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Synthesis of (*Z*) isomers of benzoheterocyclic derivatives of combretastatin A-4: a comparative study of several methods

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ABSTRACT

Several methods for the preparation of (*Z*) trimethoxystyrene derivatives **1** were investigated. After finding that the Wittig reaction led to unsatisfactory results, three different strategies were considered: a Suzuki coupling with a stereodefined monobromoalkene, a combination of hydrosilylation/vinylsilane hydrolysis and a palladium-catalyzed semi-hydrogenation step, using DMF/KOH as the hydrogen source. Our studies led us to prepare a series of diarylacetylene derivatives *via* a Sonogashira coupling reaction, and also to find out a copper-free basic cyclization leading to benzo[*b*]thiophenes. The final choice for the synthesis method of **1** strongly depends on the target compound but the semi-hydrogenation, which avoids the use of a toxic tin reducing agent, should be generally preferred.

1. Introduction

The design of new active molecules has always been the driving force for the development of efficient synthetic methodologies. Indeed, the preparation of original structures and their analogues to study the Structure–Activity Relationships of a future drug has prompted organic chemists to imagine new and elegant strategies.

For a research project directed towards the elaboration of new Microtubule Binding Agents,[1] we were interested in the preparation of original combretastatin A-4 (CA-4) derivatives **1**, by replacement of the B ring with various heterocycles, attached to the 2-position (Fig. 1).

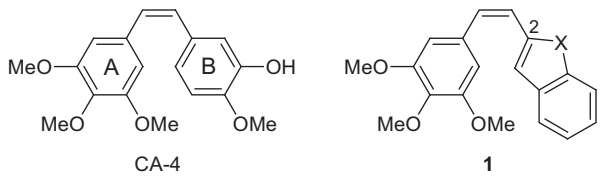

Fig. 1. Combretastatin A-4 and benzoheterocycles derivatives **1**.

Behind the numerous analogues of this natural product,[2] first isolated by Pettit and co-workers from the bark of the south-african bush willow tree *Combretum caffrum*,[3,4] 3,4,5-trimethoxystyrene derivatives appears to be of interest.[5] However, to maintain an efficient activity against the inhibition of the dynamic assembly/disassembly of the microtubules,[6] it is essential to have a *cis* configuration of the alkene.[7]

As a contributor to the design of new 3,4,5-trimethoxystyrene derivatives active against tubulin,[8] our objective was to have in hand an efficient method for the selective preparation of our *cis* derivatives **1**.

Several strategies were possible (Fig. 2), based on literature precedents for the preparation of (*Z*) alkenes and especially for the synthesis of combretastatin A-4 itself.

The simplest way could be a Wittig reaction[9] between heteroaromatic carboxaldehydes **2** and the appropriate phosphonium salt **3**. The *cis* double bond could also be obtained after a Suzuki coupling[10] between heterocyclic 2-boronic acids **4** and the stereodefined monobromoalkene **5** (Fig. 2). Another possibility lies in the stereocontrolled reduction of the triple bond in **6** into the *cis* alkene, either by using hydrolysis of a vinyl derivative precursor or a semi-hydrogenation step. The most direct access to these structures **6** could be a Sonogashira coupling reaction[11] of halogenated heterocycles **7** with the known acetylenic derivative **8** (Fig. 2).

To prepare the (*Z*) stereoisomers of compounds **1** for subsequent biological evaluations, we have investigated these strategies and we wish now to report in this paper our different approaches.

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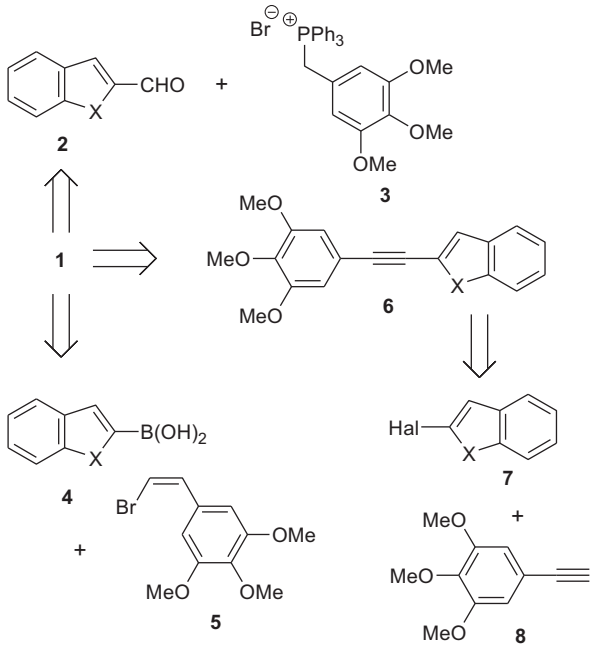
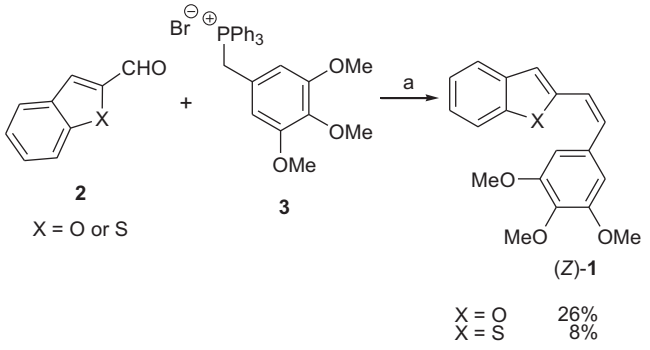


Fig. 2. Strategies for the preparation of *cis* compounds **1**.

2. Results and discussion

2.1. Wittig reaction

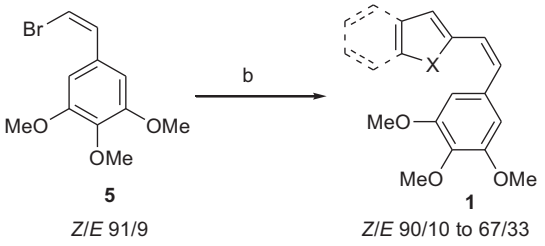
Our first attempts used a Wittig reaction between benzofuran- and benzo[*b*]thiophene-2-carboxaldehydes **2** and 3,4,5-trimethoxybenzylphosphonium salt **3**. But this led to unsatisfactory results, both in term of stereoselectivity (*Z*/*E* ratio 49/51 for **1a** and 45/55 for **1b**, determined by ^{1}H NMR on the crude product) and isolated yields for the (*Z*) stereoisomers (Scheme 1).[12]



Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 1 h then rt, 18 h; global yields 65% for **1a** (X=O) and 77% for **1b** (X=S). Yields indicated above are for isolated stereopure (*Z*)-**1**.

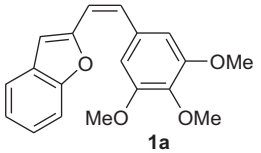
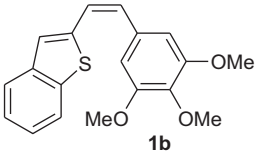
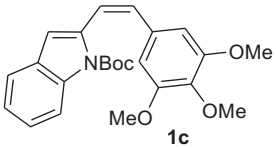
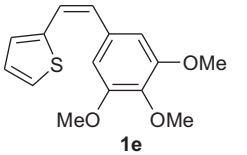
2.2. Suzuki coupling

Several coupling reactions are described for the preparation of CA-4, such as Kumada–Corriu,[13] Negishi[14] or Suzuki.[15,16] During the preparation of *N*-methylindole analogues of the B ring of CA-4 using a Negishi coupling, Mass and co-workers first made the selective reduction of a dibromovinyl substrate, using tributyltin hydride as the reducing agent and a catalytic amount of $Pd(PPh_3)_4$.[17] In our hands, this palladium-catalyzed monodehalogenation afforded the monobromo derivative **5** with a fairly good 91/9 stereopurity, in the favour of the (*Z*) isomer. This compound was used for subsequent Suzuki couplings with oxygen, sulfur and nitrogen-containing boronic reagents. After the coupling reaction, under classical conditions (Scheme 2),[16] the crude product was analyzed by ^{1}H NMR and we were surprised to see that the *Z*/*E* ratio significantly decreased in most of the cases, except when benzo[*b*]thiophene-2-boronic acid was used (Table 1, entry 2). With benzofuran- and thiophene boronic acids, this ratio dropped to 77/23 and 67/33, respectively, and the (*Z*) isomer of **1a** and **1e** were isolated with 57 and 38% yields (Table 1, entries 1 and 4).[18]



Scheme 2. Reagents and conditions: (b) $HetArB(OH)_2$ or $HetArBF_3K$ 1.15 equiv, $Pd(PPh_3)_4$ 5 mol %, Na_2CO_3 1.0 equiv, DME/water, 90 °C, 20 h.

Table 1
Suzuki coupling reaction to derivatives **1**

Entry	(Benzo) heterocycle	Product	*Z*/*E* ratio	Yield[d] % (*Z*)
1	Benzofuran[a]	 **1a**	77/23[c]	57
2	Benzo[*b*] thiophene[a]	 **1b**	90/10[c]	57
3	*N*-Boc indole[b]	 **1c**	nd	47
4	Thiophene[a]	 **1e**	67/33[c]	38[e]

nd: not determined.
[a] 2-Boronic acid was used.
[b] 2-Potassium trifluoroborate was used.
[c] Determined by ^{1}H NMR on the crude product.
[d] Yield of stereopure (*Z*) isomer of compound **1**.
[e] Beside isolation of pure (*Z*), a *Z*/*E* mixture (36%) was also obtained after chromatographic purification.

When the reaction was carried out using *N*-Boc indole-2-boronic acid, no traces of the desired *N*-Boc protected (*Z*)-**1c** was detected in the reaction mixture: after purification, only indole, 1,4-bis(3,4,5-trimethoxyphenyl)buta-1,3-diene and deprotected (*E*) indole-3,4,5-trimethoxy styrene **1d** were obtained.[19] The use of the

potassium salt of trifluoroborate[20] drastically improved the reaction outcome as stereopure (*Z*)-**1c** was obtained with a 47% yield (Table 1, entry 3).

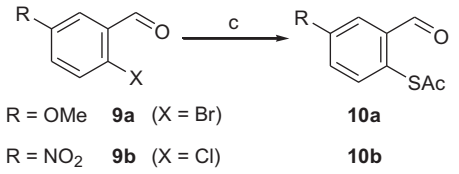
2.3. Reduction of diarylacetylene derivatives

Regarding the moderate yields and selectivity obtained using the Suzuki coupling strategy, we believed at this stage that a significant improvement could be achieved using another approach: the reduction of diarylacetylenes **6**.

*2.3.1. Synthesis of the diarylacetylene derivatives **6**.* One of the most efficient ways for the preparation of diacetylenes derivatives is the Sonogashira coupling. This reaction, though discovered almost 40 years ago, remains a very efficient tool for the creation of C–C bonds between vinyl/aryl halides or triflates and acetylenic substrates.[21]

To synthesize the diarylacetylene derivatives **6**,[22,23] different 2-halogeno (benzo)heterocycles **7** were prepared and coupled with 3,4,5-trimethoxyphenylacetylene **8**, obtained in two steps starting from 3,4,5-trimethoxybenzaldehyde.[24] The 2-iodo derivatives **7** (except commercially available 2-iodo-thiophene) were prepared using a deprotonation/iodination strategy, either by using the Zn/Li mixed aggregates developed by Mongin[25] and co-workers (for benzofuran and benzo[*b*]thiophene), or taking advantage of the *ortho*-directing properties of the sulfonyl group during the deprotonation of the indole core.[26] 2-Iodo-*N*-phenylsulfonyl-indole was also the precursor of 2-iodo-indole after its fluoride-mediated deprotection.[27]

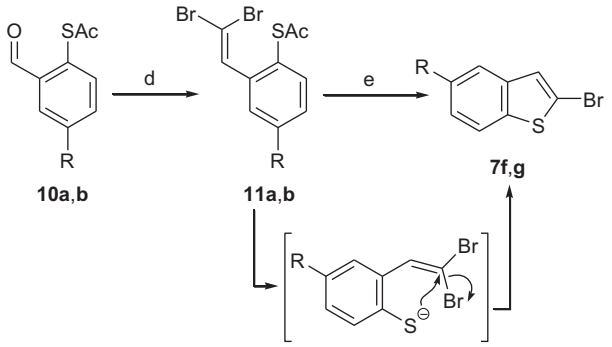
Concerning the 5-substituted 2-bromo-benzothiophenes, an alternative strategy based on a copper-catalyzed ring closure of *ortho*-dibromoalkene thiophenols was envisaged.[28] After bromination of *m*-methoxybenzaldehyde using *N*-bromosuccinimide (NBS) in refluxing acetonitrile,[29] the resulting *para*-methoxy bromo derivative **9a** underwent an aromatic nucleophilic substitution with a sulfur atom, using sodium sulfide. The resulting thiophenol was protected as a thioester by *in situ* action of acetic anhydride (Scheme 3).



Scheme 3. Reagents and conditions: (c) (1) $Na_2S{\cdot}9H_2O$ 1.2 equiv, DMAc, 90 °C, 6.5 h for **10a** and 4.5 h for **10b**. (2) Ac_2O, 0 °C, 50% for **10a**.

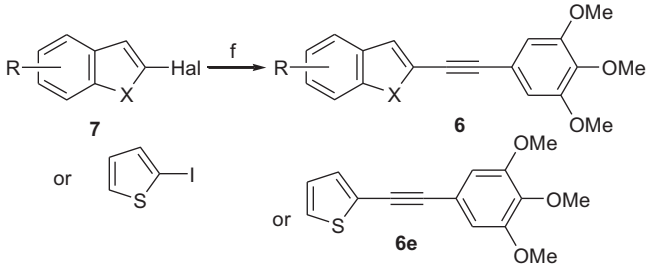
The nitro derivative **10b** was synthesized following a similar procedure from commercially available 2-chloro-5-nitro-benzaldehyde **9b** (Scheme 3).

These two protected aromatic aldehydes **10** were then engaged in Corey–Fuchs reactions[30] with carbon tetrabromide to give the dibromoalkenes **11** (Scheme 4). Following Lautens' protocol, the acetyl group should have been removed under basic conditions to get the free thiophenols, which could be cyclized using a copper catalyst and a soft phosphate base (intramolecular Ullmann coupling). But when the basic deprotection using potassium carbonate in methanol was realized on 5-methoxy compound **11a**, the cyclized product **7f** was isolated with an excellent 89% yield, after the intramolecular attack of the thiolate anion onto the vinyl bromide. Applied to the 5-nitro substrate **11b**, these copper-free conditions led to the formation of the corresponding benzothiophene **7g** with a very disappointing 12% yield (Scheme 4). Changing the base to NaOH significantly improved the yield of **7g** to 44%, albeit lower compared to the methoxy analogue synthesis (Scheme 4).



Scheme 4. Reagents and conditions: (d) CBr_4 1.5 equiv, PPh_3 3 equiv, CH_2Cl_2, 0 °C, 2 h then rt, 3 h, 58% for **11a** (R=OMe) and 23% over the last two steps for **11b** (R=NO_2). (e) K_2CO_3 1.5 equiv, MeOH, rt, 6 h, 89% for **7f** (R=OMe) and rt, 2 h, 12% for **7g** (R=NO_2).

These two partners, the acetylenic derivative **8** and 2-halogenoheteroaromatics **7**, were then engaged under classical Sonogashira coupling conditions[31] to prepare a series of seven diarylacetylenes **6** (Scheme 5 and Table 2).



Scheme 5. Reagents and conditions: (f) 3,4,5-trimethoxyphenylacetylene **8** 1.15 equiv, $PdCl_2(PPh_3)_2$ 2 mol %, CuI 4 mol %, Et_3N 1.3 equiv, THF, rt, 5–23 h.

The cross-coupling reaction was very efficient with 2-iodobenzofuran and 2-iodobenzo[*b*]thiophene and, to a lesser extent, with 2-iodo-thiophene, as these compounds were isolated in almost quantitative yields for **6a** and **6b** (Table 2, entries 1 and 2) and 79% for **6e**[32] (Table 2, entry 5).

When carried out with *N*-phenylsulfonyl-2-iodo-indole, the product **6c** was obtained with a fairly good 67% yield (Table 2, entry 3) but led to a more disappointing result when the NH of indole was not protected (Table 2, entry 4). Lastly, with 5-substituted 2-bromo-benzo[*b*]thiophene **7f**,**g**, the reaction allowed us to obtain the 5-methoxy derivative **6f** with a moderate yield (Table 2, entry 6) whereas the reaction appears to be more efficient when realized on a substrate bearing a strong electron-withdrawing nitro group (Table 2, entry 7).

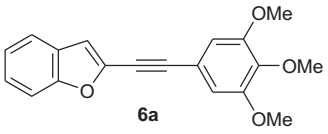
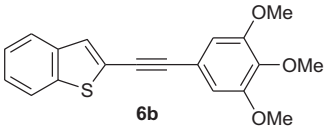
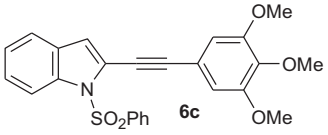
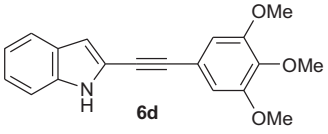
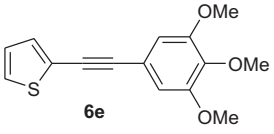
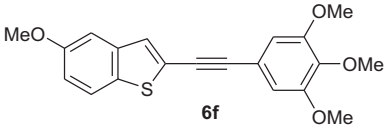
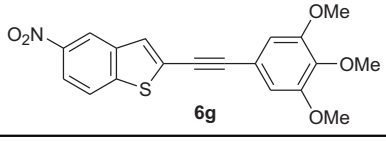
Several protocols are known in the literature for the selective transformation of acetylenic substrates into *cis* alkenes, such as Lindlar hydrogenation,[33] alkyne hydroboration,[21] or hydrolysis of a preformed titanium complex.[34]

Rather than a lead-poisoned Lindlar palladium catalyst (to avoid lead traces in the final product **1**, which could have an influence during subsequent biological evaluations), we were looking for alternative strategies: in the following, we will describe our results using two of these alternatives: a hydrosilylation/deprotection sequence and a semi-hydrogenation using the $PdOAc_2$/KOH/DMF system.

2.3.2. Reduction via a hydrosilylation/deprotection sequence. First described by Alami and co-workers for the preparation of CA-4 and analogues,[35] this method implies two steps that could also be realized in a one-pot fashion: first a platinum-catalyzed hydrosilylation of the triple bond with a silicon hydride reagent followed by a fluoride-mediated deprotection of the vinylsilane compound.

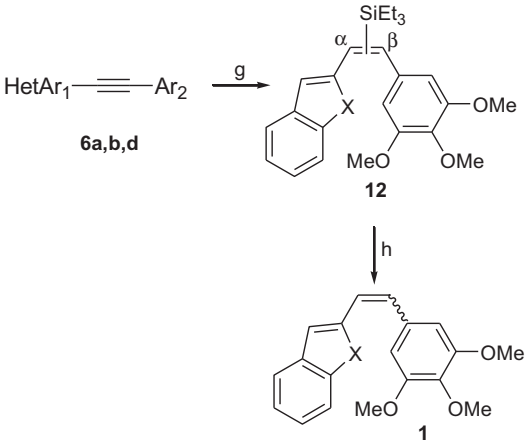
Applied to our unsymmetrical diarylacetylene derivatives **6a**,**b**,**d**, the hydrosilylation step using triethylsilane (Scheme 6) led

Table 2
Synthesis of diarylacetylenes **6**

Entry	Substrate	Product	Yield %
1	2-Iodo-benzofuran	 **6a**	94
2	2-Iodo-benzothiophene	 **6b**	94
3	*N*-Phenylsulfonyl-2-iodo-indole	 **6c**	67
4	2-Iodo-indole	 **6d**	39
5	2-Iodo-thiophene	 **6e**	79
6	2-Bromo-5-methoxy-benzothiophene	 **6f**	30[a]
7	2-Bromo-5-nitro-benzothiophene	 **6g**	66

[a] Homo-coupling product of starting material **8** was isolated with a 19% yield.

to the expected vinylsilanes **12** with very good (Table 3, entry 4) to excellent yields (Table 3, entries 1 and 3). Compounds **12a**,**b** were obtained as a mixture a two regioisomers (not separable by flash chromatography), depending on the position of the triethylsilyl group on the double bond, i.e., α or β.[36] However, we were surprised to see that, with the free indole substrate **6d**, the reaction gave only one regioisomer. In addition, this single regioisomer of **12d** gave, after treatment with a TBAF solution, stereopure (*Z*) isomer of the trimethoxystyrene derivative **1d** (Table 3, entry 4).[37] With the other vinylsilane compounds **12a** (X=O) and **12b** (X=S), *Z*/*E* mixtures were obtained after the deprotection step (Table 3, entries 1 and 3).[38]



Scheme 6. Reagents and conditions: (g) Et_3SiH 3 equiv, PtO_2 5 mol %, 60 °C, 4–23 h. (h) TBAF 1.1 equiv, THF, 60 °C, 1–2.5 h.

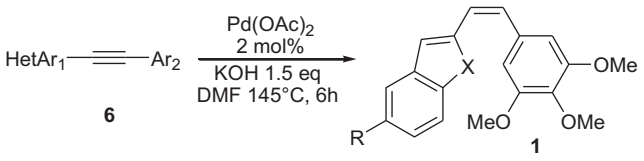
Table 3
Preparation of trimethoxystyrenes **1** using a hydrosilylation/deprotection sequence

Entry	X	Hydrosilylation step[a]	Deprotection step[c]
1	O (**6a**)	95%, α/β ratio 79/21	84%, *Z*/*E* 62/38[d]
2	O (**6a**)[b]	72%, α/β ratio 54/46	68%, *Z*/*E* 57/43[d]
3	S (**6b**)	92%, α/β ratio 18/82	94%, *Z*/*E* 24/76[e]
4	NH (**6d**)	78%, α/β ratio 100/0	80%, *Z*/*E* 100/0

[a] α/β Ratio was determined by ^1H NMR on the purified product, without attribution of the major regioisomer.
[b] Et_3SiH was replaced by $Me_2EtOSiH$.
[c] Isolated yields of trimethoxystyrenes **1**, obtained as a mixture of (*Z*) and (*E*) stereoisomers, except for entry 4.
[d] *Z*/*E* Ratio was determined by ^1H NMR on the crude product.
[e] *Z*/*E* Ratio was determined after purification of the crude product by flash chromatography.

By using another hydrosilylating agent, $Me_2EtOSiH$, that gave better α/β regioselectivities during the synthesis of CA-4,[35] no improvement of this regioselectivity was observed on benzofuran substrate as **1a** was obtained with a lower global yield and a less favourable *Z*/*E* ratio (Table 3, entry 2).

2.3.3. Palladium acetate/DMF/KOH hydrogenation. When looking for other semi-hydrogenation protocols, our attention was attracted by a method recently developed by Li and co-workers: the partial reduction of acetylenic derivatives using the *in situ* hydrogen generation, after hydrolysis of DMF under basic conditions, and catalyzed by palladium acetate.[39] This method appeared us to be practical and proved to have excellent stereoselectivities: so, we decided to apply it on substrates **6** (Scheme 7).



Scheme 7.

When the reaction was performed on the oxygen-containing substrate **6a**, we observed in 6 h the complete conversion of the starting material and the major formation of the (*Z*)-alkene, together with a small amount of its (*E*) stereoisomer (Table 4, entry 1). After a careful purification by flash chromatography, the desired isomer (*Z*)-**1a** was obtained with a 66% yield.

Table 4
Semi-hydrogenation of acetylenes **6**

Entry	X	R	*Z*/*E* Ratio,[a] global yield	(*Z*) Isomer, yield %
1	O	H (**6a**)	93/7, 92%	**1a**, 66
2	S	H (**6b**)	91/9, 74%	**1b**, 63
3	S	OMe (**6f**)	100/0, 40%	**1f**, 40
4	S	NO_2 (**6g**)	—[b]	—[b]

[a] Determined by ^{1}H NMR on the crude product.
[b] No traces of the desired product was observed.

With its sulfur analogue **6b**, the selectivity was slightly higher (Table 4, entry 2) and the reaction afforded (*Z*)-**1b** with a good 63% yield. The electron-donating 5-methoxy substituent on the benzothiophene ring seems to be of interest since the *cis* selectivity of this hydrogenation increased: only (*Z*)-**1f** was detected, with a low 40% yield as the major drawback (Table 4, entry 3). However, the presence at the same position of a strong electron-withdrawing nitro group completely inhibited the reaction (Table 4, entry 4).

To complete our study, we wished to determine the kinetic profile of the semi-hydrogenation reaction on the substrate **6b**,[40] to see if the *Z*/*E* ratio was modified during the reaction. The reaction was carried out in a Schlenk tube, under an argon atmosphere and aliquots of the reaction mixture were periodically collected after the beginning of the heating at 145 °C and analyzed by uHPLC/MS.

We observed fast consumption of the starting material, which was not further detected by MS after a 5 h reaction time (Fig. 3).

In parallel, the quantity of the desired (*Z*)-**1b** rapidly increased. The *Z*/*E* ratio did not evolve during all the heating time and remains around 92/8, which matches with an NMR estimation on the crude product. This observation means that the (*Z*) to (*E*) isomerization did not occur under the reaction conditions: once the stereoisomer was formed during the hydrogen approach onto the triple bond, no further change took place.

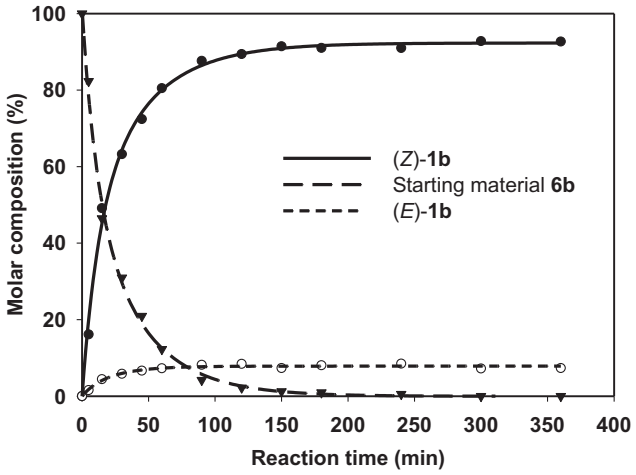


Fig. 3. Kinetic profile of the semi-hydrogenation of **6b**.

2.4. Biological evaluations

Compounds (*Z*) and (*E*)-**1** were thereafter evaluated for their abilities to inhibit tubulin polymerization and the results were quite encouraging, as described in our preliminary communication.[8] Compound (*Z*)-**1b** appeared to be the most active derivative having an IC_{50}=2.6 μM, comparable to that of colchicine (IC_{50}=1.7 μM).

It showed also an interesting anti-proliferative activity against keratinocyte cell lines (on HaCaT cells, IC_{50}=16 nM whereas IC_{50} of colchicine=12 nM), although lower than CA-4 itself. Flow cytometry experiments also demonstrated that (*Z*)-**1b** caused the cell mitosis arrest at G2/M transition, a common feature with CA-4.

3. Conclusion

The objective of this study was to have in hand new CA-4 derivatives (*Z*)-**1** for biological evaluations. As a consequence, it allows us to establish a comparison between methods used for the preparation of (*Z*) stereoisomer of these tubulin-targeting agents. The final choice was in fact strongly dependent on the structure of the target compound. Concerning the Suzuki coupling, the desired stereochemistry was fixed by a palladium-catalyzed reduction step with tributyltin hydride but could be altered by subsequent coupling conditions, except in the case of benzothiophene compound **1b**. Although efficient for the preparation of CA-4,[35] the triple bond hydrosilylation/hydrolysis sequence was quite disappointing when applied to our benzoheterocyclic substrates **6a**,**b** as *Z*/*E* mixtures were observed for **1a**,**b**. Nevertheless, this strategy would be the method of choice for the preparation of the indole analogue **1d**, for which a perfect stereoselectivity and very good yield were observed. The semi-hydrogenation method, using the *in situ* hydrogen formation after basic hydrolysis of DMF, proved to be practical and very efficient in term of stereoselectivity. This latter method is preferable as it would avoid traces of toxic tin (coming from $HSnBu_3$) in the final product.

4. Experimental

4.1. General

All reactions were carried out under a positive pressure of argon and with oven-dried glassware. Melting points were measured on a Büchi B-540 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker ALS300, DRX300 and DRX 400 Fourier transform spectrometers, using an internal deuterium lock, operating at 300 or

400 MHz. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_H=0.00; $CDCl_3$, δ_H=7.26 and DMSO-d_6, δ_H=2.50).[41] Data are presented as follows: chemical shift (δ, ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad), coupling constant, integration. Atom numbering refers to and benzoheterocycle nomenclature. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on Bruker ALS300 or DRX 400 Fourier transform spectrometers, using an internal deuterium lock, operating at 75 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to internal standard (tetramethylsilane, δ_C=0.00; $CDCl_3$, δ_C=77.16 and DMSO-d_6, δ_C=39.52).[41] Carbon multiplicities (indicated in parentheses) were determined by DEPT experiments. High-resolution mass spectra were recorded on a Bruker MicroTOF Q or Thermoquest Finnigan MAT 95 XL spectrometer (for chemical ionizations, isobutane was used).

Agilent uHPLC/MS consists of a 1290 Infinity system with a binary pump, degasser, autosampler, thermostated column compartment, 1260 Infinity Diode Array Detector and 6120 single quadrupole mass spectrometer. The entire system was controlled by ChemStation (Agilent Technologies, Rev B.04.02 SP1). The column was a Zorbax Eclipse Plus C18 RRHD, 2.1×50 mm, 1.8 μm. The samples were analyzed in the positive ion mode of the Electron Spray Ionization (ESI) source, whose conditions were as follow: gas temperature, 350 °C, drying gas at 12.0 L/min, nebulizer gas at 35 psig, Vcap at 3000 V, fragmentor at 110 or 115 V.

Reactions were monitored with analytical Thin Layer Chromatography (TLC), which was carried out using Merck commercial aluminium sheets coated (0.2 mm layer thickness) with Kieselgel 60 F_{254}, with visualization by ultraviolet and anisaldehyde stain solution.

Product purification by flash column chromatography was performed using Merck Kieselgel 60 Å (40–63 μm). *N*,*N*-Dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMAc), 1,2-dimethoxyethane (DME) and methanol were of analytical grade and were used as received without purification. THF (Acroseal®, over molecular sieves) are purchased by Acros Organics. Dichloromethane was distilled over $LiAlH_4$ prior to use. For extraction/purification, diethyl ether, cyclohexane and ethyl acetate (AcOEt) were of reagent grade. Petroleum ether (PE) refers to the 40–60 °C boiling point fraction. Resveratrol trimethyl ether (≥98% purity) was used as the internal standard for kinetic studies and was purchased from Sigma–Aldrich.

All other chemical reagents were used as received. Commercial *n*-BuLi solutions in hexanes were titrated using *N*-Benzylbenzamide.[42] 3,4,5-Trimethoxybenzyl-triphenylphosphonium bromide,[43] 3,4,5-trimethoxy-phenylacetylene[24] and tetrakis(triphenylphosphine) palladium(0)[44] were prepared according to known procedures.

4.2. Wittig reactions

4.2.1. Preparation of 2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran ***1a****.* To a stirred suspension of 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (1.83 g, 3.5 mmol) in THF (35 mL) at −78 °C was added dropwise (10 min) *n*-BuLi 2.5 M in hexane (2.8 mL, 7.0 mmol). The stirring was continued at −78 °C for 30 min and at room temperature for 1 h. The dark red reaction mixture was cooled to −78 °C and a solution of benzofuran-2-carboxaldehyde (0.512 g, 3.5 mmol) in THF (13 mL) then was added dropwise (15 min). The stirring was continued at −78 °C for 1 h and at room temperature for 18 h. Subsequently, the mixture was quenched with ice-cold water (35 mL) and ethyl acetate (35 mL) was then added. After decantation, the aqueous layer was extracted with ethyl acetate (2×35 mL) and dichloromethane (3×35 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow residue. The crude product (*Z*/*E* ratio 49/51, determined by ^{1}H NMR) was purified by silica gel flash column chromatography (PE/AcOEt, 75:25 to 60:40) to afford the (*Z*) isomer of **1a** as a pale yellow viscous oil (0.282 g, 26%), a mixture of (*Z*) and (*E*) isomers (0.040 g, 4%) and the (*E*) isomer as a white solid (0.384 g, 35%).

Stereoisomer (*Z*). IR: ν_{max} (film, cm^{-1}) 2997, 2937, 2835, 1581, 1505, 1463, 1452, 1418, 1328, 1240, 1183, 1167, 1129, 1007, 970, 940, 890, 854, 811, 751. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.83 (s, 6H), 3.91 (s, 3H), 6.44 (d, *J*=12.7 Hz, 1H), 6.59 (d, *J*=12.7 Hz, 1H), 6.70 (s, 1H), 6.84 (s, 2H), 7.18–7.27 (m, 2H), 7.36–7.38 (m, 2H), 7.37 (d, *J*=8.0 Hz, 1H), 7.50 (d, *J*=7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 61.0 (CH_3), 106.2 (CH), 106.9 (CH), 110.8 (CH), 117.3 (CH), 120.9 (CH), 123.0 (CH), 124.7 (CH), 128.6 (C), 131.2 (CH), 132.1 (C), 137.9 (C), 152.9 (C), 153.8 (C), 154.3 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{18}O_4Na$ [MNa^+]: 333.1097; found: 333.1084.

Stereoisomer (*E*). Mp 121–124 °C. IR: ν_{max} (film, cm^{-1}) 2959, 2934, 1581, 1503, 1449, 1416, 1335, 1326, 1254, 1242, 1197, 1152, 1123, 1044, 1006, 992, 983, 967, 948, 840, 816, 784, 748, 670, 636, 616, 499. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.87 (s, 3H), 3.90 (s, 6H), 6.66 (s, 1H), 6.75 (s, 2H), 6.90 (d, *J*=16.0 Hz, 1H), 7.14–7.28 (m, 3H), 7.45 (d, *J*=8.1 Hz, 1H), 7.52 (d, *J*=8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 60.9 (CH_3), 103.8 (CH), 105.0 (CH), 110.8 (CH), 115.9 (CH), 120.8 (CH), 122.9 (CH), 124.6 (CH), 129.1 (C), 130.2 (CH), 132.2 (C), 138.4 (C), 153.4 (C), 154.8 (C), 154.9 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{19}O_4$ [MH^+]: 311.1278; found: 311.1276.

4.2.2. Preparation of (Z)-2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene ***1b****.* To a stirred suspension of 3,4,5-trimethoxybenzyl-triphenylphosphonium bromide (0.806 g, 1.54 mmol) in THF (16 mL) at −78 °C was added dropwise (10 min) *n*-BuLi 2.5 M in hexane (1.23 mL, 3.08 mmol). The stirring was continued at −78 °C for 30 min and at room temperature for 1 h. The dark red reaction mixture was cooled to −78 °C and a solution of benzo[*b*]thiophene-2-carboxaldehyde (0.250 g, 1.54 mmol) in THF (6 mL) then was added dropwise (15 min). The stirring was continued at −78 °C for 1 h and at room temperature for 18 h. Subsequently, the mixture was quenched with ice-cold water (20 mL) and ethyl acetate (20 mL) was then added. After decantation, the aqueous layer was extracted with ethyl acetate (2×20 mL) and dichloromethane (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow residue. The crude product (*Z*/*E* ratio 45/55, determined by ^{1}H NMR) was purified by silica gel flash column chromatography (PE/AcOEt, 80:20) to afford the (*Z*) isomer of **1b** as a yellow oil (0.040 g, 8%), a mixture of (*Z*) and (*E*) isomers (0.198 g, 39%) and the (*E*) isomer as a yellow solid (0.149 g, 30%).

Stereoisomer (*Z*). IR: ν_{max} (film, cm^{-1}) 3056, 2999, 2936, 2833, 1579, 1502, 1463, 1430, 1413, 1395, 1328, 1238, 1182, 1149, 1127, 1040, 1007, 966, 855, 834, 746, 726. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79 (s, 6H), 3.91 (s, 3H), 6.65 (d, *J*=11.7 Hz, 1H), 6.65 (s, 2H), 6.76 (d, *J*=12 Hz, 1H), 7.22–7.31 (m, 3H), 7.65–7.68 (m, 2H). (300 MHz, DMSO-d_6): δ=3.70 (s, 3H), 3.7 (s, 6H), 6.70 (d, *J*=11.7 Hz, 1H), 6.71 (s, 2H), 6.88 (d, *J*=12.3 Hz, 1H), 7.25–7.34 (m, 2H), 7.48 (s, 1H), 7.75–7.78 (m, 1H), 7.81–7.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0 (CH_3), 61.0 (CH_3), 106.0 (CH), 122.0 (CH), 123.2 (CH), 123.6 (CH), 124.2 (CH), 124.6 (CH), 125.4 (CH), 130.9 (CH), 131.9 (C), 137.8 (C), 138.9 (C), 139.8 (C), 140.0 (C), 153.1 (C). HRMS (ESI$^+$): *m*/*z* calcd for $C_{19}H_{18}O_3SNa$ [MNa^+]: 349.0869; found: 349.0864.

Stereoisomer (*E*). Mp 158–160 °C. IR: ν_{max} (film, cm^{-1}) 3001, 2926, 2831, 1723, 1579, 1505, 1450, 1415, 1350, 1326, 1245, 1234, 1184, 1155, 1123, 1002, 963, 858, 835, 811, 754, 727, 707, 683, 635, 566, 521, 496. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.88 (s, 3H), 3.92 (s, 6H), 6.73 (s, 2H), 6.92 (d, *J*=16.0 Hz, 1H), 7.22 (d, *J*=16.0 Hz, 1H), 7.24 (s, 1H), 7.28–7.34 (m, 2H), 7.68–7.70 (m, 1H), 7.76–7.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 60.9 (CH_3), 103.6 (CH), 121.8 (CH), 122.2 (CH), 123.1 (CH), 123.3 (CH), 124.5 (CH), 124.7 (CH), 130.8

(CH), 132.3 (C), 138.3 (C), 138.8 (C), 140.2 (C), 142.7 (C), 153.4 (C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{19}O_3S$ [MH$^+$]: 327.1049; found: 327.1040.

4.3. Suzuki couplings

4.3.1. Substrates synthesis. Benzofuran-, benzo[*b*]thiophene- and thiophene-2-boronic acids were purchased from Acros Organics. *N*-Boc indole-2-boronic acid and *N*-Boc indole-2-potassium trifluoroborate were synthesized according to known protocols.[20] 1-(2-Bromovinyl)-3,4,5-trimethoxybenzene (*Z*/*E* 91/9) was prepared according to a literature reference by palladium-catalyzed selective halogenolysis of the dibromovinyl precursor.[17a]

4.3.2. General procedure 1. Suzuki coupling reactions: preparation of 2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran ***1a****.* 1-(2-Bromovinyl)-3,4,5-trimethoxybenzene (*Z*/*E* ratio 91/9, determined by ^{1}H NMR) (0.126 g, 0.46 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.027 g, 0.023 mmol) were stirred in 1,2-dimethoxyethane (7 mL) under argon for 20 min. Benzofuran-2-ylboronic acid (0.086 g, 0.53 mmol) and sodium carbonate (0.049 g, 0.46 mmol) in water (4.2 mL) were added, the mixture was heated under reflux during 20 h. After cooling and decantation, the aqueous layer was separated and extracted with ethyl acetate (2×7 mL). The combined organic phases were washed with brine (7 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR and has shown a mixture of (*Z*) (77%) and (*E*) isomers (33%). This crude product was purified by column chromatography (cyclohexane/ethyl acetate 80:20) to give the (*Z*) isomer of **1a** as a yellow oil (0.081 g, 57%) and a mixture of (*Z*) and (*E*) isomer (0.047 g, 33%). This fraction was purified a second time by column chromatography (cyclohexane/ethyl acetate 80:20) followed by washing with diethyl ether to obtain (*E*)-**1a** (0.032 g, 22%) as a white solid.

4.3.3. Preparation of (Z)-2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene ***1b****.* According to general procedure 1, scale: 1-(2-bromovinyl)-3,4,5-trimethoxybenzene (*Z*/*E* 91/9) (0.137 g, 0.5 mmol), tetrakis(triphenylphosphine)palladium(0) (0.029 g, 0.025 mmol), 1,2-dimethoxyethane (7.6 mL), benzo[*b*]thiophen-2-yl-boronic acid (0.101 g, 0.57 mmol), sodium carbonate (0.053 g, 0.5 mmol), water (4.6 mL). The residue containing 90% of (*Z*)- and 10% of (*E*)-**1b** was purified by column chromatography on silica gel deactivated by Et_3N (cyclohexane/ethyl acetate, 80:20) to give (*Z*)-**1b** as a yellow oil (0.093 g, 57%) and a mixture of (*Z*) and (*E*) isomer (0.062 g, 38%).

4.3.4. Preparation of (Z)-2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-indole-1-carboxylic acid tert-butyl ester ***1c****.* According to general procedure 1, scale: 1-(2-bromovinyl)-3,4,5-trimethoxybenzene (*Z*/*E*=91:9) (0.297 g, 1.09 mmol), tetrakis(triphenylphosphine)palladium(0) (0.063 g, 0.054 mmol), 1,2-dimethoxyethane (16.5 mL), 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl potassium trifluoroborate (0.402 g, 1.24 mmol), sodium carbonate (0.116 g, 1.09 mmol), water (10 mL). The residue was purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to give (*Z*)-**1c** as a yellow oil (0.210 g, 47%) and a mixture of two isomers (0.040 g, 9%, *Z*/*E*=78:22).

Stereoisomer (*Z*). IR: ν_{max} (KBr, cm^{-1}) 2978, 2936, 2835, 1732, 1580, 1556, 1505, 1452, 1418, 1395, 1370, 1330, 1240, 1210, 1160, 1128, 1085, 1039, 1008, 980, 942, 847, 798, 770, 748, 662. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.68 (s, 9H), 3.62 (s, 6H), 3.84 (s, 3H), 6.56 (d, *J*=12.3 Hz, 1H), 6.57 (2s, 3H), 6.80 (dd, *J*=12.3–1.2 Hz, 1H), 7.17–7.22 (m, 1H), 7.26–7.31 (m, 1H), 7.41–7.45 (m, 1H), 8.11–9.14 (m, 1H). (300 MHz, DMSO-d_6): δ=1.56 (s, 9H), 3.48 (s, 6H), 3.60 (s, 3H), 6.54 (s, 2H), 6.60 (d, *J*=12.1 Hz, 1H), 6,60 (s, 1H), 6.73 (dd, *J*=12.4–1.1 Hz, 1H), 7.16–7.22 (m, 1H), 7.26–7.31 (m, 1H), 7.52 (d, *J*=6.9 Hz, 1H), 8.05 (d, *J*=8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.2 (CH_3), 55.8 (CH_3), 60.8 (CH_3), 84.2 (C), 105.8 (CH), 109.5 (CH), 115.3 (CH), 120.4 (CH), 121.7 (CH), 122.8 (CH), 124.1 (CH), 129.3 (C), 130.7 (CH), 132.2 (C), 136.0 (C), 136.2 (C), 137.4 (C), 150.3 (C), 152.9 (C). HRMS (ESI$^+$): m/z calcd for $C_{24}H_{27}NO_5Na$ [MNa$^+$]: 432.1781; found: 432.1785.

4.3.5. Preparation of (Z)-2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-thiophene ***1e****.* According to general procedure 1, scale: 1-(2-bromovinyl)-3,4,5-trimethoxybenzene (*Z*/*E*=91:9) (0.132 g, 0.48 mmol), tetrakis(triphenylphosphine)palladium(0) (0.028 g, 0.024 mmol), 1,2-dimethoxyethane (7 mL), thiophen-2-ylboronic acid (0.070 g, 0.55 mmol), sodium carbonate (0.051 g, 0.48 mmol), water (4.2 mL). The residue containing 67% of (*Z*)- and 33% of (*E*)-2-(2-(3,4,5-trimethoxyphenyl)vinyl)thiophene was purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to give (*Z*)-**1e** as a yellow oil (0.050 g, 38%) and a mixture of (*Z*) and (*E*) isomer (0.048 g, 36%).

Stereoisomer (*Z*). IR: ν_{max} (film, cm^{-1}) 2935, 2833, 1737, 1577, 1501, 1462, 1451, 1429, 1411, 1326, 1234, 1184, 1122, 1036, 1004, 966, 849, 700, 573, 527, 478. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.80 (s, 6H), 3.88 (s, 3H), 6.50 (d, *J*=12.0 Hz, 1H), 6.61 (s, 2H), 6.67 (d, *J*=12.3 Hz, 1H), 6.91 (dd, *J*=5.2–3.6 Hz, 1H), 7.01 (d, *J*=3.6 Hz, 1H), 7.13 (dd, *J*=4.8–1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0 (CH_3), 61.0 (CH_3), 105.8 (CH), 123.1 (CH), 125.6 (CH), 126.4 (CH), 128.4 (CH), 128.8 (CH), 132.5 (C), 137.5 (C), 139.6 (C), 153.2 (C). HRMS (ESI$^+$): m/z calcd for $C_{15}H_{16}O_3SNa$ [MNa$^+$]: 299.0712; found: 299.0714.

4.4. 2-Halogenated heterocycles

2-Iodothiophene was purchased by Alfa Aesar. 2-Iodobenzofuran, 2-iodobenzothiophene were synthesized via a zinc/lithium mixed aggregate 2-deprotonation and subsequent iodination, according to Mongin's method.[25] 5-Nitro and 5-methoxy-2-bromobenzo[*b*]thiophene **7f,g** were prepared according to the following protocols.

4.4.1. Preparation of 2-bromo-5-methoxybenzaldehyde. A solution of *m*-anisaldehyde (3.66 mL, 30 mmol) and *N*-bromosuccinimide (5.874 g, 33 mmol) in acetonitrile (90 mL) was heated at 90 °C for 11 h then at 70 °C for 18 h. After cooling, the reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to afford a first fraction (2.80 g, white solid). The second fraction (1.60 g) was further purified by flash chromatography (cyclohexane/ethyl acetate, 97.5:2.5) to give another fraction (0.82 g, white solid). These two fractions were collected to give the title compound (2.80+0.82=3.62 g, 56%) as a white solid; mp 78–79 °C (lit.[45] 78–80 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.84 (s, 3H), 7.04 (dd, *J*=8.7–3.0 Hz, 1H), 7.42 (d, *J*=3.6 Hz, 1H), 7.53 (d, *J*=9.3 Hz, 1H), 10.32 (s, 1H). Spectral data were in agreement to those reported in the literature.[45]

4.4.2. Preparation of thioacetic acid S-(2-formyl-4-methoxy-phenyl) ester ***10a****.* To a two-neck round-bottomed flask (fitted with a condenser and an addition funnel) containing $Na_2S{\cdot}9H_2O$ (3.757 g, 15.6 mmol) was added DMAc (39 mL) and the resulting suspension was heated at 90 °C. After stirring for 90 min, 2-bromo-5-methoxybenzaldehyde (2.796 g, 13 mmol) was added, the suspension turned from blue/green to reddish brown and the reaction was stirred at 90 °C until TLC indicated consumption of starting material (5 h). The reaction was then cooled to 0 °C and freshly distilled Ac_2O (15 mL, 158.7 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h, then warmed to room temperature and stirred overnight (16 h). The reaction was then diluted with

Et_2O (60 mL) and 10% aqueous HCl (40 mL): after decantation, the aqueous phase was extracted with Et_2O (2×40 mL). The combined organic phases were washed by water (40 mL) and brine (40 mL). The organic phase was dried over Na_2SO_4, filtered and the volatiles were removed under vacuum. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to give compound **10a** (1.388 g, 50%) as a yellow oil; IR: ν_{max} (KBr, cm^{-1}) 3006, 2938, 2848, 2747, 1705, 1593, 1566, 1478, 1422, 1388, 1354, 1311, 1278, 1231, 1192, 1165, 1111, 1060, 1025, 951, 870, 828, 757, 617. ^1H NMR (300 MHz, $CDCl_3$): δ=2.48 (s, 3H), 3.89 (s, 3H), 7.17 (dd, J=8.4–3 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H), 7.54 (d, J=3 Hz, 1H), 10.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.1 (CH_3), 55. 7 (CH_3), 112.3 (CH), 121.6 (CH), 122.2 (C), 137.8 (CH), 138.0 (C), 161.2 (C), 190.7 (CH), 193.5 (C). HRMS (CI): m/z calcd for $C_{10}H_{11}O_3S$ [MH^+]: 211.0423; found: 211.0421.

*4.4.3. Preparation of thioacetic acid S-(2-formyl-4-nitro-phenyl) ester **10b**.* Following the same experimental procedure as for compound **10a**, scale: $Na_2S{\cdot}9H_2O$ (5.76 g, 24 mmol), DMAc (60 mL), 2-chloro-5-nitrobenzaldehyde (3.711 g, 20 mmol), Ac_2O (28 mL, 296 mmol), reaction time at 90 °C: 3 h. As this compound seems not to be stable on the silica gel, the crude product was used without further purification (see § 4.4.5.).

During one reaction, an analytic sample of **10b** was obtained after a flash chromatography purification (cyclohexane/ethyl acetate, 80:20); mp 72–75 °C. IR: ν_{max} (film/cm^{-1}) 2920, 2850, 1693, 1599, 1573, 1517, 1456, 1342, 1299, 1247, 1186, 1112, 1053, 968, 935, 922, 845, 816, 741, 732, 609, 546, 502. ^1H NMR (300 MHz, $CDCl_3$): δ=2.57 (s, 3H), 7.74 (d, J=8.4 Hz, 1H), 8.43 (dd, J=8.4–2.7 Hz, 1H), 8.84 (d, J=2.4 Hz, 1H), 10.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.7 (CH_3), 123.9 (CH), 127.6 (CH), 137.4 (CH), 137.5 (C), 137.9 (C), 148.8 (C), 188.2 (CH), 190.5 (C). HRMS (CI): m/z calcd for $C_9H_8NO_4S$ [MH^+]: 226.0169; found: 226.0168.

*4.4.4. Preparation of thioacetic acid S-[2-(2,2-dibromo-vinyl)-4-methoxy-phenyl] ester **11a**.* In a round-bottom flask fitted with an addition funnel, a solution of aldehyde **10a** (1.143 g, 5.44 mmol) and CBr_4 (2.706 g, 8.16 mmol) in freshly distilled dichloromethane (32.5 mL) was cooled at 0 °C. PPh_3 (4.281 g, 16.32 mmol) in freshly distilled dichloromethane (22 mL) was added dropwise during 1 h. The reaction was stirred at 0 °C for 2 h, then at room temperature for 3 h. Petroleum ether was added until no more precipitation of triphenylphosphine oxide was observed. Insoluble solids were eliminated by filtration on a sintered-glass funnel, washing with Et_2O. After evaporation of the solvents under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate, 90:10) to give compound **11a** (1.155 g, 58%) as a yellow solid; mp 60–62 °C. IR: ν_{max} (film/cm^{-1}) 3011, 2937, 1737, 1694, 1590, 1477, 1457, 1434, 1349, 1313, 1233, 1171, 1098, 1062, 1023, 951, 873, 827, 816, 732, 712, 691, 654, 638, 626, 610, 577, 554, 518, 508, 468. ^1H NMR (300 MHz, $CDCl_3$): δ=2.42 (s, 3H), 3.84 (s, 3H), 6.92 (dd, J=8.7, 3 Hz, 1H), 7.19 (d, J=2.7 Hz, 1H), 7.35 (d, J=8.7 Hz, 1H), 7.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.0 (CH_3), 55.5 (CH_3), 92.8 (C), 115.0 (CH), 115.4 (CH), 117.9 (C), 135.7 (CH), 137.3 (CH), 141.0 (C), 160.7 (C), 193.8 (C). HRMS (CI): m/z calcd for $C_{11}H_{11}Br_2OS$ [MH^+]: 364.8841; found: 364.8841.

*4.4.5. Preparation of thioacetic acid S-[2-(2,2-dibromo-vinyl)-4-nitro-phenyl] ester **11b**.* The crude product obtained after nucleophilic substitution reaction with sodium sulfide/thioester formation (§ 4.4.3.) was used in this step, according to procedure used for the preparation of **11a**, scale: crude thioacetic acid *S*-(2-formyl-4-nitro-phenyl) ester **10b** (4.193 g), CBr_4 (8.95 g, 27 mmol) in dichloromethane (90 mL), PPh_3 (14.16 g, 54 mmol) in dichloromethane (60 mL). The crude product was purified by flash chromatography (cyclohexane/ethyl acetate, 90:10) to give compound **11b** (1.751 g, 23% for two steps) of as a light yellow solid; mp 125–126 °C. IR: ν_{max} (film/cm^{-1}) 2923, 1714, 1592, 1568, 1517, 1455, 1345, 1300, 1264, 1115, 1102, 1051, 947, 912, 850, 831, 815, 800, 740, 720, 606, 577, 539, 519, 453. ^1H NMR (300 MHz, $CDCl_3$): δ=2.51 (s, 3H), 7.47 (s, 1H), 7.68 (d, J=8.7 Hz, 1H), 8.22 (dd, J=8.7–2.1 Hz, 1H), 8.51 (d, J=2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.7 (CH_3), 95.8 (C), 123.2 (CH), 124.6 (CH), 133.5 (CH), 134.9 (CH), 136.7 (C), 140.6 (C), 148.3 (C), 190.5 (C). HRMS (CI): m/z calcd for $C_{10}H_8Br_2NO_3S$ [MH^+]: 379.8586; found: 379.8584.

*4.4.6. Preparation of 2-bromo-5-methoxy-benzo[b]thiophene **7f**.* A suspension of compound **11a** (0.207 g, 0.56 mmol) in methanol (2.8 mL) and K_2CO_3 (0.117 g, 0.85 mmol) was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate and washed with 10 mL of brine. Aqueous phases were extracted with ethyl acetate (3×10 mL). Organic layers were combined, dried over Na_2SO_4, filtered and evaporated to obtained crude product, which was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate, 95:5) to afford 2-bromo-5-methoxy-benzo[*b*]thiophene **7f** as a yellow solid (0.163 g, 89%); IR: ν_{max} (KBr, cm^{-1}) 3007, 2958, 2934, 2833, 1591, 1560, 1462, 1438, 1417, 1304, 1283, 1233, 1165, 1067, 1026, 958, 942, 872, 817, 703. ^1H NMR (400 MHz, $CDCl_3$): δ=3.83 (s, 3H), 6.83 (dd, J=6.6–2.1 Hz, 1H), 7.15 (d, J=2.1 Hz, 1H), 7.40 (d, J=6.3 Hz, 1H), 7.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.5 (CH_3), 92.2 (C), 115.1 (2CH), 126.5 (C), 135.7 (CH), 136.2 (CH), 139.8 (C), 160.2 (C). HRMS (EI): m/z calcd for C_9H_8BrOS [MH^+]: 241.9396; found: 241.9395.

*4.4.7. Preparation of 2-bromo-5-nitro-benzo[b]thiophene **7g**.* According to the procedure used for the preparation of **7f**, scale: compound **11b** (0.482 g, 1.26 mmol), methanol (6.3 mL), K_2CO_3 (0.261 g, 1.89 mmol), reaction time at room temperature: 2 h. The crude product (0.084 g) was purified by flash column chromatography (cyclohexane) to afford 2-bromo-5-nitrobenzo[*b*]thiophene **7g** (0.039 g, 12%) as a light yellow solid.

Optimized procedure. A suspension of compound **11b** (0.100 g, 0.26 mmol), in methanol (1.3 mL) and NaOH (0.150 g, 3.64 mmol) was stirred at room temperature for 8 h. The reaction mixture was quenched with water (5 mL), extracted with ethyl acetate (3×15 mL). Organic phases were washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash column chromatography (cyclohexane/ethyl acetate, 95:5) to afford 2-bromo-5-nitrobenzo[*b*]thiophene **7g** (0.030 g, 44%) as a light yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ=7.50 (s, 1H), 7.86 (d, J=9.3 Hz, 1H), 8.19 (dd, J=8.7–2.4 Hz, 1H), 8.59 (d, J=2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=118.1 (CH), 118.8 (CH), 119.2 (C), 122.2 (CH), 127.1 (CH), 139.2 (C), 145.8 (C), 146.6 (C). Spectral data were in agreement to those reported in the literature.[28a]

4.5. Diacetylene derivatives 6

*4.5.1. General procedure 2. Sonogashira coupling reactions: preparation of 2-(3,4,5-trimethoxy-phenylethynyl)-benzofuran **6a**.* To a solution of 2-iodo-benzofuran (1.030 g, 4.60 mmol) and $PdCl_2(PPh_3)_2$ (0.065 g, 0.09 mmol) in THF (28 mL) under an argon atmosphere was added CuI (0.034 g, 0.18 mmol), triethylamine (0.83 mL, 5.98 mmol) and then 3,4,5-trimethoxyphenylacetylene **8** (1.061 g, 5.22 mmol). After stirring for 5 h at room temperature, the reaction mixture was filtered over a 0.45 μm porosity glass fibre filter and washed with diethyl ether (2×20 mL). The combined organic layers were concentrated under vacuum. The crude brown oil was purified by column chromatography (cyclohexane/ethyl acetate 80:20) to afford compound **6a** (1.333 g, 94%) as an orange yellow solid; mp 89–91 °C. IR: ν_{max} (film, cm^{-1}) 2934, 1574, 1501, 1448, 1425, 1411, 1345, 1267, 1237, 1185, 1165, 1126, 1105, 1003, 986,

927, 823, 811, 771, 745, 656, 646, 628, 555, 525, 510. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.88 (s, 6H), 3.89 (s, 3H), 6.82 (s, 2H), 7.00 (d, J=0.8 Hz, 1H), 7.24–7.28 (m, 1H), 7.32–7.36 (m, 1H), 7.47–7.49 (m, 1H), 7.57–7.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.2 (CH_3), 61.0 (CH_3), 78.7 (C), 95.2 (C), 108.8 (CH), 111.2 (CH), 111.4 (CH), 116.7 (C), 121.1 (CH), 123.3 (CH), 125.6 (CH), 127.7 (C), 138.6 (C), 139.5 (C), 153.1 (C), 154.8 (C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{17}O_4$ [MH^+]: 309.1121; found: 309.1111.

4.5.2. Preparation of 2-(3,4,5-trimethoxy-phenylethynyl)benzo[b]thiophene ***6b***. According to general procedure 2, scale: 2-iodobenzo[*b*]thiophene (0.520 g, 2.00 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol), THF (12 mL), CuI (0.015 g, 0.08 mmol), triethylamine (0.36 mL, 2.6 mmol), trimethoxyphenylacetylene **8** (0.461 g, 2.40 mmol), reaction time at room temperature: 19 h. The crude product was then purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to afford compound **6b** (0.610 g, 94%) as a pale orange solid; mp 95–98 °C. IR: ν_{max} (film, cm^{-1}) 2928, 1738, 1573, 1497, 1452, 1433, 1424, 1351, 1326, 1236, 1183, 1171, 1124, 1099, 1069, 1039, 1002, 944, 970, 849, 838, 823, 752, 726, 691, 630, 564, 524, 505. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 9H), 6.80 (s, 2H), 7.35–7.39 (m, 2H), 7.50 (s, 1H), 7.74–7.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 61.0 (CH_3), 82.0 (C), 94.9 (C), 108.7 (CH), 117.4 (C), 122.0 (CH), 123.1 (C), 123.7 (CH), 124.7 (CH), 125.4 (CH), 128.6 (CH), 139.1 (C), 139.2 (C), 140.2 (C), 159.1 (C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{17}O_3S$ [MH^+]: 325.0893; found: 325.0893.

4.5.3. Preparation of 1-benzenesulfonyl-2-(3,4,5-trimethoxy-phenylethynyl)-1H-indole ***6c***. According to general procedure 2, scale: 2-iodo-1-benzenesulfonyl-1*H*-indole (0.766 g, 2.00 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol), THF (12 mL), CuI (0.015 g, 0.08 mmol), triethylamine (0.36 mL, 2.6 mmol), trimethoxyphenylacetylene **8** (0.461 g, 2.40 mmol), reaction time at room temperature: 23 h. The crude product was then purified by silica gel column chromatography (cyclohexane/ethyl acetate, 80:20) to afford compound **6c** (0.604 g, 67%) as an off-white solid; mp 121–123 °C. IR: ν_{max} (film, cm^{-1}) 2939, 1738, 1576, 1499, 1448, 1411, 1367, 1354, 1289, 1229, 1181, 1150, 1123, 1091, 1050, 995, 836, 819, 757, 731, 686, 631, 583, 566, 550. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.73 (s, 3H), 3.85 (s, 6H), 6.89 (s, 2H), 7.24 (d, J=0.6 Hz, 1H), 7.31–7.36 (m, 1H), 7.44–7.50 (m, 1H), 7.59–7.65 (m, 3H), 7.69–7.75 (m, 1H), 7.93 (d, J=1.5 Hz, 1H), 7.95 (d, J=1.5 Hz, 1H), 8.14–8.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 56.2 (CH_3), 61.0 (CH_3), 79.7 (C), 96.9 (C), 108.6 (CH), 109.6 (CH), 114.6 (CH), 116.8 (CH), 117.4 (C), 120.9 (C), 121.0 (CH), 124.0 (CH), 126.0 (CH), 126.9 (CH), 129.0 (C), 129.1 (CH), 133.9 (CH), 136.5 (C), 138.6 (C), 139.4 (C), 153.1 (C), 153.2 (C). HRMS (ESI$^+$): m/z calcd for $C_{25}H_{21}NO_5SNa$ [MNa^+]: 470.1033; found: 470.1012.

4.5.4. Preparation of 2-(3,4,5-trimethoxy-phenylethynyl)-1H-indole ***6d***. According to general procedure 2, scale: 2-iodo-1*H*-indole (0.437 g, 1.80 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol), THF (12 mL), CuI (0.015 g, 0.08 mmol), triethylamine (0.36 mL, 2.6 mmol), trimethoxyphenylacetylene **8** (0.461 g, 2.40 mmol), reaction time at room temperature: 5 h. The reaction mixture was filtered; the solid was washed with diethyl ether (2×10 mL). The combined organic layers were concentrated in vacuo. The crude brown oil was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate, 70:30) to afford **6d** (0.216 g, 39%) as a pale orange solid; mp 175–177 °C. IR: ν_{max} (film, cm^{-1}) 3328, 2933, 1736, 1575, 1498, 1458, 1430, 1409, 1362, 1344, 1327, 1234, 1184, 1169, 1128, 1004, 992, 938, 841, 828, 801, 790, 769, 749, 739, 732, 655, 626, 610, 574, 555, 526. ^{1}H NMR (400 MHz, DMSO): δ=3.71 (s, 3H), 3.82 (s, 6H), 6.80 (d, J=2 Hz, 1H), 6.88 (s, 2H), 7.04 (1H, t, J=7.6, Hz), 7.17 (t, J=7.6 Hz, 1H), 7.34 (d, J=8.4 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 11.68 (br s, 1H). ^{13}C NMR (100 MHz, DMSO): δ=56.0 (CH_3), 60.1 (CH_3), 81.7 (C), 91.9 (C), 107.4 (CH), 108.5 (CH), 111.2 (CH), 116.9 (C), 118.1 (C), 119.7 (CH), 120.3 (CH), 122.8 (CH), 127.2 (C), 136.4 (C), 138.55 (C), 153.0 (C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{18}NO_3$ [MH^+]: 308.1281; found: 308.1267.

4.5.5. Preparation of 2-(3,4,5-trimethoxy-phenylethynyl)-thiophene ***6e***. According to general procedure 2, scale: 2-iodothiophene (0.23 mL, 2.2 mmol), $PdCl_2(PPh_3)_2$ (0.031 g, 0.044 mmol), THF (12 mL), CuI (0.017 g, 0.09 mmol), triethylamine (0.40 mL, 2.8 mmol), trimethoxyphenylacetylene **8** (0.508 g, 2.64 mmol), reaction time at room temperature: 5 h. The crude product was then purified by silica gel column chromatography (cyclohexane/ethyl acetate, 80:20) to afford **6e** (0.477 g, 79%) as a brown solid; mp 79–81 °C (lit.[32] 80–81 °C). IR: ν_{max} (film, cm^{-1}) 3100, 2933, 2832, 1572, 1522, 1498, 1461, 1407, 1364, 1329, 1231, 1204, 1180, 1128, 995, 951, 851, 834, 816, 778, 737, 720, 685, 623, 590, 523, 506. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.80 (s, 9H), 6.75 (s, 2H), 7.01 (dd, J=4.8–3.6 Hz), 7.27–7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1 (CH_3), 60.9 (CH_3), 81.7 (C), 93.0 (C), 108.5 (CH), 117.8 (C), 123.1 (C), 127.1 (CH), 127.2 (CH), 131.8 (CH), 138.9 (C), 153.1 (C). HRMS (ESI$^+$): m/z calcd for $C_{15}H_{15}O_3S$ [MH^+]: 275.0736; found: 275.0736.

4.5.6. Preparation of 5-methoxy-2-(3,4,5-trimethoxy-phenylethynyl)-benzo[b]thiophene ***6f***. According to general procedure 2, scale: 5-methoxy-2-bromobenzo[*b*]thiophene (0.163 g, 0.67 mmol), $PdCl_2(PPh_3)_2$ (0.009 g, 0.013 mmol), THF (5 mL), CuI (0.005 g, 0.03 mmol), triethylamine (0.12 mL, 0.87 mmol), trimethoxyphenylacetylene **8** (0.154 g, 0.80 mmol), reaction time at room temperature: 18 h. The crude product was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate, 85:15) to afford compound **6f** (0.072 g, 30%) as a yellow solid and homocoupling diacetylenic product 1,4-bis(3,4,5-trimethoxyphenyl) buta-1,3-diyne (0.023 g, 19%) as a yellow solid.

Less polar fraction: compound **6f**; mp 105–106 °C. IR: ν_{max} (film, cm^{-1}) 2993, 2928, 2843, 1728, 1599, 1573, 1499, 1448, 1407, 1344, 1299, 1233, 1223, 1154, 1131, 1098, 1069, 1026, 995, 943, 855, 824, 794, 777, 698, 624, 537. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.86 (s, 3H), 3.88 (s, 9H), 6.79 (s, 2H), 7.02 (dd, J=6.6–1.8 Hz, 1H), 7.20 (d, J=1.8 Hz, 1H), 7.41 (s, 1H), 7.63 (d, J=6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.5 (CH_3), 56.1 (CH_3), 61.0 (CH_3), 82.2 (C), 94.8 (C), 105.5 (CH), 108.7 (CH), 115.9 (CH), 117.5 (C), 122.6 (CH), 124.2 (C), 128.3 (CH), 132.6 (C), 139.2 (C), 140.1 (C), 153.1 (C), 157.8 (C). HRMS (ESI$^+$): m/z calcd for $C_{20}H_{19}O_4S$ [MH^+]: 355.0999; found: 355.0981.

More polar fraction: 1,4-bis(3,4,5-trimethoxyphenyl)buta-1,3-diyne; mp 199–201 °C (lit.[46] 199–201 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.86 (s, 12H), 3.87 (s, 6H), 6.76 (s, 4H). Spectral data were in agreement to those reported in the literature.[46]

4.5.7. 5-Nitro-2-(3,4,5-trimethoxy-phenylethynyl)-benzo[b]thiophene ***6g***. According to general procedure 2, scale: 5-nitro-2-bromobenzo[*b*]thiophene (0.152 g, 0.41 mmol), $PdCl_2(PPh_3)_2$ (0.006 g, 0.008 mmol), THF (2.5 mL), CuI (0.003 g, 0.016 mmol), triethylamine (0.074 mL, 0.53 mmol), trimethoxyphenylacetylene **8** (0.095 g, 0.49 mmol), reaction time at room temperature: 23 h. The crude product was purified by silica gel flash column chromatography (cyclohexane/ethyl acetate, 85:15) to afford compound **6g** (0.099 g, 66%) as a pale orange solid; mp 164–166 °C. IR: ν_{max} (film, cm^{-1}) 2928, 2200, 1731, 1576, 1510, 1468, 1435, 1412, 1343, 1246, 1177, 1124, 1098, 1062, 1038, 995, 946, 889, 839, 825, 806, 775, 736, 691, 626, 578, 527, 499. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.89 (s, 3H), 3.90 (s, 6H), 6.80 (s, 2H), 7.60 (s, 1H), 7.89 (d, J=9 Hz, 1H), 8.22 (dd, J=9–2.4 Hz, 1H), 8.64 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.2 (CH_3), 60.1 (CH_3), 80.8 (C), 97.4 (C), 108.9 (CH), 116.7 (C), 119.1 (CH), 119.5 (CH), 122.5 (CH), 127.1 (C), 128.5 (CH), 138.9 (C),

139.7 (C), 145.7 (C), 145.8 (C), 153.2 (C). HRMS (ESI^+): *m*/*z* calcd for $C_{19}H_{16}NO_5S$ [MH^+]: 370.0744; found: 370.0737.

4.6. Preparation of compounds 1 by using hydrosilylation/deprotection sequence

4.6.1. General procedure 3 for the synthesis of vinylsilane derivatives: preparation of [2-benzofuran-2-yl-1-(3,4,5-trimethoxy-phenyl)-vinyl]-triethylsilane ***12a****.* In a 3 mL tube, PtO_2 (0.011 g, 0.05 mmol) and 2-((3,4,5-trimethoxyphenyl)ethynyl)benzofuran **6a** (0.299 g, 0.97 mmol) were placed under argon atmosphere. Triethylsilane (0.47 mL, 2.92 mmol) was slowly introduced, the tube was sealed and the mixture was stirred at 60 °C in an oil bath for 23 h. After removal of the volatiles under reduced pressure, the crude product was purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to afford compound **12a** (0.392 g, 95%), which is an inseparable mixture of α and β isomers (α/β ratio 79:21), as a light yellow solid.

Only the major product will be described. IR: ν_{max} (film, cm^{-1}) 2951, 2932, 2873, 1738, 1580, 1503, 1450, 1414, 1329, 1234, 1163, 1125, 1104, 1002, 958, 950, 911, 898, 826, 792, 750, 736, 719, 708, 678, 662, 649, 591, 528. ^1H NMR (400 MHz, $CDCl_3$): δ=0.77 (q, *J*=8 Hz, 6H), 1.00 (t, *J*=7.8 Hz, 9H), 3.47 (s, 6H), 3.79 (s, 3H), 6.33 (s, 2H), 6.43 (s, 1H), 6.89 (s, 1H), 7.18–7.21 (m, 2H), 7.40–7.43 (m, 1H), 7.48–7.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=3.0 (CH_2), 7.3 (CH_3), 55.5 (CH_3), 60.8 (CH_3), 103.0 (CH), 106.1 (CH), 110.9 (CH), 120.3 (CH), 122.6 (CH), 123.4 (CH), 129.2 (C), 130.5 (C), 132.4 (C), 137.9 (C), 144.2 (CH), 152.7 (C), 154.3 (C), 156.7 (C). HRMS (ESI^+): *m*/*z* calcd for $C_{25}H_{33}O_4Si$ [MH^+]: 425.2143; found: 425.2141.

4.6.2. Preparation of [2-benzofuran-2-yl-1-(3,4,5-trimethoxy-phenyl)-vinyl]-ethoxydimethylsilane ***12a′****.* According to general procedure 3, scale: 2-((3,4,5-trimethoxyphenyl)ethynyl)benzofuran **6a** (0.299 g, 0.97 mmol), PtO_2 (0.011 g, 0.05 mmol), $Me_2EtOSiH$ (0.40 mL, 2.92 mmol), reaction time at 60 °C: 23 h. The crude product was then purified by column chromatography (cyclohexane/ethyl acetate, 85:15) to afford compound **12a′** (0.288 g, 72%, α/β ratio 54:46) as a yellow oil. In NMR analysis, determination of peaks corresponding to each regioisomer relied on peak intensity (major product: Ar-1 and minor product: Ar-2).

IR: ν_{max} (film, cm^{-1}) 2969, 2937, 1581, 1505, 1464, 1452, 1417, 1330, 1254, 1184, 1169, 1127, 1105, 1078, 1009, 950, 903, 873, 821, 786, 751, 742, 646, 612. ^1H NMR (400 MHz, $CDCl_3$): δ=0.146 (s, 6H, Ar-2), 0.28 (s, 6H, Ar-1), 1.06 (t, *J*=6.8 Hz, 3H, Ar-2), 1.16 (t, *J*=7.2 Hz, 1H, Ar-1), 3.44 (s, 6H, Ar-1), 3.53–3.58 (m, 2H, Ar-2), 3.68–3.74 (m, 5H, Ar-1), 3.80 (s, 3H, Ar-2), 3.81 (s, 6H, Ar-2), 6.25 (s, 1H, Ar-2), 6.33 (s, 2H, Ar-1), 6.49 (s, 1H, Ar-1), 6.63 (s, 2H, Ar-2), 6.75 (s, 1H, Ar-2), 6.96 (s, 1H, Ar-1), 7.08–7.19 (m, 4H, Ar-1 and Ar-2), 7.30–7.31 (m, 1H, Ar-1), 7.36 (d, *J*=6 Hz, 1H, Ar-2), 7.40–7.42 (m, 1H, Ar-1), 7.45–7.47 (m, 1H, Ar-2).

Major product: ^{13}C NMR (100 MHz, $CDCl_3$): δ=−1.9 (CH_3), 18.4 (CH_3), 55.6 (CH_3), 58.8 (CH_2), 60.8 (CH_3), 104.2 (CH), 106.3 (CH), 110.9 (CH), 120.4 (CH), 122.7 (CH), 123.7 (CH), 129.1 (C), 130.6 (C), 132.3 (C), 138.1 (C), 143.7 (CH), 152.7 (C), 153.7 (C), 154.3 (C).

Minor product: ^{13}C NMR (100 MHz, $CDCl_3$): δ=0.3 (CH_3), 18.2 (CH_3), 56.1 (CH_3), 58.5 (CH_2), 61.0 (CH_3), 103.9 (CH), 106.3 (CH), 110.7 (CH), 120.6 (CH), 122.6 (CH), 124.0 (CH), 129.3 (C), 130.6 (C), 134.1 (C), 138.0 (C), 145.8 (CH), 152.7 (C), 154.2 (C), 155.6 (C).

HRMS (ESI^+): $C_{21}H_{24}O_5Si$: *m*/*z* calcd for $C_{21}H_{25}O_5Si$ [(M−Et)H^+]: 385.1466; found: 385.1445.

4.6.3. Preparation of [2-benzo[b]thiophen-2-yl-1-(3,4,5-trimethoxy-phenyl)-vinyl]-triethylsilane ***12b****.* According to general procedure 3, scale: 2-((3,4,5-trimethoxyphenyl)ethynyl)benzo[*b*]thiophene **6b** (0.324 g, 1.00 mmol), PtO_2 (0.011 g, 0.05 mmol), Et_3SiH (0.48 mL, 3.00 mmol), reaction time at 60 °C=5.5 h. The crude product was then purified by column chromatography (cyclohexane/ethyl acetate, 90:10) to afford compound **12b** (0.404 g, 92%, α/β ratio 18:82) as a light yellow solid. Only the major product will be described. IR: ν_{max} (film, cm^{-1}) 2919, 2908, 2871, 1572, 1501, 1454, 1431, 1327, 1234, 1184, 1151, 1119, 1066, 1038, 1001, 977, 958, 915, 886, 826, 783, 743, 734, 725, 717, 698, 635, 594, 515. ^1H NMR (300 MHz, $CDCl_3$): δ=0.74 (q, *J*=8.4 Hz, 6H), 1.01 (t, *J*=7.8 Hz, 9H), 3.42 (s, 6H), 3.76 (s, 3H), 6.42 (s, 2H), 6.80 (s, 1H), 6.90 (s, 1H), 7.18–7.24 (m, 1H), 7.27–7.32 (m, 1H), 7.67 (d, *J*=7.5 Hz, 1H), 7.75 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=2.6 (CH_2), 7.4 (CH_3), 55.4 (CH_3), 60.8 (CH_3), 106.7 (CH), 119.7 (CH), 122.0 (CH), 122.7 (CH), 123.4 (CH), 124.1 (CH), 135.5 (C), 137.6 (C), 140.0 (C), 140.7 (C), 142.5 (CH), 145.2 (C), 152.5 (C), 153.7 (C). HRMS (ESI^+): *m*/*z* calcd for $C_{25}H_{33}O_3SSi$ [MH^+]: 441.1914; found: 441.1923.

4.6.4. Preparation of 2-[2-triethylsilanyl-2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-indole ***12d****.* According to general procedure 3, scale: 2-((3,4,5-trimethoxyphenyl)ethynyl)-1*H*-indole **6d** (0.079 g, 0.26 mmol), PtO_2 (0.003 g, 0.013 mmol), Et_3SiH (0.125 mL, 0.78 mmol), reaction time at 60 °C=4 h. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 85:15) to afford α- or β-(*Z*)-2-(triethylsilanyl-2-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole **12d** as a light yellow solid (0.086 g, 78%); IR: ν_{max} (film, cm^{-1}) 3360, 2922, 2871, 2851, 1737, 1581, 1505, 1454, 1412, 1331, 1321, 1279, 1247, 1233, 1187, 1128, 1006, 974, 960, 926, 908, 896, 823, 780, 725, 696, 680, 647, 610, 574. ^1H NMR (300 MHz, $CDCl_3$): δ=0.75 (q, *J*=6.2 Hz, 6H), 1.00 (t, *J*=7.8 Hz, 9H), 3.37 (s, 6H), 3.77 (s, 3H), 6.19 (s, 2H), 6.32–6.33 (m, 1H), 6.80 (s, 1H), 7.02–7.12 (m, 2H), 7.21–7.24 (m, 1H), 7.53–7.56 (m, 1H), 7.68 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=5.8 (CH_2), 6.6 (CH_3), 55.5 (CH_3), 60.8 (CH_3), 100.1 (CH), 106.2 (CH), 110.5 (CH), 119.7 (CH), 119.8 (CH), 121.3 (CH), 129.3 (C), 132.3 (C), 133.5 (C), 135.8 (C), 137.6 (C), 141.9 (CH), 152.7 (2C). HRMS (ESI^+): *m*/*z* calcd for $C_{25}H_{34}NO_3Si$ [MH^+]: 424.2302; found: 424.2287.

4.6.5. General procedure 4 for the hydrolysis of vinylsilane derivatives: preparation of 2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzofuran ***1a****.* To a TBAF 1 M solution in THF (0.55 mL, 0.55 mmol) was added compound **12a** (0.213 g, 0.5 mmol). The resulting mixture was stirred at 60 °C for 1 h. After concentration in vacuo, the crude product containing 62% (*Z*) and 38% (*E*) isomer was purified by column chromatography (cyclohexane/ethyl acetate, 80:20) to obtain the *Z*/*E* mixture of **1a** (0.132 g, 84%) (both stereoisomers were collected in a single fraction) as a yellow viscous oil.

4.6.6. Preparation of 2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-benzo[b]thiophene ***1b****.* According to general procedure 4, scale: TBAF 1 M solution in THF (0.84 mL, 0.84 mmol), compound **12b** (0.334 g, 0.76 mmol), reaction time at 60 °C=2.5 h. The crude product was then purified by flash chromatography (cyclohexane/ethyl acetate, 80:20) to give (*Z*)-2-(3,4,5-trimethoxystyryl)benzo[*b*]thiophene **1b** (0.058 g, 23%) as a light yellow oil and (*E*)-2-(3,4,5-trimethoxystyryl)benzo[*b*]thiophene **1b** (0.175 g, 71%) as a light yellow solid.

4.6.7. Preparation of (Z)-2-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-1H-indole ***1d****.* According to general procedure 4, scale: TBAF 1 M solution in THF (0.19 mL, 0.19 mmol), (*Z*)-2-(triethylsilyl-2-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole **12d** (0.074 g, 0.18 mmol), reaction time at 60 °C=2.5 h. The crude product was purified by column chromatography (cyclohexane/ethyl acetate, 80:20) to afford (*Z*)-2-(2-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole **1d** (0.043 g, 80%) as a light yellow solid.

Stereoisomer (*Z*). Mp 97–99 °C. IR: ν_{max} (film, cm^{-1}) 3333, 2933, 1738, 1583, 1501, 1443, 1428, 1396, 1330, 1294, 1231, 1177, 1126, 992, 958, 854, 801, 782, 764, 748, 692, 618, 601, 576, 528, 596. ^1H NMR

(400 MHz, DMSO): δ=3.65 (s, 6H), 3.69 (s, 3H), 6.48 (d, J=1.2 Hz, 1H), 6.52 (d, J=12.8 Hz, 1H), 6.55 (d, J=12.4 Hz, 1H) (coalescence of these last two peaks), 6.79 (s, 2H), 6.93 (t, J=7.4 Hz, 1H), 7.04 (t, J=7.4 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.44 (d, J=8 Hz, 1H), 10.97 (s, br, 1H). ^{13}C NMR (100 MHz, DMSO): δ=55.6 (CH_3), 60.0 (CH_3), 101.6 (CH), 105.7 (CH), 111.0 (CH), 119.1 (CH), 119.8 (CH), 119.9 (CH), 121.5 (CH), 127.9 (C), 129.6 (CH), 132.2 (C), 134.2 (C), 135.9 (C), 137.0 (C), 152.6 (C). HRMS (ESI$^+$): m/z calcd for $C_{19}H_{20}NO_3$ [MH$^+$]: 310.1438; found: 310.1427.

*4.6.7.1. Alternative method by basic deprotection of the Boc-protected derivative **1c**.* A solution of (*Z*)-1-(*tert*-butoxycarbonyl)-2-(3,4,5-trimethoxystyryl)-1*H*-indole (0.065 g, 0.16 mmol) and K_2CO_3 (0.066 g, 0.48 mmol) in MeOH (1.5 mL) and water (0.5 mL) was stirred at room temperature for 22 h then at 60 °C for 24 h. The solvent was evaporated. The residue was quenched with water and extracted with ethyl acetate. The organic phases were combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (cyclohexane/ethyl acetate, 80:20) to afford (*Z*)-2-(2-(3,4,5-trimethoxyphényl)vinyl)-1*H*-indole (0.014 g, 28%) as a light yellow solid. ^{1}H NMR spectrum was identical to the one described above.

4.7. Preparation of compounds 1 after semi-hydrogenation reaction

*4.7.1. General procedure 5 for the semi-hydrogenation of diarylacetylene derivatives **6** using palladium acetate/DMF/KOH system: preparation of compound **1a**.* In a reactor flushed with argon was introduced 2-((3,4,5-trimethoxyphenyl)ethynyl)benzofuran **6a** (0.308 g, 1 mmol), KOH (0.084 mg, 1.5 mmol), $Pd(OAc)_2$ (0.0045 mg, 0.02 mmol) and then DMF (2.5 mL). The tube was sealed and heated at 145 °C under stirring for 6 h, then cooled to room temperature and quenched with 10 mL of water. The mixture was extracted with EtOAc (3×30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product containing 93% of (*Z*)- and 7% of (*E*)-2-(2-(3,4,5-trimethoxyphenyl) vinyl)benzofuran **1a** was purified by column chromatography (cyclohexane/ethyl acetate, 80:20) to give (*Z*) isomer as a yellow oil (0.180 g, 58%) and a mixture of (*Z*) and (*E*) isomer (0.106 g, 34%). This second fraction was further purified by flash chromatography to give stereopure (*Z*)-**1a** (0.025 g, 8%) and a mixture (0.074 g, 24%) of *Z*/*E* isomers.

*4.7.2. Preparation of compound **1b**.* According to general procedure 5, scale: 2-((3,4,5-trimethoxyphenyl)ethynyl)benzo[*b*]thiophene **6b** (0.162 g, 0.5 mmol), KOH (0.042 g, 0.75 mmol), $Pd(OAc)_2$ (0.002 g, 0.01 mmol), DMF (1.25 mL), reaction time at 145 °C=6 h. The crude product (*Z*/*E*=91/9) was purified by column chromatography on silica gel deactivated by Et_3N (cyclohexane/ethyl acetate, 90:10) to give (*Z*)-2-(2-(3,4,5-trimethoxyphenyl)vinyl)benzo [*b*]thiophene **1b** (0.103 g, 63%) as a yellow oil and a mixture of *Z* and *E* isomer (0.018 g, 11%).

*4.7.3. Preparation of compound **1f**.* According to general procedure 5, scale: 5-methoxy-2-((3,4,5-trimethoxyphenyl)ethynyl)benzo[*b*] thiophene **6f** (0.044 g, 0.124 mmol), KOH (0.011 g, 0.187 mmol), $Pd(OAc)_2$ (0.0006 g, 0.0025 mmol), DMF (0.2 mL), reaction time at 145 °C=6 h. The crude product (*Z*/*E*=100/0) was purified by column chromatography on silica gel deactivated by Et_3N (cyclohexane/ethyl acetate, 85:15) to give (*Z*)-5-methoxy-2-[2-(3,4,5-trimethoxyphenyl)-vinyl]-benzo[*b*]thiophene **1f** (0.018 g, 40%) as a very viscous yellow oil. IR: ν_{max} (film, cm^{-1}) 2997, 2934, 2832, 1726, 1597, 1577, 1501, 1452, 1411, 1384, 1327, 1300, 1235, 1214, 1182, 1160, 1123, 1070, 1025, 1005, 965, 946, 854, 805, 772, 718, 690, 621, 548, 460. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.79 (s, 6H), 3.84 (s, 3H), 3.90 (s, 3H), 6.63 (d, J=12.0 Hz, 1H), 6.64 (s, 2H), 6.73 (d, J=12.0 Hz, 1H), 6.91 (dd, J=8.7–2.4 Hz, 1H), 7.11 (d, J=2.4 Hz, 1H), 7.17 (s, 1H), 7.53 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.5 (CH_3), 56.0 (CH_3), 61.0 (CH_3), 150.2 (CH), 105.9 (CH), 114.9 (CH), 122.7 (CH), 123.7 (CH), 125.1 (CH), 130.8 (CH), 132.0 (C), 132.5 (C), 137.7 (C), 139.9 (C), 141.0 (C), 153.2 (C), 157.4 (C). HRMS (ESI$^+$): m/z calcd for $C_{20}H_{21}O_4S$ [MH$^+$]: 357; 1155; found: 357.1143.

*4.7.4. Palladium acetate/DMF/KOH semi-hydrogenation of diarylacetylene derivatives **6b**: kinetic studies.* In a Schlenk tube were introduced 2-((3,4,5-trimethoxyphenyl)ethynyl)benzo[*b*]thiophene **6b** (0.324 g, 1.0 mmol), KOH (0.84 g, 1.5 mmol) and $Pd(OAc)_2$ (0.0045 g, 0.02 mmol). The Schlenk tube was put under high vacuum for 2 min and then filled with argon. After four cycles of vacuum/argon, the tube was put under argon and DMF (2.5 mL) was added. The resulting mixture was heated at 145 °C and 50 μL aliquots of the reaction mixture were taken at different heating time: 5 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h and 6 h.

In a test tube, to 25 μL of the aliquot were added NH_4Cl aqueous saturated solution (25 μL), acetonitrile (750 μL) and 0.30 g of Na_2SO_4. The resulting mixture was then submitted to a vortex stirrer for 30 s. After filtration through a 0.2 μM PTFE syringe filter, 200 μL of water was added to 300 μL of the filtrate. To 50 μL of this solution was then added 50 μL of resveratrol trimethyl ether solution (1 mg/mL) in water/acetonitrile, 40/60 v/v. 0.1 μL of this final sample was then injected in an uHPLC/MS system, with isocratic elution (solvent mixture: water/acetonitrile 40/60 v/v, HCOOH 0.1% v/v) at 40 °C, flow rate 0.5 mL/min, Single Ion Monitoring detection at m/z=271.1, 327.1 and 325.1 (MH$^+$ ions of the internal standard, (*Z*/*E*) products **1b** and starting material **6b**, respectively). Retention times: resveratrol trimethyl ether 1.74 min, (*Z*)-**1b** 2.10 min, (*E*)-**1b** 2.49 min and **6b** 3.06 min.

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