.9155.

4-(3-Iodobenzo[*b*]thiophen-2-yl)but-3-yn-1-ol (10d).[25a] (A) Compound **10d** was obtained from thioanisole **4g** (0.425 mmol, 92.0 mg) in MeCN (5.00 mL) and a solution of iodine (0.425 mmol, 108 mg) in MeCN (2.00 mL) at room temperature. Reaction time was 3 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 94.0 mg (67%) of **10d** as a yellowish solid. mp 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 2.01 (t, J = 6.5 Hz, 1H), 2.83 (t, J = 6.1 Hz, 2H), 3.88−3.93 (m, 2H), 7.38−7.46 (m, 2H), 7.67−7.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.4, 60.8, 87.6 (C_q), 96.9 (C_q), 122.1, 125.0 (C_q), 125.7, 126.0, 126.4, 138.6 (C_q), 140.3 (C_q) (one C_q signal overlaps with $CDCl_3$ signal).

(B) Compound **10d** was obtained from thioanisole **4g** (7.34 mmol, 1.59 g) in DCM (50.0 mL) and a solution of iodine (7.34 mmol, 1.86 g)

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in DCM (50.0 mL). Reaction time was 1.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 2.26 g (94%) of **10d.**

5-(3-Iodobenzo[*b*]thiophen-2-yl)pent-4-yn-1-ol (10e).[25b] (A) Compound **10e** was obtained from thioanisole **4h** (3.80 mmol, 875 mg) in MeCN (20.0 mL) and a solution of iodine (3.80 mmol, 965 mg) in MeCN (15.0 mL) at room temperature. Reaction time was 5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 1.11 g (85%) of **10e** as a yellowish solid. mp 60−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ) 1.59 (br s, 1H) overlaps with water signal, 1.91−1.98 (m, 2H), 2.68 (t, J = 7.0 Hz, 2H), 3.91 (t, J = 6.1 Hz, 2H), 7.37−7.45 (m, 2H), 7.67−7.71 (m, 2H).

(B) Compound **10e** was obtained from thioanisole **4h** (6.76 mmol, 1.56 g) in DCM (50.0 mL) and a solution of iodine (6.76 mmol, 1.72 g) in DCM (50.0 mL) at room temperature. Reaction time was 1.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 2.31 g (97%) of **10e.**

6-(3-Iodobenzo[*b*]thiophen-2-yl)hex-5-yn-1-ol (10f). The compound **10f** was obtained from thioanisole **4b** (5.20 mmol, 1.27 g) in DCM (25.0 mL) and a solution of iodine (5.72 mmol, 1.45 g) in DCM (27.0 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 1.73 g (93%) of **10f** as a white solid. mp 55−57 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.35 (br s, 1H), 1.73−1.83 (m, 4H), 2.60 (t, J = 6.4 Hz, 2H), 3.75 (t, J = 5.8 Hz, 2H), 7.37−7.45 (m, 2H), 7.67−7.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.8, 24.7, 31.9, 62.4, 75.6 (C_q), 86.6 (C_q), 100.4 (C_q), 122.0, 125.57, 125.66 (C_q), 126.0, 126.2, 138.6 (C_q), 140.4 (C_q). HRMS (ESI) (m/z): calcd for $C_{14}H_{14}IOS$ $[M + H]^+$, 356.9810; found, 356.9804.

7-(3-Iodobenzo[*b*]thiophen-2-yl)hept-6-yn-1-ol (10g). Compound **10g** was obtained from thioanisole **4c** (12.3 mmol, 3.18 g) in DCM (50.0 mL) and a solution of iodine (13.5 mmol, 3.43 g) in DCM (70.0 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 4.23 g (93%) of **10g** as a white solid. mp 47−49 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.42 (br s, 1H), 1.57−1.76 (m, 6H), 2.56 (t, J = 6.9 Hz, 2H), 3.69 (t, J = 8.3 Hz, 2H), 7.36−7.44 (m, 2H), 7.66−7.70) (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0, 25.1, 28.1, 32.3, 62.8, 75.5 (C_q), 86.5 (C_q), 100.7 (C_q), 122.0, 125.5, 125.76 (C_q), 125.96, 126.2, 138.5 (C_q), 140.4 (C_q). HRMS (ESI) (m/z): calcd for $C_{15}H_{16}IOS$ $[M + H]^+$, 370.9967; found, 370.9957.

8-(3-Iodobenzo[*b*]thiophen-2-yl)-2-methyloct-7-yn-2-ol (10h). Compound **10h** was obtained from thioanisole **4d** (1.18 mmol, 338 mg) in DCM (5.00 mL) and a solution of iodine (1.31 mmol, 332 mg) in DCM (7.00 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (10:1) as the eluent gave 390 mg (83%) of **10h** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.25 (c, 6H), 1.39 (br s, 1H), 1.52−1.76 (m, 6H) overlaps with water signal, 2.57 (t, J = 6.8 Hz, 2H), 7.36−7.44 (m, 2H), 7.66−7.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.9, 23.6, 28.7, 29.3, 43.3, 71.0 (C_q), 75.5 (C_q), 86.5 (C_q), 100.7 (C_q), 122.0, 125.5, 125.7 (C_q), 125.9, 126.1, 138.5 (C_q), 140.4 (C_q). HRMS (m/z): calcd for $C_{17}H_{19}IOS$ $[M]^+$, 398.0201; found, 398.0200.

2-(Dec-1-ynyl)-3-iodo-1-methyl-1*H*-indole (11a). (A) Compound **11a** was obtained from *N*,*N*-dimethylaniline **6d** (0.178 mmol, 50.1 mg) in MeCN (4.00 mL) and a solution of iodine (0.178 mmol, 45.2 mg) in MeCN (2.00 mL) at 40 °C. Reaction time was 5 h. Purification of crude product by column chromatography using cyclohexane/ethyl acetate (90:1) as the eluent gave 62.0 mg (89%) of **11a** as a white solid. mp 38−39 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.7, 3H), 1.30−1.36 (m, 8H), 1.51−1.55 (m, 2H), 1.66−1.73 (m, 2H), 2.58 (t, J = 6.9, 2H), 3.83 (s, 3H), 7.16−7.23 (m, 2H), 7.28−7.30 (m, 1H), 7.38−7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 19.8, 22.7, 28.5, 28.9, 29.1, 29.2, 31.6, 31.8, 63.1 (C_q), 72.0 (C_q), 100.2 (C_q), 109.5, 120.7, 121.3, 123.5, 126.9 (C_q), 129.7 (C_q), 136.8 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 2919, 2849, 2235 (C≡C), 1459, 1375, 1337, 1315, 1234, 1191, 1150, 1128, 1100, 1008, 936, 814, 738, 727. MS (EI, 70 eV), m/z (%): 393 (100, M^+), 294 (11, $M^+-(CH_2)_6CH_3$), 267 (11), 210 (6), 196 (10), 181 (7), 169 (17). HRMS (m/z): calcd for $C_{19}H_{24}IN$ $[M^+]$, 393.0953; found, 393.0958. Anal. Calcd for $C_{19}H_{24}IN$: C, 58.20; H, 6.15; N, 3.56. Found: C, 57.95; H 6.08; N, 3.44.

(B) Compound **11a** was obtained from *N*,*N*-dimethylaniline **6d** (0.125 mmol, 35.2 mg) in DCM (2.50 mL) and a solution of iodine (0.125 mmol, 31.7 mg) in DCM (2.50 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (90:1) as the eluent gave 27.0 mg (55%) of **11a** as a yellowish solid.

3-Iodo-1-methyl-2-(phenylethynyl)-1*H*-indole (11b). (A) Compound **11b** was obtained from *N*,*N*-dimethylaniline (**6e**) (0.0780 mmol, 19.1 mg) in MeCN (2.00 mL) and a solution of iodine (0.0780 mmol, 19.8 mg) in MeCN (2.00 mL) at 40 °C. Reaction time was 5 h. Purification of the crude product by column chromatography using petroleum ether/ethyl acetate (90:1) as the eluent gave 21.0 mg (75%) of **11b** as a white solid. mp 60−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.93 (s, 3H), 7.19−7.23 (m, 1H), 7.25−7.27 (m, 1H), 7.30−7.35 (m, 1H), 7.40−7.45 (m, 4H), 7.63−7.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 31.8, 64.8 (C_q), 80.7 (C_q), 98.4 (C_q), 109.6, 120.9, 121.5, 122.4 (C_q), 124.1, 126.2 (C_q), 128.5, 128.9, 129.9 (C_q), 131.6, 137.3. IR (KBr, thin film) ν_{max} (cm^{-1}): 3055, 2935, 2210 (C≡C), 1598, 1571, 1524, 1462, 1443, 1381, 1342, 1317, 1232, 1157, 1132, 1103, 1069, 1010, 940, 837, 739, 689. MS (EI, 70 eV), m/z (9%): 357.0 (100, M^+), 230.1 (11, M^+-I), 202 (11). HRMS (m/z): calcd for $C_{17}H_{12}IN$ $[M]^+$, 357.0014; found, 357.0016.

(B) Compound **11b** was obtained from *N*,*N*-dimethylaniline **6e** (0.216 mmol, 53.0 mg) in DCM (2.50 mL) and a solution of iodine (0.216 mmol, 55.0 mg) in DCM (2.50 mL). Reaction time was 0.5 h. Purification of the crude product by column chromatography using petroleum ether/ethyl acetate (90:1) as the eluent gave 50.0 mg (65%) of **11b** as a white solid.

6-(3-Iodo-1-methyl-1*H*-indol-2-yl)hex-5-yn-1-ol (11c). (A) Compound **11c** was obtained from *N*,*N*-dimethylaniline **6a** (0.150 mmol, 36.0 mg) in MeCN (3.00 mL) and a solution of iodine (0.150 mmol, 38.0 mg) in MeCN (2.00 mL) at 40 °C. Reaction time was 5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 38.0 mg (72%) of **11c** as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.26 (t, J = 7.1 Hz, 1H, OH), 1.76−1.87 (m, 4H), 2.64 (t, J = 6.6 Hz, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.83 (s, 3H), 7.15−7.31 (m, 3H) overlaps with $CHCl_3$ signal, 7.39 (d, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.6, 24.9, 31.6, 31.8 62.4, 63.4 (C_q), 72.4 (C_q), 99.6 (C_q), 109.5, 120.7, 121.3, 123.6, 126.7 (C_q), 129.6 (C_q), 136.8 (C_q). MS (EI, 70 eV), m/z (%): 353 (100, M^+), 294 (23, $M^+ - (CH_2)_3OH$)), 227 (73), 182 (20), 168 (58), 139 (20). HRMS (ESI) (m/z): calcd for $C_{15}H_{16}INO$ $[M + H]^+$, 354.0355; found, 354.0328. Anal. Calcd for $C_{15}H_{14}INO$: C, 51.01; H, 4.57; N, 3.97. Found: C, 51.14; H 4.81; N, 3.75.

(B) Compound **11c** was obtained from *N*,*N*-dimethylaniline **6a** (2.90 mmol, 700 mg) in DCM (10.0 mL) and a solution of iodine (3.04 mmol, 771 mg) in DCM (20.0 mL) at 40 °C. Reaction time was 0.5 h. Purification of crude the product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 768 mg (75%) of **11c** as a yellow oil.

2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-yn-1-yl]-3-iodo-1-methyl-1*H*-indole (11d). To an ice-cold stirred solution of *N*,*N*-dimethylaniline **6a** (3.39 mmol, 820 mg) in DCM (3 mL) were added imidazole (6.74 mmol, 458 mg) and TBDMSCl (5.06 mmol, 761 mg) at 0 °C. The resulting mixture was stirred at room temperature overnight and quenched with H_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude *O*-TBDMS protected alcohol **6a** was purified by flash chromatography using cyclohexane/ethyl acetate (20:1) as the eluent; then, all fractions containing *O*-TBDMS-protected alcohol **6a** were concentrated under reduced pressure until reaching 1 mL. The concentrated solution of protected alcohol **6a** was diluted with DCM

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(15.0 mL) and treated with solution of iodine (3.72 mmol, 944 mg) in DCM (18.0 mL) at 40 °C in accordance with the standard procedure. Reaction time was 0.5 h. Purification of the crude product by column chromatography using cyclohexane then cyclohexane/DCM (9:1) as the eluent gave 1.22 g (77%) of **11d** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.08 (s, 6H), 0.91 (s, 9H), 1.76−1.79 (m, 4H), 2.60−2.64 (m, 2H), 3.70−3.72 (m, 2H), 3.83 (s, 3H), 7.16−7.20 (m, 1H), 7.22 (d, J = 8.1 Hz, 1H), 7.26−7.30 (m, 1H), 7.39 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3 (C_q), 19.6, 25.1, 26.0, 31.6, 31.9, 62.6, 63.2 (C_q), 72.2 (C_q), 99.9 (C_q), 109.5, 120.7, 121.3, 123.6, 126.8 (C_q), 129.7 (C_q), 136.8 (C−Ar). HRMS (m/z): calcd for $C_{21}H_{30}INOSi$ $[M]^+$, 467.1141; found, 467.1136.

Ethyl 2-(6-Hydroxyhex-1-ynyl)-3-iodo-1-methyl-1*H*-indole-5-carboxylate (11e). Compound **11e** was obtained from *N*,*N*-dimethylaniline **6c** (1.12 mmol, 350 mg) in DCM (5.00 mL) and a solution of iodine (31.0 mg, 1.23 mmol) in DCM (6.00 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (3:1) as the eluent gave 242 mg (51%) of **11e** as a slight yellowish solid. mp 70−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.39 (s, 1H), 1.43 (t, J = 7.1 Hz, 3H), 1.76−1.89 (m, 4H), 2.65 (m, 2H), 3.76 (m, 2H), 3.85 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.23 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.5, 19.6, 24.9, 31.8, 31.9, 60.8, 62.4, 65.0 (C_q), 72.1 (C_q), 100.5 (C_q), 109.3, 123.3 (C_q), 124.2, 124.9, 128.4 (C_q), 129.4 (C_q), 139.3 (C_q), 167.2. HRMS (ESI) (m/z): calcd for $C_{18}H_{21}INO_3$ $[M + H]^+$, 426.0561; found, 426.0561.

Ethyl 2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-ynyl]-3-iodo-1-methyl-1*H*-indole-5-carboxylate (11f). Compound **11f** was obtained from *N*,*N*-dimethylaniline **6f** (3.65 mmol,1.56 g) in DCM (15.0 mL) and a solution of iodine (1.01 g, 4.01 mmol) in DCM (20.0 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (50:1 → 30:1) as the eluent gave 1.49 g (76%) of **11f** as a white solid. mp 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.07 (s, 6H), 0.90 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H), 1.76−1.78 (m, 4H), 2.62 (t, J = 6.4 Hz, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.84 (s, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.21 (d, J = 8.7 Hz, 1H), 7.96 (dd, J = 8.7 Hz, J = 1.5 Hz, 1H), 8.13 (d, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 14.5, 18.3 (C_q), 19.6, 25.1, 26.0, 31.86, 31.94, 60.7, 62.5, 64.8 (C_q), 71.9 (C_q), 100.9 (C_q), 109.2, 123.3 (C_q), 124.1, 124.9, 128.5 (C_q), 129.4 (C_q), 139.3 (C_q), 167.2. HRMS (ESI) (m/z): calcd for $C_{24}H_{35}INO_3Si$ $[M + H]^+$, 540.1425; found, 540.1429.

Methyl 2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-ynyl]-3-iodo-1-methyl-1*H*-indole-5-carboxylate (11g). Compound **11g** was obtained from *N*,*N*-dimethylaniline **6g** (7.49 mmol, 3.10 g) in DCM (30.0 mL) and a solution of iodine (8.24 mmol, 2.09 g) in DCM (45.0 mL) at 40 °C. Reaction time was 0.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (30:1) as the eluent gave 3.49 g (89%) of **11g** as a white solid. mp 77−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.07 (s, 6H), 0.90 (s, 9H), 1.75−1.79 (m, 4H), 2.60−2.63 (m, 2H), 3.69−3.71 (m, 2H), 3.84 (s, 3H), 3.94 (s, 3H), 7.22 (d, J = 8.7 Hz, 1H), 7.96 (dd, J = 8.7 Hz, J = 1.6 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3 (C_q), 19.6, 25.0, 25.9, 31.87, 31.90, 52.0, 62.5, 64.8 (C_q), 71.8 (C_q), 100.9 (C_q), 109.3, 122.8 (C_q), 124.2, 124.8, 128.5 (C_q), 129.4 (C_q), 139.3 (C_q), 167.7. MS (EI, 70 eV), m/z (%): 525 (30, M^+), 342 (21), 341 (100, M^+−CO_2CH_3−I), 326 (27, M^+ − CO_2CH_3−I−CH_3), 234 (12), 171 (16). HRMS (m/z): calcd for $C_{23}H_{32}INO_3Si$ $[M]^+$, 525.1191; found, 525.1194. Anal. Calcd for $C_{23}H_{32}INO_3Si$: C, 52.57; H, 6.14; N, 2.67. Found: C, 52.35; H, 6.14; N, 2.23.

3-Iodo-2-(phenylethynyl)benzofuran (12a). (A) Compound **12a** was obtained from anisole **7b** (0.215 mmol, 50.0 mg) in MeCN (3.00 mL) using a solution of iodine (0.215 mmol, 55.0 mg) in MeCN (2.00 mL) at 40 °C. Reaction time was overnight. Purification of the crude product by column chromatography using pentane as the eluent gave 12.0 mg (16%) of **12a** as a white solid. mp 65−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.31−7.46 (m, 7H), 7.63−7.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 72.4 (C_q), 79.2 (C_q), 98.2 (C_q), 111.4, 121.5, 121.7 (C_q), 123.9, 126.7, 128.5, 129.4, 130.5 (C_q), 131.9, 141.3 (C_q), 154.3 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 2207 (C≡C), 1586, 1484, 1471, 1439, 1342, 1299, 1254, 1211, 1151, 1102, 1067, 1010, 991, 928, 911, 859, 765, 754, 739, 684. MS (EI, 70 eV), m/z (%): 344 (100, M^+), 189 (20). HRMS (m/z): calcd for $C_{16}H_9IO$ $[M]^+$, 343.9693; found, 343.9696. Anal. Calcd for $C_{16}H_9IO$: C, 55.84; H, 2.64. Found: C, 55.80; H, 2.69.

(B) To an Ar flushed solution of benzyl ether **7d** (0.130 mmol, 40.0 mg) in MeCN (3.00 mL) was added a solution of ICl (0.130 mmol, 21.0 mg) in MeCN (500 μL). The reaction mixture was stirred at room temperature overnight; then, an additional amount of ICl (0.065 mmol, 11.0 mg) in MeCN (500 μL) was added, and the resulting mixture was stirred for 3 h, diluted with a 5% aqueous solution of $Na_2S_2O_3$, and extracted with DCM. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using pentane as the eluent to give 22.0 mg (49%) of **12a** as a white solid.

2-(1-Chloro-2-iodo-2-phenylethenyl)-3-iodobenzofuran (13a). To an Ar flushed solution of anisole **7b** (0.172 mmol, 40.0 mg) in DCM (2.00 mL) was added a solution of ICl (0.172 mmol, 28.0 mg) in DCM (500 μL). The reaction mixture was stirred at room temperature overnight; then, an additional amount of ICl (0.172 mmol, 28.0 mg) in DCM (500 μL) was added, and the resulting mixture was stirred for 1 h, diluted with a 5% aqueous solution of $Na_2S_2O_3$, and extracted with DCM. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using pentane as the eluent to give 51.0 mg (59%) of **13a** as a yellowish solid. mp 97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.31−7.39 (m, 2H), 7.42−7.55 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 68.9 (C_q), 103.7 (=CI(Ph)), 111.8, 120.5 (CCl), 122.1, 123.9, 126.9, 128.4, 128.6, 130.4 (C_q), 141.1 (C_q), 153.8 (C_q), 154.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3057, 2922, 1588, 1487, 1444, 1384, 1342, 1302, 1249, 1173, 1106, 1072, 1022, 1003, 946, 884, 853, 746, 703. MS (EI, 70 eV), m/z (%): 505 (4, M^+), 343 (10), 256 (72), 255 (100), 237 (12), 197 (22), 181 (40), 177 (97), 135 (30), 117 (56), 105 (33). HRMS (m/z): calcd for $C_{16}H_9OCII_2$ $[M]^+$, 505.8426; found, 505.8433.

2-(1-Chloro-2-iododec-1-en-1-yl)-3-iodobenzofuran (13b). To an Ar flushed solution of anisole **7a** (0.134 mmol, 36.0 mg) in MeCN (2.00 mL) was added a solution of ICl (0.134 mmol, 22.0 mg) in MeCN (500 μL). The reaction mixture was stirred at room temperature overnight; then, an additional amount of ICl (0.067 mmol, 11.0 mg) in MeCN (500 μL) was added, and the resulting mixture was stirred for 3 h and worked up as was described for **13a**, giving 27.0 mg (38%) of **13b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.9 (t, J = 6.8 Hz, 3H), 1.26−1.40 (m, 8H), 1.43−1.50 (m, 2H), 1.65−1.73 (m, 2H), 2.89 (t, J = 7.0 Hz, 2H), 7.32−7.36 (m, 1H), 7.39−7.45 (m, 2H), 7.48−7.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.3 (CH_3), 22.7 (CH_2), 28.37 (CH_2), 28.40 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 41.5 (CH_2), 68.5 (CI), 111.7 (=CI(C_8H_{17})), 111.8 (CH_{Ar}), 118.8 (CCl), 122.0 (CH_{Ar}), 123.8 (CH_{Ar}), 126.7 (CH_{Ar}), 130.4 (C_q), 153.9 (C_q), 154.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3064, 2953, 2926, 2855, 1446, 1378, 1341, 1302, 1247, 1177, 1124, 1106, 1019, 930, 868, 773, 745. MS (EI, 70 eV), m/z (%): 542 (76, M^+), 380 (18), 317 (20), 281 (27), 257 (23), 190 (49), 155 (17), 126 (19), 43 (100). HRMS (m/z): calcd for $C_{18}H_{21}ClI_2O$ $[M]^+$, 541.9365; found, 541.9372.

2-(Dec-1-yn-1-yl)-3-iodobenzofuran (12b). To an Ar flushed solution of *o*-(buta-1,3-diynyl)anisole **7a** (0.373 mmol, 100 mg) in DCM (4.00 mL) was added Py_2IBF_4 (0.410 mmol, 152 mg) followed by HBF_4·Et_2O (0.373 mmol, 60.3 mg, 50.7 μL). The reaction mixture was stirred at room temperature overnight and then for additional 24 h at 30 °C and worked up as was described for **13a**, giving 20.0 mg (14%) of **12b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (t, J = 6.8 Hz, 3H), 1.26−1.37 (m, 8H), 1.46−1.53 (m, 2H), 1.65−1.72 (m, 2H), 2.55 (t, J = 7.0 Hz, 2H), 7.27−7.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 19.7, 22.7, 28.2, 28.9, 29.1, 29.2, 31.8, 70.6 (C_q), 70.9 (C_q), 100.6 (C_q), 111.2, 121.4, 123.7, 126.2, 130.5 (C_q), 141.8 (C_q), 153.9 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 2925, 2854,

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2232 (C≡C), 1557, 1446, 1377, 1344, 1 251, 1110, 1185, 1107, 1036, 744. MS (EI, 70 eV), *m/z* (%): 380.2 (100, M^+), 310 (15), 283 (40), 281 (32), 196 (13), 182 (19), 169 (20), 156 (30), 126 (26). HRMS (*m/z*): calcd for $C_{18}H_{21}IO$ $[M]^+$, 380.0632; found, 380.0639.

One-Pot Appel Reaction/Electrophilic Cyclization Sequence. Methyl 3-iodo-2-(6-iodohex-1-ynyl)-1-methyl-1*H*-indole-5-carboxylate (11h). To a degassed stirred solution of *N*,*N*-dimethylaniline **6b** (3.67 mmol, 1.10 g) in anhydrous DCM (50.0 mL) were added PPh_3 (4.04 mmol, 1.06 g) and imidazole (4.41 mmol, 300 mg). After the formation of a homogeneous solution, the reaction mixture was cooled to −20 °C, and I_2 (4.41 mmol, 1.12 g) was added. The mixture obtained was stirred at −20 °C for 1 h, resulting in the conversion of alcohol **6b** to the corresponding iodide **6h** (TLC monitoring). Then, the cooling bath was removed, the reaction mixture was allowed to warm to room temperature, and the second portion of I_2 (4.41 mmol, 1.02 g) as a solution in anhydrous DCM (50.0 mL) was added dropwise. The reaction mixture was refluxed for 18 h (TLC monitoring), cooled, poured into a saturated solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with saturated solution of $Na_2S_2O_3$ and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (20:1) as the eluent to give 1.81 g (94%) of **11h** as a beige solid. mp 149−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.79−1.86 (m, 2H), 2.08−2.15 (m, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.94 (s, 3H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.96 (dd, *J* = 8.7 Hz, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 6.0, 18.7, 29.0, 31.9, 32.3, 52.0, 65.2 (C_q), 72.4 (C_q), 99.8 (C_q), 109.4, 122.9 (C_q), 124.2, 124.9, 128.2 (C_q), 129.3 (C_q), 139.3 (C_q), 167.6. HRMS (FAB) (*m/z*): calcd for $C_{17}H_{17}I_2NO_2$ $[M]^+$, 520.9343; found, 520.9347. Anal. Calcd for $C_{17}H_{17}I_2NO_2$: C, 49.95; H, 4.41; N, 3.41. Found: C, 50.56; H, 4.52; N, 3.17.

3-Iodo-2-(4-iodobut-1-ynyl)benzo[*b*]thiophene (10i). Diiodobenzothiophene **10i** was obtained from thioanisole **4g** (0.509 mmol, 110 mg) by the same procedure as was described for indole **11h**. Purification of the crude product by column chromatography using pentane as the eluent gave 176 mg (79%) of **10i** as a beige solid. mp 74−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.14 (t, *J* = 7.3 Hz, 2H), 3.38 (t, *J* = 7.3 Hz, 2H), 7.38−7.46 (m, 2H), 7.68−7.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 25.1, 76.9 (C_q), 87.4 (C_q), 98.3 (C_q), 122.1, 124.8 (C_q), 125.7, 126.1, 126.4, 138.7 (C_q), 140.4 (C_q). IR (neat) ν_{max} (cm^{-1}): 3058, 2946, 2891, 2215 (C≡C), 1451, 1424, 1305, 1247, 1168, 1016, 941, 869, 765, 749, 722, 640, 598. MS (EI, 70 eV), *m/z* (%): 437 (100, M^+), 310 (11), 296 (5), 184 (62), 139 (16). HRMS (*m/z*): calcd for $C_{12}H_8I_2S$ $[M]^+$, 437.8431; found, 437.8438. Anal. Calcd for $C_{12}H_8I_2S$: C, 32.90; H, 1.84; S, 7.32. Found: C, 32.99; H, 1.90; S, 7.40.

3-Iodo-2-(5-iodopent-1-yn-1-yl)benzo[*b*]thiophene (10j). A solution of benzothiophene **10e** (0.500 mmol, 170 mg), PPh_3 (0.500 mmol, 131 mg), and imidazole (0.750 mmol, 51.0 mg) in anhydrous THF (5.00 mL) was cooled to −5 °C, and well-ground powder of iodine (0.658 mmol, 164 mg) was added to the reaction mixture in one portion in a stream of Ar. The reaction mixture was stirred at 0 °C over 2 h. To reach the full conversion of **10e**, an additional amount of PPh_3 (0.575 mmol, 151 mg), imidazole (0.863 mmol, 59.0 mg), and iodine (0.56 mmol, 142 mg) was added to the reaction mixture at −5 °C under Ar, and the reaction mixture was stirred for additional 1 h at 0 °C. Then, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and extracted with diethyl ether, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using pentane as the eluent to give 206 mg (91%) of **10j** as a yellowish solid. mp 53−54 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.14−2.20 (m, 2H), 2.70 (t, *J* = 6.7 Hz, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 7.38−7.46 (m, 2H), 7.67−7.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 5.2, 21.0, 31.7, 76.5 (C_q), 87.2 (C_q), 98.2 (C_q), 122.1, 125.2 (C_q), 125.6, 126.0, 126.3, 138.6 (C_q), 140.3 (C_q). IR (neat) ν_{max} (cm^{-1}): 3050, 2940, 2892, 2223 (C≡C), 1449, 1428, 1418, 1346, 1324, 1295, 1263, 1249, 1211, 1146, 1019, 967, 915, 843, 764, 749. MS (EI, 70 eV), *m/z* (%): 459 (63, M^+), 296 (100), 198 (73), 169 (23), 153 (10), 126 (11). HRMS (*m/z*): calcd for $C_{13}H_{10}I_2S$ $[M]^+$, 451.8587; found, 451.8594. Anal. Calcd for $C_{13}H_{10}I_2S$: C, 34.54; H, 2.23; S, 7.09. Found: C, 34.67; H, 2.23; S, 7.11

2-(Cyclopropylethynyl)-3-iodobenzo[*b*]thiophene (14). A stirred cooled (−5 °C) solution of diiodobenzothiophene **10j** (0.166 mmol, 75.0 mg) in anhydrous THF (5.00 mL) was treated with a 1.0 M solution of *t*-BuOK in THF (0.216 mmol, 216 μL) over 15 min under Ar. The resulting reaction mixture was stirred at 0 °C for 2 h and then quenched with a saturated solution of NH_4Cl (5 mL) and water (5 mL), and the reaction mixture was allowed to warm to room temperature. Then, it was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using pentane as the eluent to give 49.0 mg (91%) of **14** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.93−1.01 (m, 4H), 1.55−1.61 (m, 1H) overlaps with water signal, 7.36−7.40 (m, 2H), 7.65−7.70 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.8, 9.3, 70.3 (C_q), 86.6 (C_q), 104.1 (C_q), 122.0, 125.5, 125.7 (C_q), 125.9, 126.1, 138.5 (C_q), 140.4 (C_q). IR (neat) ν_{max} (cm^{-1}): 3055, 3008, 2924, 2218 (C≡C), 1452, 1431, 1351, 1316, 1297, 1248, 1218, 1161, 1084, 1052, 1028, 944, 893, 811, 781, 750, 723, 708. MS (EI, 70 eV), *m/z* (%): 324 (100, M^+), 197 (68), 195 (26), 169 (52), 152 (44), 125 (13), 93 (15). HRMS (*m/z*): calcd for $C_{13}H_9IS$ $[M]^+$, 323.9464; found, 323.9469.

Synthesis of Heteroindene-Fused Enediynes by Sonogashira Coupling (See Table 3). Method A. To a stirred solution of 2-ethynyl-3-iodoheteroindene (1.00 equiv) in DMF were added the alkyne (2.00−3.00 equiv), $Pd(PPh_3)_4$ (5 mol %), PPh_3 (10 mol %), and DIPA (4.00 equiv). The reaction vial was evacuated and flushed with Ar several times. After that, CuI (15 mol %) was added, and the reaction vial was sealed and flushed with Ar. The reaction mixture was allowed to stir at 40−70 °C for the corresponding time (TLC monitoring). After cooling, the reaction mixture was poured into a saturated solution of NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of NH_4Cl and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

Method B. $Pd(PPh_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), DIPA (4.00 equiv) were added to an Ar flushed, stirred 0.1 M solution of 2-ethynyl-3-iodoheteroindene (1.00 equiv) in DMF. Then, alkyne was added, and the reaction mixture was stirred at room temperature under Ar for 40−60 min. Then, CuI (15 mol %) was added, and the reaction mixture was warmed to 50 °C and stirred at this temperature for 3−18 h (TLC monitoring) and worked up as was described in Method A.

Method C. To a stirred solution of 2-ethynyl-3-iodobenzo[*b*]-thiophene (1.00 equiv) in DMF was added $Pd(PPh_3)_4$ (5 mol %). The reaction vial was evacuated and flushed with Ar several times. Afterward, K_2CO_3 (8.00 equiv) followed by CuI (15 mol %) was added, the reaction vial was sealed and degassed once again, and the reaction mixture was stirred for 3 min. Then, MeOH (8.00 equiv) followed by TMS-protected enyne (2.00 equiv) was added. The reaction mixture was allowed to stir at 50 °C for 3 h and worked up as was described in Method A.

Method D. To a stirred solution of 2-ethynyl-3-iodobenzo[*b*]-thiophene (1.00 equiv) in DMF were added $Pd(PPh_3)_4$ (5 mol %) and DIPA (4.00 equiv). The reaction vial was evacuated and flushed with Ar several times. Afterward, KF (5.00 equiv) followed by CuI (15 mol %) was added, and the reaction vial was sealed, degassed once again, and stirred for 3 min. Then, MeOH (10.0 equiv) followed by TMS-protected enyne (2.00 equiv) was added. The reaction mixture was allowed to stir at 40 °C for 3−12 h and worked up as was described in Method A.

3-(Oct-1-ynyl)-2-(phenylethynyl)benzo[*b*]thiophene (16a). Enediyne **16a** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10a** (0.111 mmol, 40.0 mg) and octyne **15a** (0.220 mmol, 25.0 mg, 32.0 μL) in DMF (3.00 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using pentane as the eluent gave 27.0 mg

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(70%) of **16a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.90 (t, J = 7.0 Hz, 3H), 1.32−1.39 (m, 4H), 1.53−1.61 (m, 2H), 1.76−1.78 (m, 2H), 2.60 (t, J = 7.0 Hz, 2H), 7.37−7.45 (m, 5H), 7.58−7.61 (m, 2H), 7.73−7.75 (m, 1H), 7.87−7.90 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 19.9, 22.5, 28.6, 28.8, 31.4, 73.9 (C_q), 82.7 (C_q), 98.0 (C_q), 98.5 (C_q), 122.0, 122.7 (C_q), 123.4, 123.6 (C_q), 124.92, 124.95 (C_q), 126.0, 128.3, 128.8, 131.6, 138.5 (C_q), 139.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 2954, 2929, 2856, 2201 (C≡C), 1597, 1484, 1458, 1432, 1382, 1319, 1247, 1155, 1068, 1016, 755, 730, 688. MS (EI, 70 eV), m/z (%): 342 (86, M^+), 328 (16), 322 (28), 299 (22), 284 (42), 271 (100), 258 (17), 239 (22). HRMS (m/z): calcd for $C_{24}H_{22}S$ $[M]^+$, 342.1437; found, 342.1440. Anal. Calcd for $C_{24}H_{22}S$: C, 84.16; H, 6.47; S, 9.36. Found: C, 84.53; H, 6.39; S, 9.23.

5-[2-(Phenylethynyl)benzo[*b*]thiophen-3-yl]pent-4-yn-1-ol (16b). Enediyne **16b** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10a** (0.111 mmol, 40.0 mg) and pent-4-yn-1-ol **15b** (0.222 mmol, 19.0 mg, 20.0 μL) in DMF (3.00 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (5:1) as the eluent gave 25.0 mg (72%) of **16b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.52 (br s, 1H), 1.94−2.00 (m, 2H), 2.74 (t, J = 6.8 Hz, 2H), 3.91−3.94 (m, 2H), 7.37−7.43 (m, 5H), 7.58−7.61 (m, 2H), 7.73−7.75 (m, 1H), 7.85−7.87 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.4, 31.4, 61.7, 74.5 (C_q), 82.6 (C_q), 96.7 (C_q), 98.7 (C_q), 122.1, 122.6 (C_q), 123.1, 123.4 (C_q), 125.0, 125.4 (C_q), 126.1, 128.4, 128.9, 131.7, 138.5 (C_q), 138.9 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3355, 3060, 2947, 2220 (C≡C), 2200 (C≡C), 1597, 1484, 1458, 1432, 1370, 1320, 1248, 1157, 1053, 935, 913, 756, 730, 689. MS (EI, 70 eV), m/z (%): 316 (100, M^+), 284 (20), 271 (67), 260 (21), 239 (20). HRMS (m/z): calcd for $C_{21}H_{16}OS$ $[M]^+$, 316.0916; found, 316.0919.

Trimethyl{[2-(phenylethynyl)benzo[*b*]thiophen-3-yl]ethynyl}-silane (16c). Enediyne **16c** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10a** (0.111 mmol, 40.0 mg) and trimethylsilylacetylene **15c** (0.222 mmol, 22.0 mg, 30.0 μL) in DMF (1.10 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane as the eluent gave 30.0 mg (83%) of **16c** as a yellow solid. mp 55−57 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.35 (s, 9H), 7.38−7.47 (m, 5H), 7.58−7.60 (m, 2H), 7.73−7.75 (m, 1H), 7.88−7.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 82.5 (C_q), 97.7 (C_q), 99.6 (C_q), 102.0 (C_q), 122.0, 122.6 (C_q), 122.8 (C_q), 123.5, 125.1, 126.2, 127.2 (C_q), 128.4, 128.9, 131.7, 138.4 (C_q), 138.7 (C_q). IR (neat) ν_{max} (cm^{-1}): 3058, 2954, 2204 (C≡C), 2142 (C≡C), 1478, 1457, 1429, 1351, 1248 (C−Si), 1067, 1033, 1013, 886, 836 (C−Si), 751, 726, 684, 642. MS (FAB), m/z: 330 (100, M^+). HRMS (FAB) (m/z): calcd for $C_{21}H_{18}SSi$ $[M]^+$, 330.0893; found, 330.0896.

4-{3-[(Trimethylsilyl)ethynyl]benzo[*b*]thiophen-2-yl}but-3-yn-1-ol (16d).[25a] Enediyne **16d** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10d** (0.110 mmol, 40.0 mg) and trimethylsilylacetylene **15c** (0.220 mmol, 22.0 mg, 30.0 μL) in DMF (1.10 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (5:1) as the eluent gave 20.1 mg (63%) of **16d** as a yellow solid. mp 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.32 (s, 9H), 2.01 (t, J = 6.5 Hz, 1H), 2.83 (t, J = 6.1 Hz, 2H), 3.88−3.93 (m, 2H), 7.37−7.45 (m, 2H), 7.70−7.72 (m, 1H), 7.83−7.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 24.5, 60.8, 75.8 (C_q), 97.5 (C_q), 97.5 (C_q), 101.5 (C_q), 122.0, 122.8 (C_q), 123.3, 125.1, 126.1, 127.3 (C_q), 138.0 (C_q), 138.6 (C_q).

5-{3-[(Trimethylsilyl)ethynyl]benzo[*b*]thiophen-2-yl}pent-4-yn-1-ol (16e). Enediyne **16e** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10e** (1.50 mmol, 513 mg) and trimethylsilylacetylene **15c** (4.50 mmol, 441 mg, 640 μL) in DMF (45.0 mL) at 50 °C. Reaction time was 12 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (7:1) as the eluent gave 397 mg (85%) of **16e** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.33 (s, 9H), 1.63 (br s, 1H), 1.88−1.95 (m, 2H), 2.69 (t, J = 6.9 Hz, 2H), 3.88 (t, J = 6.1 Hz, 2H), 7.36−7.44 (m, 2H), 7.68−7.71 (m, 1H), 7.82−7.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 16.6, 31.0, 61.5, 74.2 (C_q), 97.7 (C_q), 100.6 (C_q), 101.1 (C_q), 121.95, 122.02 (C_q), 123.2, 125.0, 125.9, 127.9 (C_q), 137.9 (C_q), 138.7 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3346, 3061, 2956, 2897, 2221 (C≡C), 2149 (C≡C), 1458, 1432, 1348, 1318, 1249 (C−Si), 1217, 1161, 1082, 1048, 938, 911, 847 (C−Si), 759, 731, 687, 643. MS (FAB), m/z: 313 (99, M + H^+), 313 (100, M^+). HRMS (FAB) (m/z): calcd for $C_{18}H_{20}OSSi$ $[M]^+$, 312.0999; found, 312.1002.

6-{3-[(Trimethylsilyl)ethynyl]benzo[*b*]thiophen-2-yl}hex-5-yn-1-ol (16f). Compound **16f** was synthesized in accordance with Method B from 3-iodobenzo[*b*]thiophene **10f** (4.78 mmol, 1.70 g) dissolved in DMF (47.0 mL) and trimethylsilylacetylene **15c** (16.75 mmol, 1.64 g) at 50 °C. Reaction time was 6 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 1.29 g (83%) of **16f** as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.32 (s, 9H), 1.28 (br s, 1H), 1.76−1.79 (m, 4H), 2.61 (t, J = 6.4 Hz, 2H), 3.73 (t, J = 5.9 Hz, 2H), 7.36−7.43 (m, 2H), 7.68−7.70 (m, 1H), 7.81−7.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 19.8, 24.7, 31.8, 62.3, 74.0 (C_q), 97.8 (C_q), 101.0 (C_q), 101.2 (C_q), 121.8 (C_q), 121.9, 123.2, 125.0, 125.9, 128.0 (C_q), 137.8 (C_q), 138.7 (C_q). HRMS (ESI) (m/z): calcd for $C_{19}H_{23}OSSi$ $[M + H]^+$, 327.1233; found, 327.1233.

7-{3-[(Trimethylsilyl)ethynyl]benzo[*b*]thiophen-2-yl}hept-6-yn-1-ol (16g). Compound **16g** was synthesized in accordance with Method B from benzo[*b*]thiophene **10g** (9.26 mmol, 3.43 g) dissolved in DMF (92.0 mL) and trimethylsilylacetylene **15c** (32.42 mmol, 3.18 g) at 50 °C. Reaction time was 5 h. Purification of crude product by column chromatography using hexane/ethyl acetate (5:1) as the eluent gave 2.39 g (80%) of **16g** as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.32 (s, 9H), 1.35 (br s, 1H), 1.55−1.76 (m, 6H), 2.57 (t, J = 7.0 Hz, 2H), 3.68 (t, J = 5.8 Hz, 2H), 7.37−7.43 (m, 2H), 7.68−7.70 (m, 1H), 7.81−7.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.1, 20.0, 25.1, 28.3, 32.3, 62.8, 73.9 (C_q), 97.9 (C_q), 101.0 (C_q), 101.4 (C_q), 121.8 (C_q), 121.9, 123.3, 125.0, 125.9, 128.2 (C_q), 137.9 (C_q), 138.8 (C_q). HRMS (ESI) (m/z): calcd for $C_{20}H_{24}NaOSSi$ $[M + Na]^+$, 363.1209; found, 363.1208.

4,4′-(Benzo[*b*]thiophene-2,3-diyl)bis(but-3-yn-1-ol) (16h). *O*-THP monoprotected diol **16h** was synthesized in accordance with Method A from 3-iodobenzo[*b*]thiophene **10d** (0.287 mmol, 94.0 mg) and *O*-THP-protected but-3-yn-1-ol **15d**[S2d] (0.86 mmol, 133 mg) in DMF (3.00 mL) at 65 °C. Reaction time was 36 h. The crude product was purified by flash chromatography using cyclohexane/ethyl acetate (3:1). A concentrated under reduce pressure solution of monoprotected diol was dissolved in methanol (5 mL), and to the stirred solution obtained was added Amberlyst 15 (20.0 mg). The reaction mixture was stirred under Ar at 45 °C for 3.5 h and cooled to rt, Amberlyst 15 was filtered off, MeOH was removed under reduced pressure, and the residue was purified by column chromatography using cyclohexane/ethyl acetate (1:2) as the eluent to give 55.0 mg (71%) of diol **16h** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.25 (br s, 2H), 2.80−2.85 (m, 4H), 3.85−3.90 (m, 4H), 7.37−7.43 (m, 2H), 7.70−7.73 (m, 1H), 7.80−7.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.2, 24.5, 60.7, 60.9, 75.8 (C_q), 76.2 (C_q), 93.5 (C_q), 97.4 (C_q), 122.1, 122.8 (C_q), 123.2, 125.0, 126.1, 126.3 (C_q), 138.0 (C_q), 138.5 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3356, 3059, 2939, 2887, 2222 (C≡C), 1458, 1432, 1372, 1320, 1217, 1044, 847, 759, 730, 643. MS (EI, 70 eV), m/z (%): 270 (5, M^+), 239 (2), 208 (3), 197 (2), 184 (3) 171 (2), 43 (100). HRMS (m/z): calcd for $C_{16}H_{14}O_2S$ $[M]^+$, 270.0709; found, 270.0715.

5[2-(4-Hydroxybut-1-ynyl)benzo[*b*]thiophen-3-yl]pent-4-yn-1-ol (16i). *O*-THP-monoprotected diol **16i** was synthesized in accordance with Method A from benzo[*b*]thiophene **10d** (0.287 mmol, 94.0 mg) and *O*-THP-protected pent-4-yn-1-ol **15e**[S2d] (0.860 mmol, 144 mg) in DMF (3.00 mL) at 65 °C. Reaction time was 36 h. The crude product was purified by flash chromatography using cyclohexane/ethyl acetate (3:1). Deprotection followed by purification, as was described for **16h**, gave 54.0 mg (66%) of **16i** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.91−1.97 (m, 2H), 2.31 (br s, 2H), 2.71 (t, J = 6.5 Hz, 2H), 2.82 (t, J = 5.8 Hz, 2H), 3.86 (t, J = 5.8 Hz, 2H), 3.93 (t, J = 5.9 Hz, 2H), 7.36−7.42 (m, 2H), 7.69−7.71 (m, 1H), 7.80−7.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.7, 24.6, 31.1, 60.6, 62.1, 75.0 (C_q), 75.7 (C_q), 96.3 (C_q), 97.5 (C_q), 122.0, 122.7 (C_q), 123.2, 125.0, 125.9

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(C_q), 126.0, 138.1 (C_q), 138.6 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3346 (OH), 3060, 2937, 2883, 2213 (C≡C), 1458, 1364, 1320, 1281, 1217, 1047, 933, 848, 759, 730, 643. MS (EI, 70 eV), *m*/*z* (%): 284 (100, M^+), 253 (21), 239 (18), 221 (44), 208 (67), 197 (48), 184 (33) 163 (31), 43 (36). HRMS (*m*/*z*): calcd for $C_{17}H_{16}O_2S$ $[M]^+$, 284.0866; found, 284.0873.

5,5′-(Benzo[*b*]thiophene-2,3-diyl)bis(pent-4-yn-1-ol) (16j).[25b] *O*-THP-monoprotected diol **16j** was synthesized in accordance with Method A from benzo[*b*]thiophene **10e** (3.51 mmol, 1.20 g) and *O*-THP-protected pent-4-yn-1-ol **15e**[52d] (10.5 mmol, 1.76 g) in DMF (25.0 mL) at 65 °C. Reaction time was 36 h. The crude product was purified by flash chromatography using cyclohexane/ethyl acetate (3:1). Deprotection followed by purification, as was described for **16h**, gave 867 mg (83%) of **16j** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.86−1.95 (m, 4H), 2.66−2.71 (m, 6H), 3.86−3.92 (m, 4H), 7.34−7.41 (m, 2H), 7.68−7.70 (m, 1H), 7.80−7.82 (m, 1H).

(Hex-5-en-1-yn-1-yl)trimethylsilane (15f). To a mechanically stirred cooled (−10 °C) mixture of a 1.0 M solution of allyl magnesium bromide (100 mmol, 100 mL) and anhydrous Et_2O (60.0 mL) was added propargyl chloride (50.0 mmol, 3.73 g, 3.61 mL) dropwise. The resulting solution was allowed to warm to room temperature slowly (0.5 h) in order to avoid an exothermic reaction. The suspension formed was stirred at room temperature for 5 h, cooled to 0 °C, and treated dropwise with trimethylsilyl chloride (58.0 mmol, 6.30 g, 7.37 mL). The resulting reaction mixture was warmed to room temperature and vigorously stirred for 24 h. Then, it was cooled to −5 °C and quenched with H_2O (200 mL) followed by 0.05 M hydrochloric acid (20.0 mL), affording two clear layers. The upper layer was separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure (not lower than 700 Torr) until reaching $^1/_3$ of the original volume. The residual solvent was removed by distillation under atmospheric pressure using Vigreux column, which gave the crude product that was purified by distillation under reduced pressure. Yield, 3.87 g (51%). Colorless liquid, bp 50−52 °C/12 Torr (lit.[59] bp 58−61/15 Torr). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.14 (s, 9H), 2.23−2.33 (m, 4H), 5.00−5.09 (m, 2H), 5.80−5.90 (m, 2H).

3-(Hex-5-en-1-ynyl)-2-(phenylethynyl)benzo[*b*]thiophene (16k). Enediyne **16k** was synthesized in accordance with Method C from 3-iodobenzo[*b*]thiophene **10a** (0.158 mmol, 57.0 mg) and (hex-5-en-1-ynyl)trimethylsilane (**15f**) (0.314 mmol, 48.0 mg) in DMF (3.00 mL) at 50 °C. Reaction time was 12 h. Purification of the crude product by column chromatography using pentane as the eluent gave 42.0 mg (85%) of **16k** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.37−2.42 (m, 2H), 2.62 (t, J = 7.1 Hz, 2H), 5.00 (dq, ^3J = 10.2 Hz, $^4J = {}^2J$ = 1.6 Hz, 1H, CH^B), 5.12 (dq, ^3J = 17.1 Hz, $^4J = {}^2J$ = 1.6 Hz, 1H, CH^A), 5.90−6.00 (m, 1H, CH^X), 7.28−7.37 (m, 5H), 7.49−7.54 (m, 2H), 7.64−7.67 (m, 1H), 7.79−7.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.8, 33.0, 74.4 (C_q), 82.7 (C_q), 97.0 (C_q), 98.6 (C_q), 116.0, 122.0, 122.7 (C_q), 123.3 (C_q), 123.5, 125.0, 125.2 (C_q), 126.0, 128.4, 128.8, 131.7, 136.8, 138.5 (C_q), 139.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3062, 2978, 2920, 2201 (C≡C), 1641, 1597, 1597, 1483, 1433, 1367, 1319, 1248, 1155, 1069, 1015, 991, 914, 755, 730, 689. MS (EI, 70 eV), *m*/*z* (%): 312 (70, M^+), 271 (100), 239 (8), 153 (5), 77 (6). HRMS (*m*/*z*): calcd for $C_{22}H_{16}S$ $[M]^+$, 312.0967; found, 312.0974.

2-(Cyclopropylethynyl)-3-(hex-5-en-1-ynyl)benzo[*b*]thiophene (16l). Enediyne **16l** was synthesized in accordance with Method D from 3-iodobenzo[*b*]thiophene **14** (0.083 mmol, 27.0 mg) and (hex-5-en-1-ynyl)trimethylsilane (**15f**) (0.167 mmol, 26.0 mg) in DMF (2.00 mL) at 40 °C. Reaction time was 3 h. Purification of the crude product by column chromatography using pentane as the eluent gave 20.0 mg (85%) of **16l** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89−0.99 (m, 4H), 1.56−1.63 (m, 1H), 2.43−2.48 (m, 2H), 2.66 (t, J = 7.1 Hz, 2H), 5.11 (dq, ^3J = 10.2 Hz, $^4J = {}^2J$ = 1.7 Hz, 1H, CH^B), 5.20 (dq, ^3J = 17.1 Hz, $^4J = {}^2J$ = 1.7 Hz, 1H, CH^A), 5.97−6.07 (m, 1H, CH^X), 7.33−7.41 (m, 2H), 7.66−7.69 (m, 1H), 7.80−7.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.8, 9.2, 19.7, 33.1, 68.9 (C_q), 74.4 (C_q), 96.0 (C_q), 103.9 (C_q), 115.9, 121.9, 122.4 (C_q), 123.2, 124.8, 125.7, 126.2, 136.8, 137.9 (C_q), 139.0 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3074, 3009, 2978, 2921, 2845, 2215 (C≡C), 1642, 1434, 1372, 1346, 1319, 1228, 1180, 1060, 1075, 1053, 1029, 1016, 993, 950, 914, 810, 759, 730, 642. MS (EI, 70 eV), *m*/*z* (%): 276 (67, M^+), 235 (29), 234 (36), 221 (8), 202 (11), 195 (7), 163 (7), 153 (14), 43 (100). HRMS (*m*/*z*): calcd for $C_{19}H_{16}S$ $[M]^+$, 276.0967; found, 276.0974.

5-[3-(Pent-4-en-1-ynyl)benzo[*b*]thiophen-2-yl]pent-4-yn-1-ol (16m). Enediyne **16m** was synthesized in accordance with Method D from 3-iodobenzo[*b*]thiophene **10e** (1.00 mmol, 342 mg) and (pent-5-en-1-ynyl)trimethylsilane (**15g**)[52e] (2.00 mmol, 276 mg) in DMF (6.00 mL) at 40 °C. Reaction time was 3 h. Purification of the crude product by column chromatography using pentane as the eluent gave 258 mg (92%) of **16m** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.88−1.94 (m, 2H), 2.68 (t, J = 6.9 Hz, 2H), 3.36 (dt, ^3J = 5.1 Hz, $^4J = {}^2J$ = 1.7 Hz, 2H), 3.86 (t, ^3J = 6.1 Hz, 2H), 5.23 (dq, ^3J = 10.0 Hz, $^4J = {}^2J$ = 1.7 Hz, 1H, CH^B), 5.56 (dq, ^3J = 17.0 Hz, $^4J = {}^2J$ = 1.7 Hz, 1H, CH^A), 5.93−6.02 (m, 1H, CH^X), 7.35−7.42 (m, 2H), 7.69−7.71 (m, 1H), 7.83−7.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.6, 24.1, 31.0, 61.6, 74.4 (C_q), 76.3 (C_q), 93.0 (C_q), 99.8 (C_q), 116.4, 122.0, 122.4 (C_q), 123.2, 124.9, 125.8, 126.2 (C_q), 132.2, 138.0 (C_q), 138.9 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3356, 3060, 3012, 2949, 2880, 2218 (C≡C), 1640, 1458, 1432, 1416, 1363, 1319, 1282, 1217, 1060, 1052, 1017, 991, 916, 803, 759, 643. MS (EI, 70 eV), *m*/*z* (%): 280 (3, M^+), 235 (1), 234 (1), 221 (1), 43 (100). HRMS (*m*/*z*): calcd for $C_{18}H_{16}OS$ $[M]^+$, 280.0922; found, 280.0924.

6-[3-(3-Hydroxyprop-1-ynyl)benzo[*b*]thiophen-2-yl]hex-5-yn-1-ol (16n). Compound **16n** was synthesized in accordance with Method B from 3-iodobenzo[*b*]thiophene **10f** (0.674 mmol, 240 mg) dissolved in DMF (5.00 mL) and propargyl alcohol **15h** (2.36 mmol, 132 mg) at 50 °C. Reaction time was 3 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent gave 150 mg (78%) of **16n** as a white solid. mp 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.64−1.71 (m, 2H), 1.88−1.95 (m, 2H), 2.57 (t, J = 6.5 Hz, 2H), 2.81 (br s, 1H), 3.67 (t, J = 7.0 Hz, 2H), 4.02 (br s, 1H), 4.61 (s, 2H), 7.32−7.40 (m, 2H), 7.68 (dd, J = 6.6 Hz, J = 2.2 Hz, 1H), 7.81 (dd, J = 6.6 Hz, J = 2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.7, 24.2, 31.4, 51.3, 62.5, 74.5 (C_q), 78.4 (C_q), 93.9 (C_q), 100.9 (C_q), 121.6 (C_q), 122.0, 123.0, 125.0, 125.9, 127.6 (C_q), 137.8 (C_q), 138.5 (C_q). MS (EI, 70 eV), *m*/*z* (%): 284 (100, M^+), 237 (43), 210 (54), 209 (55), 208 (35), 197 (39), 184 (33). HRMS (*m*/*z*): calcd for $C_{17}H_{16}O_2S$ $[M]^+$, 284.0866; found, 284.0873. Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67; S, 11.28. Found: C, 71.76; H, 5.63; S, 11.15.

6-{3-[4-(*tert*-Butyldimethylsilyloxy)but-1-ynyl]benzo[*b*]thiophen-2-yl}hex-5-yn-1-ol (16o). Compound **16o** was synthesized in accordance with Method B from 3-iodobenzo[*b*]thiophene **10f** (3.34 mmol, 1.19 g,) dissolved in DMF (26.0 mL) and *O*-TBDMS-protected but-3-yn-1-ol **15i**[52f] (11.7 mmol, 2.15 g) at 50 °C. Reaction time was 3 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (9:1) as the eluent gave 1.12 g (81%) of **16o** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.11 (s, 6H), 0.93 (s, 9H), 1.58 (br s, 1H), 1.71−1.84 (m, 4H), 2.59 (t, J = 6.7 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 3.73 (t, J = 6.2 Hz, 2H), 3.90 (t, J = 7.1 Hz, 2H), 7.32−7.41 (m, 2H), 7.66−7.71 (m, 1H), 7.81−7.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3 (C_q), 19.8, 24.2, 24.7, 25.9, 31.8, 62.1, 62.4, 74.2 (C_q), 74.9 (C_q), 93.6 (C_q), 100.3 (C_q), 121.9, 122.2 (C_q), 123.2, 124.8, 125.8, 126.2 (C_q), 137.9 (C_q), 139.0 (C_q). MS (EI, 70 eV), *m*/*z* (%): 412 (69, M^+), 355 (88), 263 (64), 235 (64), 75 (100), 73 (54). HRMS (*m*/*z*): calcd for $C_{24}H_{32}O_2SSi$ $[M]^+$, 412.1887; found, 412.1895. Anal. Calcd for $C_{24}H_{32}O_2SSi$: C, 69.85; H, 7.82; S, 7.77. Found: C, 69.71; H, 7.82; S, 7.61.

8-{3-[4-(*tert*-Butyldimethylsilyloxy)but-1-ynyl]benzo[*b*]thiophen-2-yl}-2-methyloct-7-yn-2-ol (16p). Compound **16p** was synthesized in accordance with Method B from benzothiophene **10h** (0.151 mmol, 60.0 mg) dissolved in DMF (2.00 mL) and *O*-TBDMS-protected but-3-yn-1-ol **15i**[52f] (0.53 mmol, 97.2 mg) at 50 °C. Reaction time was 5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (9:1) as the eluent

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gave 55.0 mg (81%) of **16p** as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.11 (s, 6H), 0.92 (s, 9H), 1.24 (s, 6H), 1.31 (br s, 1H), 1.50−1.61 (m, 4H), 1.65−1.72 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 3.90 (t, J = 7.2 Hz, 2H), 7.34−7.41 (m, 2H), 7.67−7.69 (m, 2H), 7.82−7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3 (C_q), 20.0, 23.7, 24.3, 25.9, 28.9, 29.3, 43.3, 62.1, 70.9 (C_q), 73.9 (C_q), 74.8 (C_q), 93.5 (C_q), 100.5 (C_q), 121.88, 121.94 (C_q), 123.3, 124.8, 125.7, 126.2 (C_q), 137.9 (C_q), 139.0 (C_q). MS (EI, 70 eV), m/z (%): 454 (56, M^+), 397 (93), 305 (50), 249 (100), 75 (45), 73 (57), 69 (54). HRMS (m/z): calcd for $C_{27}H_{38}O_2SSi$ $[M]^+$, 454.2356; found, 454.2365. Anal. Calcd for $C_{27}H_{38}O_2SSi$: C, 71.31; H, 8.42; S, 7.05. Found: C, 71.03; H, 7.84; S, 6.00.

2-(Dec-1-ynyl)-1-methyl-3-(phenylethynyl)-1*H*-indole (17a). Enediyne **17a** was synthesized in accordance with Method A from indole **11a** (0.0763 mmol, 30.0 mg) and phenylacetylene **15j** (0.152 mmol, 16.0 mg, 17.0 μL) in DMF (2.00 mL) at 40 °C. Reaction time was overnight. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (90:1) as the eluent gave 21.0 mg (74%) of **17a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.88 (t, J = 6.7 Hz, 3H), 1.28−1.37 (m, 8H), 1.51−1.58 (m, 2H) overlaps with water signal, 1.67−1.75 (m, 2H), 2.60 (t, J = 7.0 Hz, 2H), 3.80 (s, 3H), 7.18−7.22 (m, 1H), 7.28−7.37 (m, 5H), 7.57−7.59 (m, 2H), 7.74−7.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 20.0, 22.6, 28.6, 28.9, 29.16, 29.20, 30.9, 31.9, 71.2 (C_q), 83.0 (C_q), 93.7 (C_q), 101.2 (C_q), 101.9 (C_q), 109.5, 120.1, 120.7 (C_q), 123.5, 124.4 (C_q), 126.6 (C_q), 127.4, 127.9 (C_q), 128.2, 131.4, 136.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3057, 2927, 2855, 2229 (C≡C), 2203 (C≡C), 1599, 1488, 1466, 1441, 1412, 1373, 1331, 1265, 1155, 1129, 1113, 1069, 1015, 742, 690, 661. MS (EI, 70 eV), m/z (%): 367 (100, M^+), 311 (3), 281 (6), 268 (14), 220 (17), 144 (7). HRMS (m/z): calcd for $C_{27}H_{29}N$ $[M]^+$, 367.2295; found, 367.2298.

2-(Dec-1-ynyl)-1-methyl-3-[(trimethylsilyl)ethynyl]-1*H*-indole (17b). Compound **17b** was synthesized in accordance with Method B from indole **11a** (0.0763 mmol, 30.0 mg) dissolved in DMF (1.00 mL) and trimethylsilylacetylene **15c** (0.23 mmol, 22.0 mg) at 60 °C. Reaction time was overnight. Purification of the crude product by column chromatography using hexane/ethyl acetate (50:1) as the eluent gave 20.0 mg (70%) of **17b** as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.30 (s, 9H), 0.87−0.92 (m, 3H), 1.27−1.40 (m, 8H), 1.48−1.55 (m, 2H), 1.65−1.72 (m, 2H), 2.57 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 7.14−7.21 (m, 1H), 7.24−7.29 (m, 2H), 7.65−7.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 0.4, 14.1, 19.9, 22.7, 28.6, 28.9, 29.1, 29.2, 30.9, 31.9, 71.0 (C_q), 98.3 (C_q), 98.4 (C_q), 101.2 (C_q), 101.9 (C_q), 109.4, 120.2, 120.7, 123.5, 127.3 (C_q), 128.1(C_q), 136.0(C_q). HRMS (ESI) (m/z): calcd for $C_{24}H_{34}NSi$ $[M + H]^+$, 364.2455; found, 364.2444.

Ethyl 2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-ynyl]-1-methyl-3-[(trimethylsilyl)ethynyl]-1*H*-indole-5-carboxylate (17c). Compound **17c** was synthesized in accordance with Method B from indole **11f** (4.08 mmol, 2.20 g) dissolved in DMF (40.0 mL) and trimethylsilylacetylene **15c** (14.27 mmol, 1.40 g) at 50 °C. Reaction time was 5 h. Purification of the crude product by column chromatography using hexane/ethyl acetate (50:1) as the eluent gave 1.66 g (80%) of **17c** as a white solid. mp 81−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.06 (s, 6H), 0.30 (s, 9H), 0.90 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H), 1.70−1.81 (m, 4H), 2.62 (t, J = 6.4 Hz, 2H), 3.69 (t, J = 5.5 Hz, 2H), 3.77 (s, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.23 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 8.7 Hz, J = 1.6 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 0.3, 14.4, 18.3 (C_q), 19.7, 25.1, 26.0, 31.1, 31.9, 60.7, 62.5, 70.8 (C_q), 97.5 (C_q), 99.4 (C_q), 101.9 (C_q), 103.5 (C_q), 109.1, 122.9, 123.1 (C_q), 124.8, 127.5 (C_q), 128.6 (C_q), 138.2 (C_q), 167.4. HRMS (FAB) (m/z): calcd for $C_{29}H_{44}NO_3Si_2$ $[M + H]^+$, 510.2854; found, 510.2876.

Ethyl 2-(6-Hydroxyhex-1-ynyl)-1-methyl-3-[(trimethylsilyl)-ethynyl]-1*H*-indole-5-carboxylate (17d). Compound **17d** was synthesized in accordance with Method B from indole **11e** (0.541 mmol, 230 mg) dissolved in DMF (5.00 mL) and trimethylsilylacetylene **15c** (1.89 mmol, 186 mg) at 40 °C. Reaction time was overnight. Purification of the crude product by column chromatography using hexane/ethyl acetate (10:1 → 2:1) as the eluent gave 130 mg (61%) of **17d** as a yellow solid. mp 77−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.30 (s, 9H), 1.42 (t, J = 7.1 Hz, 3H), 1.63 (s, 1H) overlaps with water signal, 1.75−1.83 (m, 4H), 2.64 (t, J = 6.3 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 3.77 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.23 (d, J = 8.6 Hz, 1H), 7.95 (dd, J = 8.6 Hz, J = 1.4 Hz, 1H), 8.39 (d, J = 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.3, 14.4, 19.7, 24.8, 30.9, 31.8, 60.7, 62.3, 71.0 (C_q), 97.5 (C_q), 99.5 (C_q), 101.6 (C_q), 103.6 (C_q), 109.1, 122.9, 123.2 (C_q), 124.9, 127.5 (C_q), 128.5 (C_q), 138.2 (C_q), 168.4. HRMS (FAB) (m/z): calcd for $C_{23}H_{30}NO_3Si$ $[M + H]^+$, 396.1989; found, 396.1992.

3-{2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-ynyl]-1-methyl-1*H*-indol-3-yl}prop-2-yn-1-ol (17e). Compound **17e** was obtained using standard Method A from indole **11d** (0.449 mmol, 210 mg) dissolved in DMF (4.00 mL) and propargyl alcohol **15h** (2.24 mmol, 126 mg, 126 μL) at 50 °C. Reaction time was 6.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (50:1 → 10:1) as the eluent gave 71.0 g (40%) of **17e** as a beige solid. mp 77−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.08 (s, 6H), 0.91 (s, 9H), 1.71−1.75 (m, 2H), 1.81−1.85 (m, 2H), 2.27 (br s, 1H), 2.62 (t, J = 6.7 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 3.77 (s, 3H), 4.60 (d, J = 5.6 Hz, 2H), 7.15−7.19(m, 1H), 7.23−7.30 (m, 2H), 7.65−7.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.4, 19.7, 24.9, 26.0, 30.9, 31.8, 52.0, 62.9, 71.4 (C_q), 78.9 (C_q), 91.7 (C_q), 100.6 (C_q), 101.2 (C_q), 109.5, 120.0, 120.7, 123.5, 126.8 (C_q), 127.9 (C_q), 136.0 (C_q). HRMS (m/z): calcd for $C_{24}H_{33}NO_2Si$ $[M]^+$, 395.2275; found, 395.2283.

Methyl 2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-ynyl]-3-(6-hydroxyhex-1-ynyl)-1-methyl-1*H*-indole-5-carboxylate (17f). Compound **17f** was synthesized in accordance with Method B from indole **11g** (2.47 mmol, 1.30 g) dissolved in DMF (24.0 mL) and hex-5-yn-1-ol **15k** (8.66 mmol, 850 mg) at 50 °C. Reaction time was 3.5 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (8:1 → 5:1) as the eluent gave 933 mg (86%) of **17f** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.06 (s, 6H), 0.90 (s, 9H), 1.66 (br s, 2H), overlaps with water signal, 1.70−1.87 (m, 8H), 2.58−2.62 (m, 4H), 3.67−3.70 (m, 2H), 3.72−3.78 (m, 5H), 3.93 (s, 3H), 7.23 (d, J = 8.7 Hz, 1H), 7.94 (dd, J = 8.7 Hz, J = 1.5 Hz, 1H), 8.38 (d, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): −5.3, 18.3 (C_q), 19.7, 25.1, 25.2, 25.9, 31.0, 31.9, 32.0, 51.9, 62.5, 62.6, 71.0 (C_q), 72.9 (C_q), 94.9 (C_q), 101.1 (C_q), 104.0 (C_q), 109.0, 122.3 (C_q), 122.9, 124.6, 127.1 (C_q), 127.7 (C_q), 138.3 (C_q), 167.9, two signals overlap with others. HRMS (FAB) (m/z): calcd for $C_{29}H_{42}NO_4Si$ $[M + H]^+$, 496.2878; found, 496.2881.

3-(Oct-1-ynyl)-2-(phenylethynyl)benzofuran (18a). Enediyne **18a** was synthesized in accordance with Method A from 3-iodobenzofuran **12a** (0.058 mmol, 20.0 mg) and oct-1-yne **15a** (0.145 mmol, 16.0 mg, 21.0 μL) in DMF (3.00 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using pentane as the eluent gave 8.90 mg (47%) of **18a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.90 (t, J = 7.0 Hz, 3H), 1.32−1.36 (m, 4H), 1.51−1.58 (m, 2H) overlaps with water signal, 1.66−1.73 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 7.28−7.31 (m, 1H), 7.35−7.45 (m, 5H), 7.60−7.64 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 19.9, 22.6, 28.6, 28.7, 31.4, 70.2 (C_q), 79.2 (C_q), 98.6 (C_q), 99.2 (C_q), 109.6 (C_q), 111.3, 120.5, 121.9 (C_q), 123.5, 126.2, 128.3 (C_q), 128.4, 129.2, 131.8, 140.7 (C_q), 154.1 (C_q). IR (KBr, thin film) ν_{max} (cm^{-1}): 3062, 2955, 2930, 2858, 2231 (C≡C), 2207 (C≡C), 1599, 1489, 1450, 1385, 1342, 1301, 1263, 1217, 1150, 1104, 1009, 862, 748, 688. MS (EI, 70 eV), m/z (%): 326 (100, M^+), 297 (9), 283 (16), 269 (21), 268 (31), 255 (63), 239 (20), 226 (64), 216 (21), 184 (15), 171 (12). HRMS (m/z): calcd for $C_{24}H_{22}O$ $[M]^+$, 326.1671; found, 326.1669. Anal. Calcd for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.64; H, 6.94.

3-[(Trimethylsilyl)ethynyl]-2-(phenylethynyl)benzofuran (18b). Enediyne **18b** was synthesized in accordance with Method A from 3-iodobenzofuran **12a** (0.154 mmol, 53.0 mg) and trimethylsilylacetylene **15c** (0.308 mmol, 30.2 mg, 45 μL) in DMF (1.50 mL) at 50 °C. Reaction time was overnight. Purification of the crude product by column chromatography using pentane as the eluent gave 33.0 mg (69%) of **18b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.34 (s, 9H), 7.30−7.47 (m, 6H), 7.61−7.67 (m, 3H). ^{13}C NMR (100 MHz,

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$CDCl_3$, δ): 0.0, 79.0 (C_q), 94.4 (C_q), 99.4 (C_q), 103.5 (C_q), 108.9 (C_q), 111.3, 120.7, 121.7 (C_q), 123.7, 126.4, 127.8 (C_q), 128.5, 129.4, 131.8, 142.1 (C_q), 154.0 (C_q). IR (neat) ν_{max} (cm^{-1}): 3065, 2960, 2210 (C≡C), 2161 (C≡C), 2142, 1599, 1488, 1449, 1377, 1342, 1302, 1250, 1216, 1147, 1125, 1099, 1009, 844 (C−Si), 748, 688, 637. MS (FAB), m/z (%): 314 (100, M^+), 299 (16). HRMS (FAB) (m/z): calcd for $C_{21}H_{18}OSi$ $[M]^+$, 314.1121; found, 314.1131.

Modification of Benzothiophene Fused Enediynes. 5-[3-(But-3-en-1-yn-1-yl)benzo[*b*]thiophen-2-yl]pent-4-yn-1-ol (16q). To a degassed stirred mixture of $Pd(PPh_3)_4$ (0.025 mmol, 29.0 mg), K_2CO_3 (3.99 mmol, 552 mg), and CuI (0.075 mmol, 14.3 mg) in DMF (5.00 mL) in a sealed vial was added a 1.0 M solution of vinyl bromide in THF (2.50 mmol, 2.50 mL) in one portion at 0 °C. Then, MeOH (3.99 mmol, 128 mg, 160 μL) followed by TMS protected enediyne **16e** (0.499 mmol, 156 mg) in DMF (2.50 mL) was added at the same temperature. The reaction mixture obtained was stirred at 0 °C for 20 min; then, it was allowed to warm to room temperature, stirred for 24 h, poured into a saturated solution of NH_4Cl, and extracted with ethyl acetate. The combined organic layers were washed with saturated solution of NH_4Cl and two times with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (3:1) as the eluent to give 120 mg (90%) of **16q** as a dark yellow oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.61 (br s, 1H), 1.89−1.96 (m, 2H), 2.69 (t, J = 6.9 Hz, 2H), 3.88 (t, J = 6.1 Hz, 2H), 5.63 (dd, ^3J = 11.2 Hz, ^2J = 2.0 Hz, 1H, CH^B), 5.85 (dd, ^3J = 17.5 Hz, ^2J = 2.0 Hz, 1H, CH^A), 6.16 (dd, ^3J = 17.5 Hz, ^3J = 11.2 Hz, 1H, CH^X), 7.37−7.44 (m, 2H), 7.70−7.72 (m, 1H), 7.84−7.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.7, 31.0, 61.6, 74.3 (C_q), 83.2 (C_q), 94.3 (C_q), 100.6 (C_q), 117.2, 121.8 (C_q), 122.0, 123.2, 125.1, 126.0, 127.0 (C_q), 127.5, 138.0 (C_q), 138.6 (C_q). IR (neat) ν_{max} (cm^{-1}): 3291, 3055, 2926, 2875, 2218 (C≡C), 2182 (C≡C), 1651, 1457, 1431, 1352, 1318, 1216, 1159, 1136, 1034, 967, 921, 755, 728, 641. MS (EI, 70 eV), m/z (%): 266 (79, M^+), 235 (6), 234 (12), 221 (42), 202 (17), 171 (20), 84 (100), 69 (27), 57 (73). HRMS (m/z): calcd for $C_{17}H_{14}OS$ $[M]^+$, 266.0760; found, 266.0768.

General Procedure for the Oxidation of Enediyne Alcohols 16q,m with Dess−Martin Periodinane. To a solution of the enediyne alcohol (1.00 equiv) in dry CH_2Cl_2 was added a 15 wt % solution of Dess−Martin periodinane (DMP) in CH_2Cl_2 (1.20 equiv) dropwise at 10 °C. The reaction mixture was stirred at 10 °C for 15 min and then at room temperature until the reaction completed (TLC monitoring). Then, a saturated solution of $Na_2S_2O_3$ was added, and the reaction mixture was stirred until the formation of two clear layers. The layers were separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with a 5% solution of $NaHCO_3$ (until neutral reaction of washes) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel.

5-[3-(But-3-en-1-ynyl)benzo[*b*]thiophen-2-yl]pent-4-ynal (19a). Aldehyde **19a** was synthesized from enediyne alcohol **16q** (0.725 mmol, 193 mg) and a 15 wt % solution of DMP in DCM (0.870 mmol, 369 mg, 2.46 mL). Reaction time was 1 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (10:1) as the eluent gave 130 mg (68%) of **19a** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 2.81−2.91 (m, 4H), 5.64 (dd, ^3J = 11.2 Hz, ^2J = 2.0 Hz, 1H, CH^B), 5.85 (dd, ^3J = 17.5 Hz, ^2J = 2.0 Hz, 1H, CH^A), 6.15 (dd, ^3J = 17.5 Hz, ^3J = 11.2 Hz, 1H, CH^X), 7.37−7.44 (m, 2H), 7.70−7.72 (m, 1H), 7.84−7.86 (m, 1H), 9.89 (t, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.3, 42.3, 74.6 (C_q), 83.0 (C_q), 94.4 (C_q), 98.8 (C_q), 117.1, 122.0, 122.2 (C_q), 123.3, 125.1, 126.1, 126.4 (C_q), 127.6, 138.0 (C_q), 138.5 (C_q), 199.9. IR (neat) ν_{max} (cm^{-1}): 3054, 2920, 2832, 2734, 2214 (C≡C), 2187 (C≡C), 1718, 1431, 1352, 1318, 1217, 1159, 1130, 1052, 1015, 968, 921, 854, 755, 727, 641. MS (EI, 70 eV), m/z (%): 264 (59, M^+), 235 (19), 234 (30), 221 (50), 208 (41), 189 (10), 58 (26), 43 (100). HRMS (m/z): calcd for $C_{17}H_{12}OS$ $[M]^+$, 264.0603; found, 264.0606.

5-[3-(Pent-4-en-1-ynyl)benzo[*b*]thiophen-2-yl]pent-4-ynal (19b). Aldehyde **19b** was synthesized from enediyne alcohol **16m** (0.806 mmol, 226 g) using a 15 wt % solution of DMP in DCM (0.967 mmol, 411 mg, 2.74 mL). Reaction time was 1 h. Purification of the crude product by column chromatography using cyclohexane/ethyl acetate (10:1) as the eluent gave 171 mg (76%) of **19b** as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 2.80−2.89 (m, 4H), 3.36 (dt, ^3J = 5.1 Hz, ^4J = ^2J = 1.8 Hz, 2H, CH_2), 5.23 (dq, ^3J = 10.0 Hz, ^4J = ^2J = 1.8 Hz, 1H, CH^B), 5.56 (dq, ^3J = 17.0 Hz, ^4J = ^2J = 1.8 Hz, 1H, CH^A), 5.93−6.02 (m, 1H, CH^X), 7.36−7.43 (m, 2H), 7.68−7.72 (m, 1H), 7.82−7.87 (m, 1H), 9.87 (t, J = 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.3, 24.0, 42.3, 74.7 (C_q), 76.2 (C_q), 93.2 (C_q), 98.0 (C_q), 116.4, 122.0, 122.8 (C_q), 123.3, 125.0, 125.7 (C_q), 126.0, 132.2, 138.1 (C_q), 138.8 (C_q), 200.0. IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 3013, 2913, 2827, 2727, 2221 (C≡C), 1726, 1641, 1458, 1433, 1414, 1362, 1321, 1283, 1219, 1161, 1117, 1054, 1016, 990, 916, 841, 756, 731. MS (EI, 70 eV), m/z (%): 278 (78, M^+), 259 (14), 235 (33), 234 (31), 221.0 (52), 153 (19), 57 (58), 43 (100). HRMS (m/z): calcd for $C_{18}H_{14}OS$ $[M]^+$, 278.0760; found, 278.0767.

6-[3-(3-Oxoprop-1-ynyl)benzo[*b*]thiophen-2-yl]hex-5-ynal (20). A 15 wt % solution of DMP in DCM (1.28 mmol, 540 mg, 3.62 mL) was added dropwise to an Ar flushed solution of benzothiophene **16n** (0.492 mmol, 140 mg) in anhydrous DCM (11.0 mL) at room temperature. The reaction mixture was stirred for 45 min. Work up procedure as for monoaldehydes **19a,b** gave the crude product, which was purified by column chromatography using hexane/ethyl acetate (5:1) as the eluent to give 96.6 mg (70%) of **20** as a white solid. mp 48−51 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.98−2.05 (m, 2H), 2.67 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H), 7.42−7.49 (m, 2H), 7.74−7.76 (m, 1H), 7.87−7.89 (m, 1H), 9.54 (s, 1H), 9.88 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.5, 20.5, 42.5, 74.1 (C_q), 88.2 (C_q), 94.3 (C_q), 103.3 (C_q), 118.2 (C_q), 122.2, 123.0, 125.8, 126.6, 134.2 (C_q), 137.8 (C_q), 138.0 (C_q), 176.3, 201.7. HRMS (FAB) (m/z): calcd for $C_{17}H_{13}O_2S$ $[M + H]^+$, 281.0631; found, 281.0639.

Methyl 2,3-Bis(6-hydroxyhex-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (17g). To Ar flushed stirred solution of monoprotected diol **17f** (1.47 mmol, 730 mg) in THF (15.0 mL) was added a 1 M solution of TBAF in THF (4.41 mmol, 4.41 mL) at −20 °C. The resulting mixture was stirred at 0 °C for 8 h. Then, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (3.5:1.5) as the eluent to give 500 mg (89%) of **17g** as a white solid. mp 58−61 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.71−1.86 (m, 8H), 2.08 (br s, 2H), 2.57−2.63 (m, 4H), 3.93 (s, 3H), 3.70−3.74 (m, 4H), 3.75 (s, 3H), 7.22 (d, J = 8.7 Hz, 1H), 7.93 (dd, J = 8.7 Hz, J = 1.5 Hz, 1H), 8.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.69, 19.70, 24.8, 25.2, 31.0, 31.8, 31.9, 51.9, 62.2, 62.4, 71.2 (C_q), 72.9 (C_q), 95.0 (C_q), 100.8 (C_q), 104.2 (C_q), 109.1, 122.3 (C_q), 122.9, 124.7, 127.1 (C_q), 127.6 (C_q), 138.3 (C_q), 167.9. MS (EI, 70 eV), m/z (%): 381 (100, M^+), 340 (43), 324 (29), 322 (34), 123 (38), 105 (31), 104 (93), 91 (70), 43 (50). HRMS (m/z): calcd for $C_{23}H_{27}NO_4$ $[M]^+$, 381.1935; found, 381.1938.

Methyl 2,3-Bis(6-iodohex-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (21). To a degassed stirred solution of indole **17g** (0.49 mmol, 185 mg) in anhydrous THF (5.0 mL) were added PPh_3 (1.07 mmol, 280 mg) and imidazole (1.47 mmol, 100 mg). After a homogeneous solution had formed, the reaction mixture was cooled to −20 °C, and I_2 (1.18 mmol, 300 mg) was added. The mixture obtained was stirred at −20 °C for 1 h, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature, diluted with a saturated solution of $NaHCO_3$, and stirred at 0 °C. The precipitate was filtered off and washed three times with Et_2O. The ether layer was separated, and the water layer was extracted with Et_2O. Combined organic layers were washed with $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (15:1 → 5:1) as the eluent to give 276 mg (94%) of **21** as a beige solid. mp 63−65 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.76−1.85 (m, 4H), 2.04−2.13 (m, 4H), 2.59−2.66 (m, 4H), 3.26−3.31 (m, 4H), 3.77 (s, 3H), 3.94 (s, 3H), 7.24

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(d, J = 8.7 Hz, 1H), 7.95 (dd, J = 8.7 Hz, J = 1.3 Hz, 1H), 8.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 5.9, 6.4, 18.9, 29.2, 29.7, 31.1, 32.4, 32.6, 51.9, 71.5 (C_q), 73.2 (C_q), 94.3 (C_q), 100.1 (C_q), 104.1 (C_q), 109.1, 122.5 (C_q), 122.9, 124.8, 126.9 (C_q), 127.6 (C_q), 138.3 (C_q), 167.8, one signal overlaps with others. MS (EI, 70 eV), m/z (%): 601 (100, M^+), 475 (26), 474 (62). HRMS (m/z): calcd for $C_{23}H_{25}I_2NO_2$ $[M]^+$, 600.9969; found, 600.9978.

Methyl 2,3-Di(hex-5-en-1-yn-1-yl)-1-methyl-1*H*-indole-5-carboxylate (22). To a degassed stirred solution of indole **21** (0.731 mmol, 440 mg) in anhydrous DMSO (73.0 mL) was added TBAF hydrate (4.01 mmol, 1.05 g) under Ar. The reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (9:1) as the eluent to give 210 mg (83%) of **22** as a light yellow solid. mp 58−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.41−2.47 (m, 4H), 2.62−2.69 (m, 4H), 3.75 (s, 3H), 3.93 (s, 3H), 5.09−5.11 (m, 2H), 5.15−5.20 (m, 2H), 5.93−6.04 (m, 2H), 7.22 (d, J = 8.7 Hz, 1H), 7.94 (dd, J = 8.7 Hz, J = 1.4 Hz, 1H), 8.39 (d, J = 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.8, 19.9, 31.0, 32.7, 33.3, 51.9, 71.4 (C_q), 72.9 (C_q), 94.5 (C_q), 100.3 (C_q), 104.1 (C_q), 109.0, 115.6, 116.1, 122.4 (C_q), 123.0, 124.7, 127.0 (C_q), 127.7 (C_q), 136.5, 137.1, 138.3, 167.9. MS (EI, 70 eV), m/z (%): 345 (98, M^+), 304 (100), 244 (30), 204 (25), 83 (58). HRMS (m/z): calcd for $C_{23}H_{23}NO_2$ $[M]^+$, 345.1723; found, 345.1725.

Methyl (10*E*)-5-Methyl-6,7,14,15-tetradehydro-8,9,12,13-tetrahydro-5*H*-cyclododeca[*b*]indole-2-carboxylate (23a). To a solution of diolefin **22** (0.57 mmol, 200 mg) in dry CH_2Cl_2 (180 mL) thoroughly flushed with argon was added 1,4-benzoquinone (0.12 mmol, 13.0 mg) followed by Grubbs II catalyst (0.04 mmol, 34.0 mg). Then, the reaction mixture was refluxed for 1.5 h. After cooling, ethylvinyl ether (1.8 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography using cyclohexane/ethyl acetate (20:1) as the eluent to give 80.0 mg (44%) of mixture of (*E*)-**23a** and (*Z*)-**23b** isomers (*E*/*Z* = 3:1) as colorless crystals and 61.0 mg (34%) of *E*-isomer **23a** as a white solid. Total ratio of the mixture **23a**/**23b** was calculated as 6:1, and the total yield was calculated as 78%. mp 195−197 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.34−2.42 (m, 4H), 2.67−2.72 (m, 4H), 3.76 (s, 3H), 3.92 (s, 3H), 5.49−5.61 (m, 2H), 7.22 (d, J = 8.7 Hz, 1H), 7.93 (dd, J = 8.7 Hz, J = 1.6 Hz, 1H), 8.38 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.9, 20.1, 31.0, 31.37, 31.41, 52.0, 73.2 (C_q), 75.6 (C_q), 94.7 (C_q), 101.5 (C_q), 106.1 (C_q), 109.3, 122.6 (C_q), 122.9, 124.7, 126.7 (C_q), 129.5 (C_q), 130.6, 132.0, 138.2 (C_q), 168.0. MS (EI, 70 eV), m/z (%): 318 (21), 317 (100, M^+), 263 (38), 262 (18). HRMS (m/z): calcd for $C_{21}H_{19}NO_2$ $[M]^+$, 317.1410; found, 317.1415. Crystal Data: single crystals of $C_{21}H_{19}NO_2$ compound **23a** were prepared by vapor exchange method from ethyl acetate/hexane. A suitable crystal was selected. The crystal was kept at 100.0 K during data collection. $C_{21}H_{19}NO_2$, M = 317.37, monoclinic, a = 16.6232(2) Å, b = 8.48700(10) Å, c = 24.2138(2) Å, β = 109.5810(10), V = 3218.55(6) Å^3, T = 100.0, space group $P2_1/c$ (no. 14), Z = 8, μ(Cu Kα) = 0.666, 70 891 reflections measured, 6760 unique (R_{int} = 0.0254), which were used in all calculations. The final wR_2 was 0.1303 (all data), and R_1 was 0.0470 (>2σ(I)). Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1019296. Copies of the data can be obtained free of charge on application to The Centre for X-ray Diffraction Studies of the Research Park of Saint Petersburg State University; e-mail: xrd@spbu.ru.

2-(Dec-1-ynyl)-3-[(4-methoxyphenyl)ethynyl]benzo[*b*]thiophene (16r). Compound **16r** was synthesized from 2-(deca-1,3-diynyl)-3-iodobenzo[*b*]thiophene (0.06 mmol, 24.0 mg) and *p*-methoxyphenylacetylene (0.120 mmol, 15.8 mg) as described earlier.[25a] Yield, 14.4 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.87 (t, J = 6.7 Hz, 3H), 1.25−1.30 (m, 8H), 1.51−1.56 (m, 2H), 1.66−1.68 (m, 2H), 2.56 (t, J = 7.0 Hz, 2H), 3.85 (s, 3H), 6.89−6.93 (m, 2H), 7.39−7.44 (m, 2H), 7.55−7.57 (m, 2H), 7.71−7.73 (m, 1H), 7.91−7.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 20.1, 22.7, 28.5, 28.9, 29.2, 31.8, 55.3, 73.9 (C_q), 81.5 (C_q), 95.5 (C_q), 101.6 (C_q), 114.0, 115.4 (C_q), 122.0, 123.2, 124.9, 125.8, 126.6 (C_q), 133.3, 138.0 (C_q), 138.8 (C_q), 159.8 (C_q), two signals overlap with others. IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 3002, 2927, 2854, 2219 (C≡C), 2202 (C≡C), 1605, 1569, 1520, 1500, 1459,1434, 1377, 1291, 1251, 1202, 1171, 1106, 1036, 831, 758, 730. MS (EI, 70 eV), m/z (%): 400 (100, M^+), 271 (11), 258 (19). HRMS (m/z): calcd for $C_{27}H_{28}OS$ $[M]^+$, 400.1855; found, 400.1858.

2-(Dec-1-ynyl)-3-(phenylethynyl)benzo[*b*]thiophene (16s). Compound **16s** was synthesized from 2-(deca-1,3-diynyl)-1-iodobenzo[*b*]thiophene (0.120 mmol, 48.0 mg) and phenylacetylene (0.240 mmol, 24.5 mg) as described earlier.[25a] Yield, 28.9 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.87 (t, J = 6.6 Hz, 3H), 1.26−1.35 (m, 8H), 1.48−1.55 (m, 2H), 1.65−1.72 (m, 2H), 2.57 (t, J = 7.0 Hz, 2H), 7.37−7.46 (m, 5H), 7.61−7.63 (m, 2H), 7.72−7.74 (m, 1H), 7.92−7.94 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1, 20.1, 22.6, 28.5, 28.9, 29.2, 31.8, 73.8 (C_q), 82.8 (C_q), 95.5 (C_q), 101.9 (C_q), 121.6 (C_q), 122.0, 123.20, 123.24 (C_q), 125.0, 125.9, 127.3 (C_q), 128.35, 128.42, 131.8, 138.0 (C_q), 138.7 (C_q), one signal overlaps with others. IR (KBr, thin film) ν_{max} (cm^{-1}): 3060, 2927, 2855, 2222 (C≡C), 1598, 1485, 1459, 1434, 1376, 1320, 1202, 1160, 1069, 1016, 933, 755, 730, 689. MS (EI, 70 eV), m/z (%): 370 (64, M^+), 284 (15) 271 (31), 204 (68), 202 (100). HRMS (m/z): calcd for $C_{26}H_{26}S$ $[M]^+$, 370.1750; found, 370.1758.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra for all compounds synthesized, ^{1}H and ^{13}C NMR spectra for all new compounds, description of structure determination for compounds **13a**,**b** by 2D NMR, homocoupled ^{1}H NMR spectrum for the macrocycle **23a**, GC−MS chromatogram of the mixture of **12a** and **13a**, DSC thermograms for compounds **16c**,**j**,**r**−**u**, **17a**, **18a**,**b**, and **23a**, details of DFT calculations, correlation between t_{BC} and $\Delta E^{\ddagger}$, and details of X-ray studies for the compound **23a**. 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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DEDICATION

Dedicated to Professor Boris A. Ivin.

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