Regioselective hydrostannation of diarylalkynes directed by a labile ortho bromine atom: An easy access to stereodefined triarylolefins, hybrids of combretastatin A-4 and isocombretastatin A-4

Evelia Rasolofonjatovo, Olivier Provot, Abdallah Hamze, Jérôme Bignon, Sylviane Thoret, Jean-Daniel Brion, Mouad Alami

► To cite this version:

Evelia Rasolofonjatovo, Olivier Provot, Abdallah Hamze, Jérôme Bignon, Sylviane Thoret, et al.. Regioselective hydrostannation of diarylalkynes directed by a labile ortho bromine atom: An easy access to stereodefined triarylolefins, hybrids of combretastatin A-4 and isocombretastatin A-4. European Journal of Medicinal Chemistry, 2010, 45 (9), pp.3617-3626. 10.1016/j.ejmech.2010.05.007 . hal-02394481

HAL Id: hal-02394481

<https://hal.science/hal-02394481>

Submitted on 4 Dec 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Regioselective Hydrostannation of Diarylalkynes Directed by a Labile *ortho* Bromine Atom: An Easy Access to Stereodefined Triarylolefins, Hybrids of Combretastatin A-4 and *iso*Combretastatin A-4

Evelia Rasolofonjatovo,^a Olivier Provot,^a Abdallah Hamze,^a Jérôme Bignon,^b Sylviane Thoret,^b Jean-Daniel Brion,^a Mouâd Alami^{a*}

^a University Paris-Sud, CNRS, BioCIS-UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 5 rue J.-B. Clément, Châtenay-Malabry, F-92296, France

^b Institut de Chimie des Substances Naturelles, UPR 2301, CNRS avenue de la terrasse, F-91198 Gif sur Yvette, France

(Dedicated to our colleague Pr. Claude Combet-Farnoux)

Abstract

A series of triarylolefins bearing the combretastatin A-4 and the *isocombretastatin* A-4 cores were synthesized and evaluated. The cooperative *ortho*-effect of a labile bromine atom in the regioselective hydrostannation of unsymmetrical diarylalkynes leading to stereo-defined triarylolefins is presented.

Keywords: Palladium, Alkyne; *Ortho*-Directing Effect; Hydrostannation; Olefin; Combretastatin

1. Introduction

The microtubule system of eukaryotic cells is an important target for the development of anticancer agents. Consequently, perturbation of normal tubulin assembly/disassembly is a popular target for new chemotherapeutic agents[1,2] Examples of clinically used antimitotic agents are paclitaxel, which promoted microtubules polymerization and inhibits microtubules depolymerization, and vincristine which inhibits microtubules assembly.[3,4] However, despite their potent antitumor activities, these drugs have undesirable side effects[5,6] and are subject to multidrug resistance.[7,8]

In recent years, there has been more and more interest in the search of antitumor molecules of easy synthesis, with high efficacy and low side effects. Combretastatin A-4 (CA-4), a naturally occurring stilbene, extracted from the South African willow *Combretum caffrum*[9,10] is the most studied substance as a highly potent inhibitor of tubulin assembly.[11-13] Moreover, CA-4 displays strong cytotoxicities (nanomolar level) against a large panel of human cancer cells, including multi-drug-resistant cell lines.[14,15] Additionally, CA-4P[16-19] the water-soluble prodrug of CA-4, as well as AC-7739 and its amino acid derivative AVE-8062[20] have been demonstrated to cause a rapid and selective vascular shutdown in established tumors *in vivo*, consistent with an antivascular mechanism of action.[21-27] Currently, CA-4P[28] either as a single agent or in combination therapy is undergoing several advanced clinical trials worldwide for the treatment of age-related macular degeneration or anaplastic thyroid cancer.

FIGURE 1

Despite their remarkable anticancer activity, these *Z*-stilbene compounds are prone to double bond isomerization during storage and administration. The *E*-isomers display dramatically reduced inhibition of cancer cell growth and tubulin assembly.[29] In our efforts to discover novel tubulin assembly inhibitors,[30-32] we recently found that *isocombretastatin* A-4 (*iso*CA-4), the third and “forgotten” structural isomer of the natural product, displayed biological activities comparable to that of CA-4.[33,34] This substance having a 1,1-diarylethylene scaffold is easy to synthesize[35,36] at a multi grams scale without the need to control the olefin geometry. By structural modifications on the B ring, we have also identified other promising antiproliferative agents such as *iso*FCA-4 and *iso*NH₂CA-4 (Figure 1).[37] In addition, these apoptosis inductors substances were found to inhibit microtubules formation and to induce cell cycle arrest in G2/M phase. To combine the anticancer effects of CA-4 and *iso*CA-4 within a single substance (e.g.; **1h**), we have synthesized a variety of hybrids **1** that bear, from one hand, the basic skeleton of CA-4 and, on the other hand, the one of *iso*CA-4 (Figure 1). Moreover, these compounds **1** may be regarded as Tamoxifen[38] or trisubstituted Combretastatin analogues of high antiproliferative activity.[39-41] The potencies of newly synthesized trisubstituted olefins **1** were evaluated for their capacity to inhibit cancer cellular growth and, to act as potential antimitotic agents.

2. Results and discussion

The strategy envisioned to prepare the target triarylolefins **1** involves a three step-sequence by achieving a regioselective hydrostannation of diarylalkynes (Scheme 1). Further direct Stille reaction or sequential iodolysis-Negishi coupling would provide **1**.

SCHEME 1

At the outset of this work, the synthesis of triarylolefin **1a** (Scheme 2) was first examined from symmetrically diarylalkyne **2** easily available by Sonogashira-Linstrumelle coupling reaction.[42,43] Palladium-catalyzed hydrostannation of **2** was achieved using Bu₃SnH (1.2 eq) in THF at room temperature in the presence of PdCl₂(PPh₃)₂ (1 mol%) to give vinylstannane **3** in good yield (79%).[44-47] Subsequent direct coupling of **3** with 3,4,5-trimethoxyiodobenzene under modified Stille conditions[48] provided a moderate 54% isolated yield of **1a**. In order to increase the overall yield of **1a**, we next evaluated a halodestannylation[49]-Negishi coupling sequence.[50,51] Iododestannylation of **3** with molecular iodine in CH₂Cl₂ at room temperature furnished cleanly and rapidly the desired electrophilic species **4**, which upon reaction with 3,4,5-trimethoxyphenylzinc chloride in the presence of a catalytic amount of PdCl₂(PPh₃)₂ (5 mol%) provided the target olefin **1a** in a quantitative yield. This result clearly indicated that the two steps iododestannylation-Negishi sequence was more efficient than the direct Stille coupling of **3**.

SCHEME 2

According to this two steps sequence (iodolysis/Negishi coupling) depicted in Scheme 2, the synthesis of other targets triarylolefins **1b-h** was envisioned from the hydrostannation of unsymmetrical diarylalkynes. In previous studies, we have reported that in the case of *ortho* substituted diarylalkynes, the *ortho* substituent, regardless of its electronic nature, directed the tributyltin addition to afford a single α -vinylstannane. We opted to use this *ortho*-directing effect (ODE)[52,53] concept to prepare the hybrids **1b-h** according to the retrosynthetic pathway depicted in Scheme 3. To control the regioselectivity of the hydrostannation reaction, we needed first to prepare diarylalkynes **5** bearing an *ortho* substituent able to exclusively directed the H-Sn bond addition across the triple bond, and therefore to provide a single vinyl stannane. To this end we have choosen as *ortho*-directing group (*o*DG) a bromine atom, as this substituent would be easy to introduce but also easy to remove at the end of the synthesis by metal-halogen exchange reaction followed by hydrolysis.

SCHEME 3

Diarylalkynes **5a-d** bearing an *ortho* bromine atom were prepared according to Scheme 4. **5a** was synthesized from terminal alkyne **6a** by Sonogashira-Linstrumelle (S-L) coupling with 3-bromo-4-iodoanisole, readily obtained by regioselective iodination of 3-bromoanisole (94%). For the preparation of diarylalkynes **5b-d**, the synthetic route involves the bromination of 3,4,5-trimethoxy-iodobenzene with molecular Br₂ or MPHT[54] to provide **7** followed by sequential S-L coupling reactions.

SCHEME 4

The palladium-catalyzed hydrostannation reaction was next applied to *ortho* substituted diarylalkynes **5a-d** (Scheme 5). As expected, a total regiochemical control was achieved by the presence of *ortho* bromine atom substituent. The reaction provide exclusively α -vinylstannanes **8a-d** where the Bu₃Sn group is proximal to the *ortho* substituted aryl nucleus.

SCHEME 5

Further iodolysis of **8a-d** was achieved as described for **3** and vinyl iodides **9a-d** were isolated in excellent yields (70-99%) as pure (*E*)-isomers. For the Negishi cross coupling reaction, organozinc species were generated by transmetallation from Grignard reagents at 0 °C using ZnCl₂ except for the synthesis of **10f**.

In this case, the organozinc species was generated after lithiation of 2-fluoro-4-iodoanisole followed by transmetalation with ZnCl₂ as above. As shown in Scheme 5, all organozinc reagents were successfully coupled with the vinyl iodides **9a-d** in good yields (50-99%). Finally, removal of the *ortho*-bromo directing group was achieved by halogen-metal exchange reaction using *n*-butyllithium followed by quenching with aqueous HCl. Subsequent MOM- or TBDMS-ether cleavage furnished the expected triarylolefins **1b-h** as pure isomers.

The cytotoxic activity of 12 newly synthesized triaryl olefins against human colon carcinoma cell-line (HCT-116) was firstly evaluated using *iso*CA-4[33] and CA-4[55] as reference compounds. The IC₅₀ values corresponding to the concentration of studied compounds leading to 50% decrease in HCT-116 cell growth are presented in Table 1.

Newly synthesized *ortho*-brominated analogues **10** were not cytotoxic. As it can be observed, most of the triarylolefins **1** retained a light cancer cell growth-inhibitory activity at a micromolar range. In particular, best inhibition results were obtained with hybrids **1e-h** bearing the greatest resemblance to CA-4 and *iso*CA-4. However, the cytotoxicities of these triarylolefins are not comparable with those of CA-4 and *iso*CA-4, even though all derivatives of type **1** carry a CA-4 and a *iso*CA-4 (for **1h**) moiety in their structure.

These trisubstituted olefinic combretastatin analogues were next evaluated as tubulin polymerization inhibitors. All samples were dissolved in DMSO, incubated at 37 °C for 10 min and at 0 °C for 5 min before evaluation of the tubulin assembly rate.

Triarylolefins were tested at different concentrations and the IC₅₀ was calculated only for compounds inhibiting tubulin assembly by more than 50% at 9.0 x 10⁻⁶ M. The tubulin assembly assay was realized according to a slightly modified Guénard's protocol.[56] The tested analogues show a moderate potency (micromolar level) related to the references compounds CA-4 and *iso*CA-4. When comparing the inhibition of tubulin polymerization *versus* the cell growth inhibitory effect, we do not find a good correlation for most of the active compounds except for the hybrid **1h**. This hybrid most closely resembling CA-4 and *iso*CA-4 in structure displayed a potent anti-mitotic activity and a weak cytotoxicity.

TABLE 1

3. Conclusion

The aim of this work was to devise a synthetic strategy to prepare stereodefined triarylolefins **1** as CA-4 and *iso*CA-4 hybrids and to evaluate the influence of the double bond substitution on antitumor activity. From a chemical perspective, the “traceless use” of an *ortho* bromo substituent to regioselectively control the addition of tributyltin hydride on internal alkynes leading to stannylated stilbenes precursors of trisubstituted olefins **1** is notable. The new CA-4 and *iso*CA-4 analogues were evaluated for their cell growth inhibition and antitubulin activity. Some of these compounds showed interesting antitubulin activities (8 μM) but are less cytotoxic than CA-4 and *iso*CA-4, indicating that the nature of the olefin substitution in combretastatin series plays an important role on activity.

4. Experimental

4.1 General Considerations

Tetrahydrofuran (THF) and diethylether were distilled from sodium-benzophenone ketyl. Piperidine, and triethylamine were distilled from potassium hydroxide under argon prior to use. The compounds were all identified by usual physical methods, i.e. ^1H -NMR, ^{13}C -NMR, IR, MS and elemental analysis. ^1H and ^{13}C NMR spectra were measured in CDCl_3 with a Bruker Avance 300. ^1H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviation are used: m (multiplet), s (singlet), bs (broad singlet), d (doublet). ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a Perkin-Elmer 240 analyser. Mass spectra were obtained with a LCT Micromass spectrometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

3-Bromo-4-iodoanisole

A stirred solution of 3-bromoanisole (500 mg, 2.15 mmol), HgO (354 mg, 1.63 mmol), Ac_2O (0.1 mL) in CH_2Cl_2 (10 mL) was refluxed for 30 min. Then, I_2 (709 mg, 2.79 mmol) was added by 6 portions every 30 min. After refluxing for 12 h and filtration over a pad of celite, the filtrate was washed with a saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried with MgSO_4 and evaporated to dryness. Purification by flash chromatography (cyclohexane) afforded the titled compound

Yield: 94 %. TLC: Rf 0.68 (cyclohexane/ Et_2O : 95/5). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2933, 2831, 2361, 2183, 2013, 1579, 1556, 1463, 1436, 1384, 1285, 1260, 1225, 1182, 1093, 1034, 1001. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.68 (d, $J=8.8$ Hz, 1H), 7.19 (d, $J=2.8$ Hz, 1H), 6.59 (dd, $J=2.8$ Hz, $J=8.8$ Hz, 1H), 3.77 (s, 3H).

2-Bromo-1-iodo-3,4,5-trimethoxybenzene (7)

Br_2 (192 mg) was slowly added to a solution of 1-iodo-3,4,5-trimethoxybenzene (1.47 g; 5 mmol) in AcOH (10 mL) and the mixture was stirred over night. After neutralization with NaOH (1N), the reaction product was extracted with EtOAc (3 x 10 mL). The organic solutions were dried with MgSO_4 and evaporated to dryness. Purification by flash chromatography (cyclohexane/ EtOAc : 9/1) afforded the titled compound.

Yield: 92 %. TLC: Rf 0.68 (cyclohexane/ EtOAc : 8/2). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 2935, 1562, 1472, 1421, 1371, 1297, 1233, 1102, 1003. ^1H NMR (300 MHz, CDCl_3) δ ppm 7.26 (m, 1H), 7.19 (s, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H).

1-Ethynyl-3,4,5-trimethoxybenzene (6a)

To a stirred solution of iodo-3,4,5-trimethoxybenzene (10 mmol) in piperidine (15 mL) was added, CuI (190 mg, 1 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (351 mg, 0.5 mmol) and trimethylsilylacetylene (15 mmol). The stirred mixture was kept for a night at room temperature and was then treated with HCl 10 % (20 mL). After extraction with CH_2Cl_2 (3 x 15 mL), the organic layers were dried with MgSO_4 and evaporated to dryness. Next, the crude mixture was diluted in MeOH (15 mL) containing K_2CO_3 (15 mmol). After stirring for 1 h at room temperature, the black mixture was concentrated under vacuum and treated with a diluted HCl solution until $\text{pH} = 6$. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried with MgSO_4 and evaporated to dryness. Purification by flash chromatography afforded **6a**.

Yield: 82 %. TLC: Rf 0.47 (cyclohexane/ EtOAc : 8/2). IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$: 3242, 2989, 2939, 2023, 1967, 1576, 1501, 1450, 1427, 1410, 1329, 1232, 1180, 1125, 1034, 998, 955, 832, 773. ^1H NMR (300 MHz, CDCl_3) δ ppm 6.72 (s, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 3.02 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ ppm 153.1 (2C), 123.68, 117.05, 114.99, 109.35 (2C), 105.21, 83.73, 76.26, 60.99, 56.17 (2C). MS (APCI) m/z : 193.22 ($\text{M}+\text{H}$) $^+$.

Synthesis of 2-Bromo-1-ethynyl-3,4,5-trimethoxybenzene (6b)

To a stirred solution of **7** (10 mmol) in THF (15 mL) and Et_3N (15 mL) was added, CuI (190 mg, 1 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (351 mg, 0.5 mmol) and trimethylsilylacetylene (15 mmol). The stirred mixture was kept for a night at room temperature and was then treated

with HCl 10 % (20 mL). After extraction with CH₂Cl₂ (3 x 15 mL), the organic layers were dried with MgSO₄ and evaporated to dryness. Next, the crude mixture was diluted in MeOH (15 mL) containing K₂CO₃ (20 mmol). After stirring for 1 h at room temperature, the black mixture was concentrated under vacuum and treated with a diluted HCl solution until pH = 6. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were dried with MgSO₄ and evaporated to dryness. Purification by flash chromatography afforded **6b**.

Yield: 72%. TLC: R_f 0.17 (cyclohexane/EtOAc: 95/5). IR (neat) ν_{max} / cm⁻¹: 3291, 2938, 1555, 1477, 1424, 1383, 1336, 1241, 1195, 1166, 1105, 1041, 1004. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.73 (s, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.17 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 155.2, 152.6, 119.3, 112.9, 112.6, 80.9, 61.3, 61.0, 56.2 (two C missing).

Synthesis of internal alkynes 5

To a mixture of required aryl iodide (0.7 mmol), PdCl₂(PPh₃)₂ (0.1 mmol), CuI (0.15 mmol), TEA (10 mL) in THF (10 mL) was added dropwise under an argon atmosphere, a solution of **6a** or **6b** (1.0 mmol). The mixture was stirred at 60°C for a night. Then Et₂O (20 mL) was added to the crude and the mixture was filtered over a short pad of celite. The organic layer was washed with brine (5 mL) twice, separated, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography afforded internal alkynes **5a-d**.

5-(2-(2-Bromo-4-methoxyphenyl)ethynyl)-1,2,3-trimethoxybenzene (**5a**)

Yield: 80 %. Anal. calcd for **5a** (C₁₈H₁₇BrO₄): C, 57.31; H, 4.54. Found: C, 57.18; H, 4.39. TLC: R_f 0.14 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm⁻¹: 3751, 2935, 1601, 1572, 1506, 1457, 1437, 1409, 1351, 1287, 1268, 1221, 1182, 1123, 1027. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.45 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 6.83 (dd, *J* = 2.6 Hz, *J* = 8.7 Hz, 1H), 6.78 (s, 2H), 3.87 (s, 6H), 3.86 (s, 3H), 3.80 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.9, 153.2, 138.9, 133.9, 126.3, 118.3, 117.9, 117.5, 113.6, 108.8, 92.3, 87.1, 61.0, 56.2, 55.7. MS (APCI) *m/z*: 377.0 ((M+H)⁺, ⁷⁹Br), 379.0 ((M+H)⁺, ⁸¹Br).

2-Bromo-3,4,5-trimethoxy-1-(2-(4-methoxyphenyl) ethynyl)benzene (**5b**)

Yield: 86 %. Anal. calcd for **5b** (C₁₈H₁₇BrO₄): C, 57.31; H, 4.54. Found: C, 57.11; H, 4.35. TLC: R_f 0.30 (cyclohexane/Et₂O: 9/1). IR (neat) ν_{max} / cm⁻¹: 2936, 2218, 1736, 1604, 1578, 1551, 1511, 1477, 1462, 1427, 1383, 1358, 1295, 1250, 1174, 1098, 1030. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.51 (d, *J* = 8.3 Hz, 2H), 6.90 (s, 2H), 6.89 (d, *J* = 10.2 Hz, 2H), 3.90 (s, 6H), 3.87 (s, 3H), 3.83 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.9, 152.6, 151.3, 143.7, 133.2, 120.9, 115.1, 114.1, 112.6, 111.6, 93.2, 86.9, 61.3, 61.1, 56.3, 55.4. MS (APCI) *m/z*: 377.0 ((M+H)⁺, ⁷⁹Br), 379.0 ((M+H)⁺, ⁸¹Br).

(5-(2-(2-Bromo-3,4,5-trimethoxyphenyl)ethynyl)-2-methoxyphen-oxy)(tert-butyl)dimethylsilane (**5c**)

Yield: 66 %. TLC: R_f 0.35 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm⁻¹: 2931, 2855, 2211, 1566, 1508, 1477, 1443, 1413, 1384, 1360, 1288, 1257, 1233, 1189, 1151, 1132, 1107, 1043, 1023. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.00 (dd, *J* = 1.9 Hz, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 6.73 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 152.6, 151.9, 151.3, 144.8, 143.6, 125.9, 123.9, 120.8, 115.1, 112.6, 111.7, 111.5, 93.2, 86.5, 61.2, 60.9, 56.2, 55.4, 25.7 (3C), 18.5, -4.6 (2C). MS (APCI) *m/z*: 509.1 (M+H)⁺. Anal. calcd for **5c** (C₂₄H₃₁BrO₅Si): C, 56.80; H, 6.16. Found: C, 56.65; H, 6.05.

4-(2-(2-Bromo-3,4,5-trimethoxyphenyl)ethynyl)-1-methoxy-2-(methoxymethoxy)benzene (**5d**)

Yield: 80 %. Anal. calcd for **5d** (C₂₀H₂₁BrO₆): C, 54.93; H, 4.84. Found: C, 54.83; H, 4.80. TLC: R_f 0.20 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm⁻¹: 2942, 1556, 1514, 1478, 1421, 1382, 1364, 1317, 1246, 1198, 1151, 1131, 1104, 1074, 1047. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.28 (d, *J* = 1.9 Hz, 1H), 7.17 (dd, *J* = 2.3 Hz, *J* = 8.8 Hz, 1H), 6.84 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H), 3.80 (s, 3H), 3.47 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 152.6, 151.3, 150.5, 146.2, 143.7, 126.6, 120.7, 119.3, 115.3, 112.6, 111.7, 95.5, 93.0, 86.7, 61.3, 60.9, 56.3, 56.2, 55.9. MS (APCI) *m/z*: 437.28 ((M+H)⁺, ⁷⁹Br), 439.0 ((M+H)⁺, ⁸¹Br).

General Procedure for the hydrostannation of diarylalkynes.

Tributyltin hydride (12 mmol) was added dropwise at room temperature to a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.1 mmol) and alkyne (10 mmol) in THF (15 mL). The dark brown reaction mixture was stirred for 90 minutes. Then, the solution was concentrated *in vacuo*. Purification by flash chromatography on silica gel gave the desired products **3** and **8a-d**.

(*E*)-(1,2-bis(4-Methoxyphenyl)vinyl)tributylstannane (**3**).

Yield: 79 %. TLC: Rf 0.82 (cyclohexane/Et₂O: 95/5). IR (neat) ν_{max} / cm^{-1} : 2954, 2920, 2361, 2162, 1965, 1604, 1503, 1462, 1376, 1279, 1242, 1173, 1106, 1071, 1038. ¹H NMR (300 MHz, CDCl₃) δ 6.87 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 6.48 (s, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 1.45-1.35 (m, 6H), 1.29-1.15 (m, 6H), 0.92-0.76 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ 158.1, 157.2, 146.8, 138.1, 137.8, 130.6, 130.4 (2C), 127.5 (2C), 114.1 (2C), 113.3 (2C), 55.2, 55.1, 30.6 (3C), 29.0 (3C), 27.5 (3C), 13.7 (3C).

(*E*)-(1-(2-Bromo-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) vinyl)tributylstannane (**8a**)

Yield: 78 %. TLC: Rf 0.29 (cyclohexane/EtOAc: 9/1). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.17 (d, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.26 (s, 2H), 3.78 (s, 6H), 3.59 (s, 6H), 1.49 (m, 6H), 1.29 (m, 6H), 0.95 (m, 6H), 0.87 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 158.0, 152.8 (2C), 148.9, 139.1, 138.7, 137.2, 133.2, 128.4, 121.7, 117.7, 114.5, 106.0, 60.9, 55.8 (3C), 28.9 (3C), 27.5 (3C), 13.8 (3C), 10.9 (3C).

(*E*)-(1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl) vinyl)tributylstannane (**8b**)

Yield: 92 %. TLC: Rf 0.2 (cyclohexane/Et₂O: 95/5). IR (neat) ν_{max} / cm^{-1} : 2928, 2847, 2168, 2029, 1973, 1604, 1554, 1508, 1476, 1420, 1378, 1319, 1286, 1248, 1175, 1161, 1106. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.95 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.57 (s, 1H), 6.31 (s, 1H), 3.91 (s, 6H), 3.74 (s, 3H), 3.73 (s, 3H), 1.52-1.43 (m, 6H), 1.35-1.23 (m, 6H), 0.98-0.93 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 158.4, 153.1, 151.2, 146.5, 142.0, 140.4, 137.9, 130.2, 129.9 (2C), 113.4 (2C), 107.2, 105.9, 61.3, 60.9, 55.9, 55.1, 28.9 (3C), 27.3 (3C), 13.7 (3C), 10.8 (3C). MS (APCI) *m/z*: 669.0 (M+H)⁺.

(*E*)-(5-(2-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(tributylstannyl) vinyl)-2-methoxyphenoxy)(*tert*-butyl)dimethyl silane (**8c**)

Yield: 75 %. TLC: Rf 0.58 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm^{-1} : 3836, 2929, 2854, 1556, 1506, 1463, 1423, 1380, 1281, 1231, 1139, 1109, 1013. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.00 (dd, *J* = 1.9 Hz, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 6.73 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 152.5, 151.5, 149.7, 146.2, 144.6, 142.8, 142.3, 138.9, 127.9, 123.3, 120.1, 111.2, 107.3, 61.3, 60.6, 56.4, 55.4, 29.1 (3C), 27.5 (3C), 25.9 (3C), 18.6, 13.5 (3C), 8.07 (3C), -2.7 (2C).

(*E*)-(1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(4-methoxy-3-(methoxymethoxy)phenyl)vinyl)tributyl stannane (**8d**)

Yield: 75 %. TLC: Rf 0.28 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm^{-1} : 2916, 1737, 1373, 1234, 1044. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.76 (s, 1H), 6.64 (s, 2H), 6.47 (s, 1H), 6.25 (s, 1H), 4.85 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.65 (s, 3H), 3.27 (s, 3H), 1.45-1.36 (m, 6H), 1.27-1.15 (m, 6H), 0.91-0.85 (m, 6H), 0.79 (t, *J* = 7.2 Hz, 9H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.1, 151.2, 148.7, 147.1, 145.8, 141.8, 140.4, 137.7, 130.5, 123.4, 116.1, 111.0, 107.0, 105.8, 95.1, 60.9, 60.7, 55.9, 55.6, 28.8 (3C), 27.2 (3C), 13.5 (3C), 10.8 (3C).

General Procedure for the iodination of **3** and **8a-d**.

To a CH₂Cl₂ (15 mL) solution containing vinyl stannane (0.39 mmol) was added in one portion I₂ (0.39 mmol) at 0°C. The mixture was then stirred at rt until the disappearance of the starting material (judged by TLC). Then a saturated Na₂S₂O₃ solution (10 mL) was added to the mixture which was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried with MgSO₄ and evaporated to dryness. Purification by flash chromatography afforded terminal alkynes **4** and **9a-d**.

(*E*)-1-Iodo-1,2-bis(4-methoxyphenyl)ethene (**4**)

Yield: 74 %. Anal. calcd for **4** (C₁₆H₁₅IO₂): C, 52.48; H, 4.13. Found: C, 52.24; H, 4.07. TLC: R_f 0.68 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} /cm⁻¹: 2932, 2938, 1596, 1568, 1504, 1462, 1440, 1421, 1286, 1245, 1174, 1161, 1109, 1024. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.22 (s, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 3.73 (s, 3H), 3.65 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.3, 158.8, 140.3, 135.6, 130.2 (2C), 130.1, 129.9 (2C), 114.0 (2C), 113.5 (2C), 96.1, 55.3, 55.2. MS (CI) *m/z*: 365.9 (M+H⁺).

(E)-2-Bromo-1-(1-iodo-2-(3,4,5-trimethoxyphenyl)vinyl)-4-methoxy benzene (**9**)

Yield: 70 %. Anal. calcd for **9a** (C₁₈H₁₈BrIO₄): C, 42.80; H, 3.59. Found: C, 42.74; H, 3.57. TLC: R_f 0.13 (cyclohexane/EtOAc: 9/1). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.32 (s, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 8.5 Hz, *J* = 2.6 Hz, 1H), 6.14 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.57 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 160.0, 152.9, 142.8, 137.8, 135.9, 132.2, 130.7, 123.2, 118.4, 114.4, 105.4 (2C), 94.5, 60.8, 55.8, 55.7 (2C). MS (APCI) *m/z*: 500.0 (M+H⁺).

(E)-1-(2-(2-Bromo-3,4,5-trimethoxyphenyl)-2-iodovinyl)-4-methoxy benzene (**9b**)

Yield: 85 %. Anal. calcd for **9b** (C₁₈H₁₈BrIO₄): C, 42.80; H, 3.59. Found: C, 42.59; H, 3.37. TLC: R_f 0.21 (cyclohexane/EtOAc: 95/5). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.31 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.62 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.5, 151.9, 145.6, 138.8, 136.0, 133.6, 130.3 (2C), 128.6, 113.5 (2C), 107.2, 106.5, 90.7, 60.93, 60.6, 56.1, 55.4. MS (ESI) *m/z*: 528.8 (M+Na⁺).

(E)-(5-(2-(2-Bromo-3,4,5-trimethoxyphenyl)-2-iodovinyl)-2-methoxy phenoxy)(*tert*-butyl)dimethyl silane (**9c**)

Yield: 99 %. TLC: R_f 0.50 (cyclohexane/EtOAc: 9/1). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.26 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.62 (s, 1H), 6.56 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 0.99 (s, 9H), 0.15 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.3, 151.8, 151.14, 144.6, 143.1, 142.1, 138.7, 129.7, 123.1, 119.9, 111.3, 109.0, 107.9, 92.2, 61.2, 61.1, 56.1, 55.3, 25.6 (3C), 16.4, -4.8 (2C). MS (ESI) *m/z*: 659.0 (M+Na⁺). Anal. calcd for **9c** (C₂₄H₃₂BrIO₅Si): C, 45.37; H, 5.08. Found: C, 45.17; H, 4.98.

(E)-2-Bromo-1-(1-iodo-2-(4-methoxy-3-(methoxymethoxy)phenyl)vinyl)-3,4,5-trimethoxybenzene (**9d**)

Yield: 88 %. TLC: R_f 0.49 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} /cm⁻¹: 2984, 1737, 1373, 134, 1044. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.27 (s, 1H), 6.72-6.61 (m, 3H), 6.63 (s, 1H), 4.92 (s, 2H), 3.92 (s, 6H), 3.82 (s, 3H), 3.80 (s, 3H), 3.34 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.4, 151.8, 149.4, 146.1, 143.1, 141.9, 138.5, 129.7, 123.4, 115.2, 110.9, 108.8, 107.8, 95.2, 92.6, 61.1, 61.0, 56.2, 55.8 (2C). Anal. calcd for **9d** (C₂₀H₂₂BrIO₆): C, 42.50; H, 3.92. Found: C, 42.38; H, 3.88.

General procedure for the PdCl₂(PPh₃)₂-catalyzed cross coupling reaction of vinyl iodides with arylzinc reagents.

To a solution of vinyl iodides **4** or **9a-d**, PdCl₂(PPh₃)₂ (5 mol%) in THF was added at room temperature, ArZnCl (2 equiv.) prepared by transmetalation from the corresponding Grignard reagent (2.2 equiv.) and anhydrous ZnCl₂ (3 equiv.). The reaction was stirred at room temperature and monitored by TLC until complete consumption of starting materials. The reaction was hydrolyzed at 0°C with aqueous HCl (1N), extracted with Et₂O, the organic extract was dried over MgSO₄ and the solvent was removed *in vacuo*. Purification by flash chromatography afforded olefins **1a**, **10a-g**.

(E)-5-(1,2-bis(4-Methoxyphenyl)vinyl)-1,2,3-trimethoxybenzene (**1a**)

Yield: 99 %. Anal. calcd for **1a** (C₂₅H₂₆O₅): C, 73.87; H, 6.45. Found: C, 73.77; H, 6.38. TLC: R_f 0.31 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} /cm⁻¹: 2930, 1603, 1576, 1507, 1463, 1412, 1332, 1285, 1238, 1173, 1119, 1028. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.13 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.53 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (s, 6H), 3.76 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 158.9, 158.3, 152.8 (2C), 140.4, 139.9, 137.6, 132.5, 131.7 (2C), 130.7 (2C), 130.2, 126.9, 113.9 (2C), 113.4 (2C), 104.9 (2C), 60.9, 56.1 (3C), 55.2. MS (CI) *m/z*: 407.2 (M+H⁺).

(Z)-5-(1-(2-bromo-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)vinyl)-1,2,3-trimethoxybenzene (**10a**)

Yield: 95 %. Anal. calcd for **10a** (C₂₇H₂₉BrO₇): C, 59.46; H, 5.36. Found: C, 59.29; H, 5.24. TLC: R_f 0.13 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 2936, 2836, 1578, 1506, 1452, 1418, 1334, 1283, 1229, 1186, 1122, 1032, 1004. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.23 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 1H), 6.71 (s, 1H), 6.54 (s, 2H), 6.26 (s, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 3.80 (s, 6H), 3.79 (s, 6H), 3.60 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.6, 153.4 (2C), 153.0 (2C), 152.8, 139.9, 137.6, 137.3, 133.1, 132.5, 132.3, 128.7, 124.9, 118.7, 114.2, 106.2 (2H), 104.0 (2C), 60.9, 60.8, 56.3, 56.1 (2C), 55.6 (2C). MS (APCI) *m/z*: 547.0 (M+H⁺).

(Z)-1-(1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl) vinyl)-4-methoxybenzene (**10b**)

Yield: 99 %. Anal. calcd for **10b** (C₂₅H₂₅BrO₅): C, 61.86; H, 5.19. Found: C, 61.65; H, 5.04. TLC: R_f 0.41 (cyclohexane/EtOAc: 8/2). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.20 (d, *J* = 8.4 Hz, 2H), 6.90 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 6.48 (s, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.0, 158.5, 153.4, 151.8, 142.5, 138.2, 136.9, 134.0, 130.1 (2C), 129.8, 127.5 (2C), 126.8, 113.8 (2C), 113.6 (2C), 110.8, 110.2, 61.4, 61.2, 56.2, 55.3, 55.2. MS (ESI) *m/z*: 485.2 (M+H⁺).

(Z)-(5-(2-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl) vinyl)-2-methoxyphenoxy)(*tert*-butyl)dimethyl silane (**10c**)

Yield: 77 %. Anal. calcd for **10c** (C₃₁H₃₉BrO₆Si): C, 60.48; H, 6.39. Found: C, 60.32; H, 6.30. TLC: R_f 0.14 (cyclohexane/EtOAc: 9/1). IR (neat) ν_{max} / cm⁻¹: 2203, 2149, 2073, 2020, 1985, 1605, 1570, 1497, 1440, 1388, 1275, 1243, 1178, 1136, 1109, 1040, 1012. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.22 (d, *J* = 7.9 Hz, 2H), 6.88 (s, 1H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.67 (s, 2H), 6.56 (s, 1H), 6.49 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 0.92 (s, 9H), 0.03 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 158.9, 153.3, 151.8, 150.3, 144.4, 142.4, 138.1, 136.8, 134.1, 130.0, 127.5 (2C), 126.9, 123.6, 120.8, 113.8 (2C), 111.4, 110.7, 110.0, 61.2, 61.1, 56.1, 55.3, 55.3, 25.6 (3C), 18.3, -6.1 (2C). MS (APCI) *m/z*: 617.1 (M+H⁺).

(Z)-2-bromo-3,4,5-trimethoxy-1-(2-(4-methoxy-3-(methoxymethoxy) phenyl)-1-*p*-tolylvinyl)benzene (**10d**)

Yield: 72 %. TLC: R_f 0.50 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{max} / cm⁻¹: 2190, 1512, 1263, 1106, 1008. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.22 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.99 (s, 1H), 6.80 (d, *J* = 1.6 Hz, 1H), 6.76 (t, *J* = 5.2 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 4.95 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.38 (s, 3H), 2.04 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.5, 151.8, 148.8, 145.9, 142.4, 138.7, 138.3, 137.1, 136.6, 130.0 (2C), 129.1, 127.5 (2C), 126.2, 124.1, 116.1, 111.1, 110.6, 110.1, 95.2, 61.1, 61.0, 56.2, 55.9, 55.8. MS (APCI) *m/z*: 551.0 (M+Na⁺, ⁷⁹Br), 553.1 (M+Na⁺, ⁸¹Br). Anal. calcd for **10d** (C₂₇H₂₉BrO₆): C, 61.25; H, 5.52. Found: C, 61.31; H, 5.52.

(Z)-2-(1-(2-Bromo-3,4,5-trimethoxyphenyl)-2-(4-methoxy-3-(methoxymethoxy)phenyl)vinyl) naphthalene (**10e**)

Yield: 72 %. Anal. calcd for **10e** (C₃₀H₂₉BrO₆): C, 63.72; H, 5.17. Found: C, 63.45; H, 5.00. TLC: R_f 0.13 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 2989, 1737, 1373, 1236, 1045. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.81 (d, *J* = 9.2 Hz, 1H), 7.81-7.50 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.61 (dd, *J* = 1.9 Hz, *J* = 3.7 Hz, 1H), 7.44 (d, *J* = 9.4 Hz, 1H), 7.44 (dd, *J* = 1.9 Hz, *J* = 3.1 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* = 1.9 Hz, *J* = 8.5 Hz, 1H), 6.66 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.6, 151.9, 149.0, 146.0, 142.6, 138.8, 138.6, 136.4, 133.5, 132.7, 129.9, 128.9, 128.3, 127.9, 127.5, 126.1, 125.9, 125.5, 124.4, 124.3, 116.3, 111.2, 110.8, 110.2, 95.2, 61.2, 61.1, 56.2, 55.9, 55.8. MS (APCI) *m/z*: 587.2 (M+Na⁺, ⁷⁹Br), 589.1 (M+Na⁺, ⁸¹Br).

(Z)-2-Bromo-1-(1-(3-fluoro-4-methoxyphenyl)-2-(4-methoxy-3-(methoxymethoxy)phenyl)vinyl)-3,4,5-trimethoxybenzene (**10f**)

Yield: 50 %. Anal. calcd for **10f** (C₂₇H₂₈BrFO₇): C, 57.56; H, 5.01. Found: C, 57.50; H, 4.98. TLC: R_f 0.33 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{max} / cm⁻¹: 2937, 1514, 1481, 1385, 1262, 1156, 1132, 1106, 1079, 1009. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.09-7.03 (m, 1H), 7.02-6.98 (m, 1H), 6.92 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 10.4 Hz, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 4.94 (s, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.6, 152.3 (1C, d, *J* = 244.9 Hz), 151.9, 148.9, 146.9, 146.8, 146.0, 142.6, 137.4, 136.0, 134.8, 129.7, 127.6, 124.2, 122.2, 116.1, 113.9 (1C, d, *J* = 19.3 Hz), 113.1, 111.2, 110.6, 110.0, 95.2, 61.2, 61.1, 56.3, 56.2, 55.9, 55.8. MS (APCI) *m/z*: 441.0 (M+H⁺).

(Z)-1-(1,2-bis(4-Methoxy-3-(methoxymethoxy)phenyl)vinyl)-2-bromo-3,4,5-trimethoxybenzene (**10 g**)

Yield: 54 %. Anal. calcd for **10g** (C₂₉H₃₃BrO₉): C, 57.53; H, 5.49. Found: C, 57.08; H, 5.10. TLC: R_f 0.20 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{max} / cm⁻¹: 2984, 1737, 1373, 1235, 1045. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.22 (d, *J* = 1.5 Hz, 1H), 6.91 (s, 1H), 6.81 (d, *J* = 2.0 Hz, 2H), 6.80-6.70 (m, 3H), 6.56 (s, 1H), 5.19 (d, *J* = 0.9 Hz, 2H), 4.92 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.5, 151.8, 149.5, 148.8, 146.3, 145.9, 142.5, 138.2, 136.5, 134.2, 129.9, 126.9, 124.1, 121.0, 116.1, 115.0, 111.5, 111.2, 110.7, 110.2, 95.9, 95.2, 61.1, 60.9, 56.2, 56.2, 55.9, 55.8, 55.8. MS (ESI) *m/z*: 627.2 (M+Na⁺, ⁷⁹Br), 629.2 (M+Na⁺, ⁸¹Br).

Typical procedure for the synthesis of triarylolefins 1b-h

To a cooled solution (-78°C) of **10a-g** (0.25 mmol) in THF (5 mL) was added a 2.5 M hexane solution of *n*-BuLi (0.5 mL, 1.25 mmol) over 2 min. After 30 min at -78°C the solution was allowed to warm to rt then HCl 1N (5 mL) was added and stirring was continued for 1 h. The aqueous phase was separated and extracted with EtOAc, the organic extract was dried over MgSO₄ and the solvent was removed in vacuo. Purification by flash chromatography afforded triarylolefins **1b-h**.

(E)-1,2,3-Trimethoxy-5-(1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)vinyl)benzene (**1b**)

Yield: 91 %. Anal. calcd for **1b** (C₂₇H₃₀O₇): C, 69.51; H, 6.48. Found: C, 69.41; H, 6.35. TLC: R_f 0.46 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 2954, 2922, 1573, 1505, 1482, 1463, 1417, 1376, 1327, 1280, 1223, 1184, 1125, 1030, 1010. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.16 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 6.55 (s, 2H), 6.29 (s, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 6H), 3.59 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ ppm: 159.1, 153.4, 152.9 (2C), 152.6 (2C), 141.8, 139.3, 137.6, 132.9, 132.4, 131.7 (2C), 127.5, 114.1 (2C), 106.7 (2C), 104.9 (2C), 60.9, 56.3, 56.1 (2C), 55.7 (2C), 55.3. MS (ESI) *m/z*: 467.3 (M+H⁺).

(Z)-1-Methoxy-4-(2-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)vinyl)benzene (**1c**)

Yield: 65 %. Anal. calcd for **1c** (C₂₅H₂₆O₅): C, 73.87; H, 6.45. Found: C, 73.73; H, 6.36. TLC: R_f 0.40 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 2934, 1605, 1577, 1508, 1461, 1410, 1280, 1237, 1175, 1124, 1032. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.28 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.42 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.69 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.1, 158.3, 153.5 (2C), 139.9, 137.3, 136.2, 135.9, 130.8 (2C), 130.6, 128.5 (2C), 125.9, 113.6 (2C), 113.4 (2C), 107.4 (2C), 61.1, 56.1 (2C), 55.3, 55.2. MS (APCI) *m/z*: 407.3 (M+H⁺).

(Z)-2-Methoxy-5-(2-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)vinyl)phenol (**1d**)

Yield: 99 %. Anal. calcd for **1d** (C₂₅H₂₆O₆): C, 71.07; H, 5.20. Found: C, 70.95; H, 6.14. TLC: R_f 0.36 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 3335, 1561, 1411, 803. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.12 (d, *J* = 8.8 Hz, 2H), 6.7 (d, *J* = 8.8 Hz, 2H), 6.61 (s, 1H), 6.51 (d, *J* = 2 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 6.38 (dd, *J* = 8.5 Hz, *J* = 2 Hz, 1H), 6.27 (s, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.55 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 159.1, 153.2 (2C), 145.4, 144.9, 140.4, 137.4, 135.9, 135.8, 131.1, 128.5 (2C), 125.9, 121.5, 115.5, 113.6 (2C), 110.2, 107.5 (2C), 61.0, 56.1 (2C), 55.7, 55.3. MS (APCI) *m/z*: 423.2 (M+H⁺).

(Z)-2-Methoxy-5-(2-*p*-tolyl-2-(3,4,5-trimethoxyphenyl)vinyl)phenol (**1e**)

Yield: 92 %. Anal. calcd for **1e** (C₂₅H₂₆O₅): C, 73.87; H, 6.45. Found: C, 73.68; H, 6.34. TLC: R_f 0.33 (cyclohexane/EtOAc: 6/4). IR (neat) ν_{max} / cm⁻¹: 3650, 2227, 2173, 2082, 2004, 1581, 1510, 1279, 1126. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.17 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.74 (s, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 6.35 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.65 (m, 6H), 2.29 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.6 (2C), 145.6, 145.1, 140.9, 140.5, 137.4 (2C), 136.1, 131.2, 129.1 (2C), 127.4 (2C), 126.9, 121.8, 115.8, 110.3, 107.6 (2C), 61.2, 56.3 (2C), 56.0, 21.3. MS (APCI) *m/z*: 407.0 (M+H⁺).

(Z)-2-Methoxy-5-(2-(naphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)vinyl)phenol (**1f**)

Yield: 95 %. Anal. calcd for **1f** (C₂₈H₂₆O₅): C, 76.00; H, 5.92. Found: C, 75.84; H, 5.97. TLC: R_f 0.35 (cyclohexane/EtOAc: 8/2). IR (neat) ν_{max} / cm⁻¹: 2983, 1737, 1373, 1235, 1054. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.81 (d, *J* = 9.2 Hz, 1H), 7.81-7.50 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.61 (dd, *J* = 1.9 Hz, *J* = 3.7 Hz, 1H), 7.44 (d, *J* = 9.4 Hz, 1H), 7.44 (dd, *J* = 1.9 Hz, *J* = 3.1 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.82 (dd, *J* = 1.9 Hz, *J* = 8.5 Hz, 1H), 6.66 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.7 (2C), 145.8, 145.2 (2C), 141.0, 140.8, 137.7, 135.9, 133.5, 132.9, 131.1, 128.4, 127.8, 127.7, 126.6, 126.3, 126.0, 125.6, 121.9, 115.8, 110.3, 107.7 (2C), 61.3, 56.3 (2C), 56.0.

(E)-5-(2-(3-Fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) vinyl)-2-methoxyphenol (**1g**)

Yield: 53 %. Anal. calcd for **1g** (C₂₅H₂₅FO₆): C, 68.17; H, 5.72. Found: C, 68.01; H, 5.66. TLC: R_f 0.20 (cyclohexane/EtOAc: 7/3). IR (neat) ν_{max} / cm⁻¹: 3650, 2983, 2190, 1739, 1373, 1239, 1047. ¹H NMR (300 MHz, CDCl₃) δ ppm 7.10-7.03 (m, 2H), 6.9-6.8 (m, 2H), 6.75 (s, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.53 (dd, *J* = 1.9 Hz, *J* = 8.4 Hz, 1H), 6.40 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.71 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.5 (2C), 152.1 (1C, d, *J* = 244.49 Hz), 145.6, 144.9, 139.4, 137.5, 136.6, 136.5, 135.4, 130.6, 126.9, 123.1, 121.7, 115.5, 114.6 (1C, d, *J* = 19.19 Hz), 112.9, 110.1, 107.3 (2C), 61.1, 56.3, 56.1, 55.9. MS (ESI) *m/z*: 587.1 (M+Na⁺).

(Z)-5-(2-(3-Hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl) vinyl)-2-methoxyphenol (**1h**)

Yield: 97 %. Anal. calcd for **1h** (C₂₅H₂₆O₇): C, 68.48; H, 5.98. Found: C, 68.34; H, 5.88. TLC: R_f 0.29 (cyclohexane/EtOAc: 6/4). IR (neat) ν_{max} / cm⁻¹: 2935, 1736, 1580, 1508, 1127, 1045. ¹H NMR (300 MHz, CDCl₃) δ ppm 6.88 (d, *J* = 1.6 Hz, 1H), 6.75-6.73 (m, 2H), 6.69 (s, 1H), 6.57 (d, *J* = 1.6 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.44 (dd, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 6.34 (s, 2H), 5.53 (s, 1H), 5.38 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.63 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 153.6 (2C), 16.3, 145.6, 145.4, 145.1, 140.5, 137.5, 136.9, 135.9, 131.1, 126.5, 121.7, 119.4, 115.7, 113.7, 110.4, 110.3, 107.5 (2C), 61.2, 56.3, 56.1, 56.0.

4.2 Biology

Cell Culture and Proliferation Assay.

Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) and were cultured according to the supplier's instructions. Briefly, A549 lung carcinoma, MDA-MB-231, MDA-MB-435 cells were grown in Dulbecco minimal essential medium (DMEM) containing 4.5 g/L glucose supplemented with 10% FCS and 1% glutamine. HCT116 colorectal carcinoma cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. Cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO₂. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5 × 10³ cells/well) containing 50 μ L growth medium. After 24 h of culture, the cells were supplemented with 50 μ L of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 μ L of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, USA). The IC₅₀ corresponds to the concentration of the tested compound that caused a decrease of 50% in fluorescence of drug treated cells compared with untreated cells. Experiments were performed in triplicate.

Tubulin Binding Assay

Sheep brain tubulin was purified according to the method of Shelanski[57] by two cycles of assembly-disassembly and then dissolved in the assembly buffer containing 0.1 M MES, 0.5 mM MgCl₂, 1 mM EGTA, and 1 mM GTP, pH 6.6 (the concentration of tubulin was about 2-3 mg/mL). Tubulin assembly was monitored and recorded continuously by turbidimetry at 350 nm in a UV spectrophotometer equipped with a thermostatted cell at 37°C. The GI₅₀ value of each compound was determined as the concentration which decreased the maximum assembly rate of tubulin by 50% compared to the rate in the absence of compound. The GI₅₀ values for all compounds were compared to the GI₅₀ of CA4 and *iso*CA-4 and measured the same day under the same conditions.

Acknowledgments

The authors gratefully acknowledge support of this project by CNRS and MNSER for doctoral fellowships to E. R.

References

- [1] A. Jordan, J. A. Hadfield, N. J. Lawrence, A. T. McGown, *Med. Res. Rev.* 18 (1998) 259–296.
- [2] T. Beckers, S. Mahboobi, *Drug Future* 28 (2003) 767–785.
- [3] F. Gueritte, J. Fahy, *Anticancer Agents from Natural Products*; G. M. Cragg, D. G. I. Kingston, D. J. Newman, Eds.; CRC Press: L. Boca Raton, (2005) 123–135.
- [4] D. G. I. Kingston, *Anticancer Agents from Natural Products*; G. M. Cragg, D. G. I. Kingston, D. J. Newman, Eds.; CRC Press: L. Boca Raton, (2005) 89–122.
- [5] R. J. Freilich, C. Balmaceda, A. D. Seidman, M. Rubin, L. M. DeAngelis, *Neurology* 47 (1996) 115–118.
- [6] P. H. Hilkens, J. Verweij, C. J. Vecht, G. Stoter, M. J. van den Bent, *Ann. Oncol.* 8 (1997) 187–190.
- [7] A. T. Fojo, M. Menefee, *Semin. Oncol.* 32 (2005) S3–S8.
- [8] C. Dumontet, B. I.; Sikic, *J. Clin. Oncol.* 17 (1999) 1061–1070.
- [9] G. R. Pettit, S. B. Singh, E. Hamel, C. M. Lin, D. S. Alberts, D. Garcia-Kendall *Experientia* 45 (1989) 209–211.
- [10] G. R. Pettit, S. B. Singh, M. R. Boyd, E. Hamel, R. K. Pettit, J. M. Schmidt, F. Hogan, *J. Med. Chem.* 38 (1995) 1666–1672.
- [11] R. Singh, H. Kaur, *Synthesis* (2009) 2471–2497.
- [12] G. C. Tron, T. Pirali, G. Sorba, F. Pagliai, S. Busacca, A. A. Genazzani, *J. Med. Chem.* 49 (2006) 3033–3044.
- [13] A. Cirila, J. Mann, *Nat. Prod. Rep.* 20 (2003) 558–564.
- [14] G. R. Pettit, M. R. Rhodel, D. L. Herald, E. Hamel, R. K. Pettit, *J. Med. Chem.* 48 (2005) 4087–4099.
- [15] A. T. McGown, B. W. Fox, *Cancer Chemother. Pharmacol.* 26 (1990) 79–81.
- [16] G. R. Pettit, C. Temple, V. L. Narayanan, R. Varma, M. J. Simpson, M. R. Boyd, G. A. Renner, N. Bansal, *Anticancer Drug Design* 10 (1995) 299–309.
- [17] D. W. Siemann, D. J. Chaplin, P. A. Walicke, *Expert. Opin. Investig. Drugs* 18 (2009) 189–197.
- [18] N. E. Mealy, B. Lupone, M. Balcells, *Drugs Future* 31 (2006) 547–548.
- [19] D. M. Patterson, G. J. S. Rustin, *Drugs Future* 32 (2007) 1025–1032.
- [20] K. Oshumi, R. Nakagawa, Y. Fukuda, T. Hatanaka, T. Tsuji, *J. Med. Chem.* 41 (1998) 3022–3032.
- [21] G. M. Tozer, C. Kanthou, C. S. Parkins, S. A. Hill, *Int. J. Exp. Pathol.* 83 (2002) 21–38.
- [22] G. D. Dark, S. A. Hill, V. E. Prise, G. M. Tozer, G. R. Pettit, D. J. Chaplin, *Cancer Res.* 57 (1997) 1829–1834.
- [23] G. M. Tozer, C. Kanthou, B. C. Baguley, *Nat. Rev. Cancer* 5 (2005) 423–435.
- [24] J. Griggs, J. C. Metcalfe, R. Hesketh, *Lancet. Oncol.* 2 (2001) 82–87.
- [25] G. M. Tozer, V. E. Prise, J. Wilson, R. J. Locke, B. Vojnovic, M. R. L. Stratford, M. F. Dennis, D. J. Chaplin, *Cancer Res.* 59 (1999) 1626–1634.
- [26] D. J. Chaplin, M. R. Horsman, D. W. Siemann, *Curr. Opin. Invest. Dr.* 7 (2006) 522–528.
- [27] A. M. Gaya, G. J. S. Rustin, *Clin. Oncol.* 17 (2005) 277–290.
- [28] J. W. Lippert, *Bioorg. Med. Chem.* 15 (2007) 605–615.
- [29] G. R. Pettit, B. Toki, D. L. Herald, M. R. Boyd, E. Hamel, R. K. Pettit, G. C. Chapuis, *J. Med. Chem.* 42 (1999) 1459–1465.
- [30] O. Provot, A. Giraud, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* 46 (2005) 8547–8550.
- [31] C. Mousset, A. Giraud, O. Provot, A. Hamze, J. Bignon, J. M. Liu, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *Bioorg. Med. Chem. Lett.* 18 (2008) 3266–3271.
- [32] C. Mousset, O. Provot, A. Hamze, J. Bignon, J.-D. Brion, M. Alami, *Tetrahedron* 64 (2008) 4287–4294.
- [33] S. Messaoudi, B. Tréguier, A. Hamze, O. Provot, J.-F. Peyrat, J. R. Rodrigo De Losada, J.-M. Liu, J. Bignon, J. Wdziczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *J. Med. Chem.* 52 (2009) 4538–4542.
- [34] M. Alami, Brion, J.-D.; O. Provot, J.-F. Peyrat, S. Messaoudi, A. Hamze, A. Giraud, J. Bignon, J. Bakala, J.-M. Liu, WO 122620 A1, 2008.
- [35] A. Hamze, D. Veau, O. Provot, J.-D. Brion, M. Alami, *J. Org. Chem.* 74 (2009) 1337–1340.
- [36] B. Tréguier, A. Hamze, O. Provot, J.-D. Brion, M. Alami, *Tetrahedron Lett.* 50 (2009) 6549–6552.
- [37] A. Hamze, A. Giraud, S. Messaoudi, O. Provot, J.-F. Peyrat, J. Bignon, J.-M. Liu, J. Wdziczak-Bakala, S. Thoret, J. Dubois, J.-D. Brion, M. Alami, *ChemMedChem*, 4 (2009) 1912–1924.
- [38] M. Clarke, R. Collins, C. Davies, J. Godwin, R. Gray, R. Peto, *The Lancet* 351 (1998) 1451–1467 and references therein.
- [39] C. Borrel, S. Thoret, X. Cachet, D. Guénard, F. Tillequin, M. Koch, S. Michel, *Bioorg. Med. Chem.* 13 (2005) 3853–3864.
- [40] K. Oshumi, R. Nakagawa, Y. Fukuda, T. Hatanaka, Y. Morinaga, Y. Nihei, K. Ohishi, Y. Suga, Y. Akiyama, T. Tsuji, *J. Med. Chem.* 41 (1998) 3022–3032.
- [41] D. Alloati, G. Giannini, W. Cabri, I. Lustrati, M. Marzi, A. Ciacci, G. Gallo, M. O. Tinti, M. Marcellini, M. B. Gugliemi, P. Carminati, C. Pisano, *J. Med. Chem.* 51 (2008) 2708–2771.
- [42] K. Sonogashira, Y. Tohda, N. Hagigara, *Tetrahedron Lett.* 16 (1975) 4467–4470.
- [43] M. Alami, F. Ferri, G. Linstrumelle, *Tetrahedron Lett.* 34 (1993) 6403–6406.
- [44] F. Liron, P. Le Garrec, M. Alami, *Synlett* (1999) 246–248.
- [45] M. Alami, F. Liron, M. Gervais, J.-F. Peyrat, J.-D. Brion, *Angew. Chem., Int. Ed.* 41 (2002) 1578–1580.
- [46] A. Hamze, O. Provot, J.-D. Brion, M. Alami, *J. Org. Chem.* 72 (2007) 3868–3874.
- [47] M. Alami, F. Ferri, Y. Gaslain, *Tetrahedron Lett.* 37 (1996) 57–60.
- [48] S. P. H. Mee, V. Lee, J. E. Baldwin, *Chem. Eur. J.* 11 (2005) 3294–3308.
- [49] S.-M. Chen, R. E. Schaub, C. Grudzinskas, *J. Org. Chem.* 72 (2007) 3868–3874.
- [50] a) F. Liron, M. Gervais, J.-F. Peyrat, M. Alami, J.-D. Brion, *Tetrahedron Lett.* 44 (2003) 2789–2792.
- [51] M. Bujard, F. Ferri, M. Alami, *Tetrahedron Lett.* 39 (1998) 4243–4246.
- [52] A. Hamze, O. Provot, M. Alami, J.-D. Brion, *Org. Lett.* 7 (2005) 5625–5628.
- [53] A. Hamze, O. Provot, M. Alami, J.-D. Brion, *Synthesis* (2007), 2025–2036.
- [54] A. Bekaert, O. Provot, O. Rasolofahona, M. Alami, J.-D. Brion, *Tetrahedron Lett.* 46 (2005) 4187–4191.
- [55] A. Giraud, O. Provot, A. Hamze, J.-D. Brion, M. Alami, *Tetrahedron Lett.* 49 (2008) 1107–1110.
- [56] F. Zavala, D. Guénard, J.-P. Robin, E. Brown, *J. Med. Chem.* 23 (1980) 546–549.
- [57] M. L. Shelanski, F. Gaskin, C. R. Cantor, *Proc. Natl. Acad. Sci. U.S.A.* 70 (1973) 765–768.

Figure 1. Representative tubulin binding agents and general structure of the synthesized hybrids **1**.

Scheme 1. Retrosynthetic pathway leading to triarylolefins **1**

Scheme 2 *Reagents and conditions* : (a) $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mol%), Bu_3SnH , (1.2 equiv), THF, 79%. (b) I_2 (1 equiv), CH_2Cl_2 , 74%. (c) 3,4,5-(OMe) $_3\text{C}_6\text{H}_2\text{ZnCl}$ (2.2 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), THF, 99%. (d) 3,4,5-(OMe) $_3\text{C}_6\text{H}_2\text{I}$ (0.9 equiv), $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), CuI (10 mol%), CsF (2 equiv), DMF, 60 °C, 54%.

Scheme 3. Retrosynthetic pathway leading to triarylolefins **1b-h**

Scheme 4. Synthesis of ortho bromodiarylkynes **5**. *Reagents and conditions:* (a) (i) HC≡CSiMe₃ (1.5 equiv), CuI (10 mol%), PdCl₂(PPh₃)₂ (5 mol%), piperidine, 20 °C; (ii) K₂CO₃, MeOH, 92%. (b) ArI (0.7 equiv), CuI (10 mol%), PdCl₂(PPh₃)₂ (5 mol%), Et₃N/THF (1/1), 60 °C, **5a**: 80%; **5b**: 86%, **5c**: 66%, **5d**: 80%. (c) Br₂, AcOH, 92%. (d) (i) HC≡CSiMe₃ (1.5 equiv), CuI (10 mol%), PdCl₂(PPh₃)₂ (5 mol%), Et₃N/THF (1/1), 60 °C, (ii) K₂CO₃, MeOH, 72%.

Scheme 5. Synthesis of triarylolefins **1b-h**. *Reagents and conditions:* (a) $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mol%), Bu_3SnH , (1.2 equiv), THF. (b) I_2 (1 equiv), CH_2Cl_2 , 20 °C. (c) ArZnCl (2.2 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol%), THF. (d) (i) $n\text{-BuLi}$ (4.5 equiv), THF, -78 °C. (ii) HCl 1M, 0.5 h, 20 °C.

Table 1. Cytotoxicity of *isoCA* on HCT 116 human cancer cell line and antitubulin activities.

Compounds	10a	10b	10c
Cytotoxicity IC ₅₀ ^[a] [M]	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
ITP ^[b] IC ₅₀ [μM]	NA ^[c]	NA	NA
Compounds	10g	1a	1b
Cytotoxicity IC ₅₀ ^[a] [M]	> 10 ⁻⁵	> 10 ⁻⁵	> 10 ⁻⁵
ITP ^[b] IC ₅₀ [μM]	8.0	8.1	NA
Compounds	1c	1d	1e
Cytotoxicity IC ₅₀ ^[a] [M]	> 10 ⁻⁵	> 10 ⁻⁵	3 10 ⁻⁶
ITP ^[b] IC ₅₀ [μM]	8.0	7.8	NA
Compounds	1f	1g	1h
Cytotoxicity IC ₅₀ ^[a] [M]	8 10 ⁻⁶	8 10 ⁻⁶	5 10 ⁻⁶
ITP ^[b] IC ₅₀ [μM]	NA	NA	8.5
References	CA-4	<i>isoCA</i>-4	
Cytotoxicity IC ₅₀ ^[a] [M]	2 10 ⁻⁹	2 10 ⁻⁹	
ITP ^[b] IC ₅₀ [μM]	1.0	2.1	

[a] IC₅₀ is the concentration of compound needed to reduce cell growth by 50% following 72 h cell treatment with the tested drug (average of three experiments). [b] ITP = Inhibition of Tubulin Polymerization; IC₅₀ is the concentration of compound required to inhibit 50% of the rate of microtubule assembly (average of three experiments). [c] NA, non active.