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## **► To cite this version:**

Evelia Rasolofonjatovo, Bret Tréguier, Olivier Provot, Abdallah Hamze, Jean-Daniel Brion, et al.. A One-Pot Three-Step Synthesis of Z-Trisubstituted Olefins from Arylalkynes and Their Cyclization into 4-Aryl-2H-chromenes. European Journal of Organic Chemistry, 2012, 2012 (8), pp.1603-1615. <10.1002/ejoc.201101735>. <hal-02394410>

**HAL Id: hal-02394410**

**<https://hal.science/hal-02394410v1>**

Submitted on 4 Dec 2019

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# A one pot three-steps synthesis of *Z*-trisubstituted olefins from arylalkynes and their cyclization into 4-aryl-2*H*-chromenes

Evelia Rasolofonjatovo,[a] Bret Tréguier,[a] Olivier Provot,[a]\* Abdallah Hamze,[a] Jean-Daniel Brion[a] and Mouâd Alami\*[a]

**Keywords:** Alkyne hydration/ Olefin / Chromene / *N*-tosylhydrazone/ Palladium

A rapid and versatile access from arylalkynes **3** to *Z*-trisubstituted olefins **2** and their cyclization into 4-aryl-2*H*-chromenes **1** is described. In a one-pot fashion, alkynes **3** were first hydrated, then transformed into *N*-tosylhydrazones and finally coupled with *ortho* substituted aryl halides under palladium catalysis to give trisubstituted olefins **2** in good yields and very high to total *Z*-selectivity.

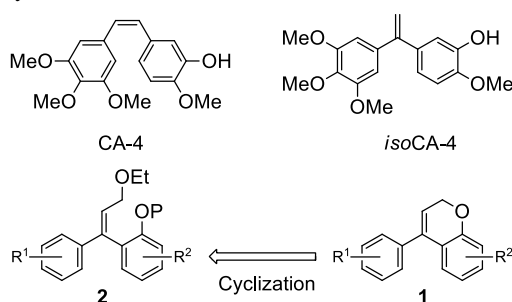
1,1-Diarylolefins **2** having an *ortho*-OMOM substituent underwent rapid cyclization in the presence of PTSA to give a variety of 4-aryl-2*H*-chromenes in good to excellent yields. This methodology was also successfully applied to prepare 5-aryl-2,3-dihydrobenzo[*b*]oxepine **4** from the required arylbutynol **3b**.

[a] Univ Paris-Sud, CNRS, BioCIS UMR 8076, Laboratoire de Chimie Thérapeutique, LabEx LERMIT, Faculté de Pharmacie, rue J.-B. Clément, Châtenay-Malabry F-92296, France  
Fax: +33-1 46.83.58.28.  
E-mail: [olivier.provot@u-psud.fr](mailto:olivier.provot@u-psud.fr) or [mouad.alami@u-psud.fr](mailto:mouad.alami@u-psud.fr)

## Introduction

Chromenes<sup>[1]</sup> (2*H*-benzopyran derivatives) are an important class of natural and synthetic compounds that exhibit a broad range of pharmacological properties.<sup>[2]</sup> Among them, 4-arylchromenes, also named neoflavones, is one of the most important subfamilies of chromenes, whose derivatives show promising biological activities, including retinoic acid receptor  $\alpha$ -selective antagonists,<sup>[3]</sup> and potassium channel activators, with smooth-muscle relaxant activity in a variety of cardiovascular and bronchopulmonary diseases.<sup>[4]</sup> This wide range of biological activity displayed by these heteroaromatic compounds has made them popular synthetic targets.

**Figure 1.** Structure of CA-4, *iso*CA-4 and synthetic tubulin assembly inhibitors **1** and **2**.



In an ongoing project aimed at developing novel antimitotic substances,<sup>[5]</sup> we reported that the bioisosteric replacement of the 1,2-ethylene bridge of CA-4 by a 1,1-ethylene linker resulted in stable and non-isomerizable compounds (e.g.; *iso*CA-4), displaying biological activities comparable to that of the natural product.<sup>[5b,c]</sup> As an outcome of the exhaustive structure-activity relationships studies of *iso*CA-4, we were interested in developing a novel methodology that provides a rapid and efficient access to 4-aryl-2*H*-chromenes **1**, regarded as constraint analogues of *iso*CA-4. A

survey of the literature showed that few routes have been developed for the preparation of 4-aryl-2*H*-chromenes, including the coupling of 4-OTf-chromene derivatives with arylboronic acids,<sup>[6]</sup> a reaction of 4-methoxycarbonylchromane-3-one with aryllead tri-acetates,<sup>[7]</sup> ring-closing metathesis<sup>[8]</sup> and so on.<sup>[9]</sup>

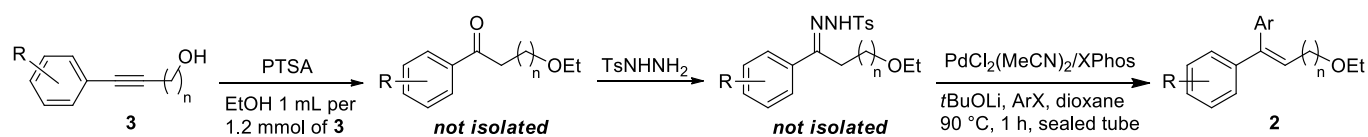
Herein, we disclose the full details of our strategy towards the synthesis of 4-aryl-2*H*-chromenes **1**, which involves the cyclization of a new series of 1,1-diarylethylene derivatives **2**.<sup>[10]</sup> These later having a trisubstituted double bond, constitute another interesting class of *iso*CA-4 analogues, potentially endowed with biological activities.<sup>[11]</sup>

## Results and Discussion

As shown in Table 1, alkynol **3a**<sup>[12]</sup> was first hydrated in EtOH using a catalytic amount of *p*-toluenesulfonic acid (PTSA).<sup>[13]</sup> Under this environmentally friendly procedure, the resulting ketone was transformed into its *N*-tosylhydrazone, and then coupled with 4-iodoanisole under palladium catalysis (PdCl<sub>2</sub>(MeCN)<sub>2</sub>/Xphos)<sup>[14, 5c]</sup> to give trisubstituted olefin **2a** in a good overall yield (63%, entry 1). It should be noted that this three-step synthesis of **2a** from alkynol **3a** was carried out without any purification of the intermediates generated in each stage.

Interestingly, we found that the position of the substituent R at the aromatic ring of aryl halides appears to play a crucial role for the reaction stereochemistry. Thus, when the Pd-coupling step was performed with meta aryl halide derivatives, such as 3-iodoanisole or 2-bromo-6-methoxynaphthalene, the reaction furnished trisubstituted olefins **2b** and **2c**, respectively, with a slight *Z*-stereoselectivity (entries 2, 3). More interestingly, this *Z*-selectivity<sup>[15]</sup> was even more remarkable when *ortho* iodoanisole was used in the Pd-coupling step, furnishing olefin **2d** in a good overall yield and a high diastereoisomeric ratio (77%, *Z/E* 90/10, entry 4). Examples depicted in entries 5-9 confirm that the effect of the *ortho* substituent is general with respect to the aryl halide. Thus, a further enhancement of *Z*-selectivity (up to *Z/E* 100/0) was also observed with other *ortho* substituted aryl halides, regardless the electronic nature, and the size of the *ortho* substituent (e.g.; OBn, Me, NO<sub>2</sub>, *i*Pr).



**Table 1.** One-pot three-steps tandem synthesis of Z-trisubstituted olefins **2**

Entry	Alkyne <b>3</b>	Aryl halide	Z-Olefin <b>2</b> <sup>a</sup>	Yield <sup>b</sup> (%)	Z/E ratio <sup>c</sup>
1				63	-
2	„			78	65/35
3	„			97	55/45
4	„			77	90/10
5	„			51	97/3
6	„			80	100/0
7	„			68	95/5
8	„			71	93/7
9	„			27	94/6
10				58	98/2



11	„			71	100/0
12	„			65	100/0
13				72	97/3
14	„			52	100/0
15				32	96/4
16	„			18	94/6

<sup>a</sup>The stereochemistry of the double bond was determined in all cases by NOESY experiments

<sup>b</sup>Overall isolated yields based from arylalkynes **3** for the three-steps sequence (arylalkyne hydration, *N*-tosylhydrazone formation, and palladium-coupling reaction).

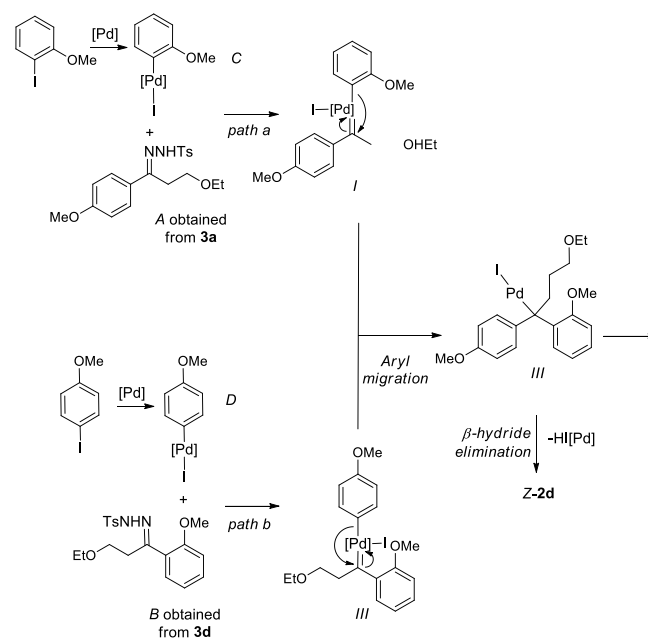
<sup>c</sup>*Z/E* ratio was determined by <sup>1</sup>H NMR in the crude reaction mixture.

In all prepared olefins **2**, the alkyl group attached to the triple bond of **3** and the ortho-substituted arene are in a *cis* arrangement. Carrying out the Pd-coupling step with a highly hindered aryl halide having ortho/ortho' *i*Pr substituent, if the reaction also occurred with a marked *Z*-preference, the overall yield of the process was low (27%, entry 9). The reaction scope with respect to the alkyne substrate was next studied. Starting from alkynol **3b** having a butynol chain, the use of ortho-substituted aryl iodides as partners in the Pd-coupling step gave very good results in terms of *Z*-selectivity (*Z/E* from 98/2 to 100/0) and overall yields (58-71%, entries 10-12). Similarly, performing the reaction with **3c** having a *n*-octynyl chain resulted in the formation of olefins **2m** and **2n** in good yields and very high to total *Z*-selectivity (entries 13 and 14).

To evaluate the impact of the ortho substituent in alkyne substrate on the reaction selectivity, the procedure was conducted with ortho-methoxy arylalkynol **3d**. As depicted in entries 15 and 16, olefins **2o** and **2d** were obtained with high *Z*-stereoselectivity. For yield considerations, it is clearly preferable to prepare **2d** using the para-substituted arylalkynol **3a** as starting material rather than its ortho-substituted isomer **3d** (compare entries 4 and 16). Altogether, the results depicted in Table 1 clearly suggest that the steric environment around the aryl halide<sup>[10, 14]</sup> as well as the alkyne substrate play a pivotal role in determining the selectivity of the trisubstituted olefins **2**.

To explain the formation of olefin **2d** (entries 4 and 16) with the same level of *Z*-selectivity from para or ortho-substituted arylalkyne **3a** and **3d**, we suggest the following mechanism which

**Scheme 1.** Proposed mechanism for the synthesis of **2d** from **3a** or **3d**.



involves a same alkylpalladium intermediate **III** (Scheme 1). In the coupling step between the ortho-aryl palladium species **C** and the para-*N*-tosylhydrazone **A** obtained from **3a**, a Pd carbene complex of type **I** would be formed (*path a*). This intermediate may evolve into an alkylpalladium complex **III** through a migratory of the



ortho anisole nucleus. According to this mechanism, the same alkylpalladium complex *III* is formed from the coupling of the ortho substituted-*N*-tosylhydrazide *B* with the para substituted palladium species *D* through the Pd-carbene species *II* (path *b*). A further  $\beta$ -hydride elimination on *III* would give olefin **2d** with the same *Z*-selectivity together with the regeneration of the Pd(0) catalyst in the presence of *t*BuOLi.

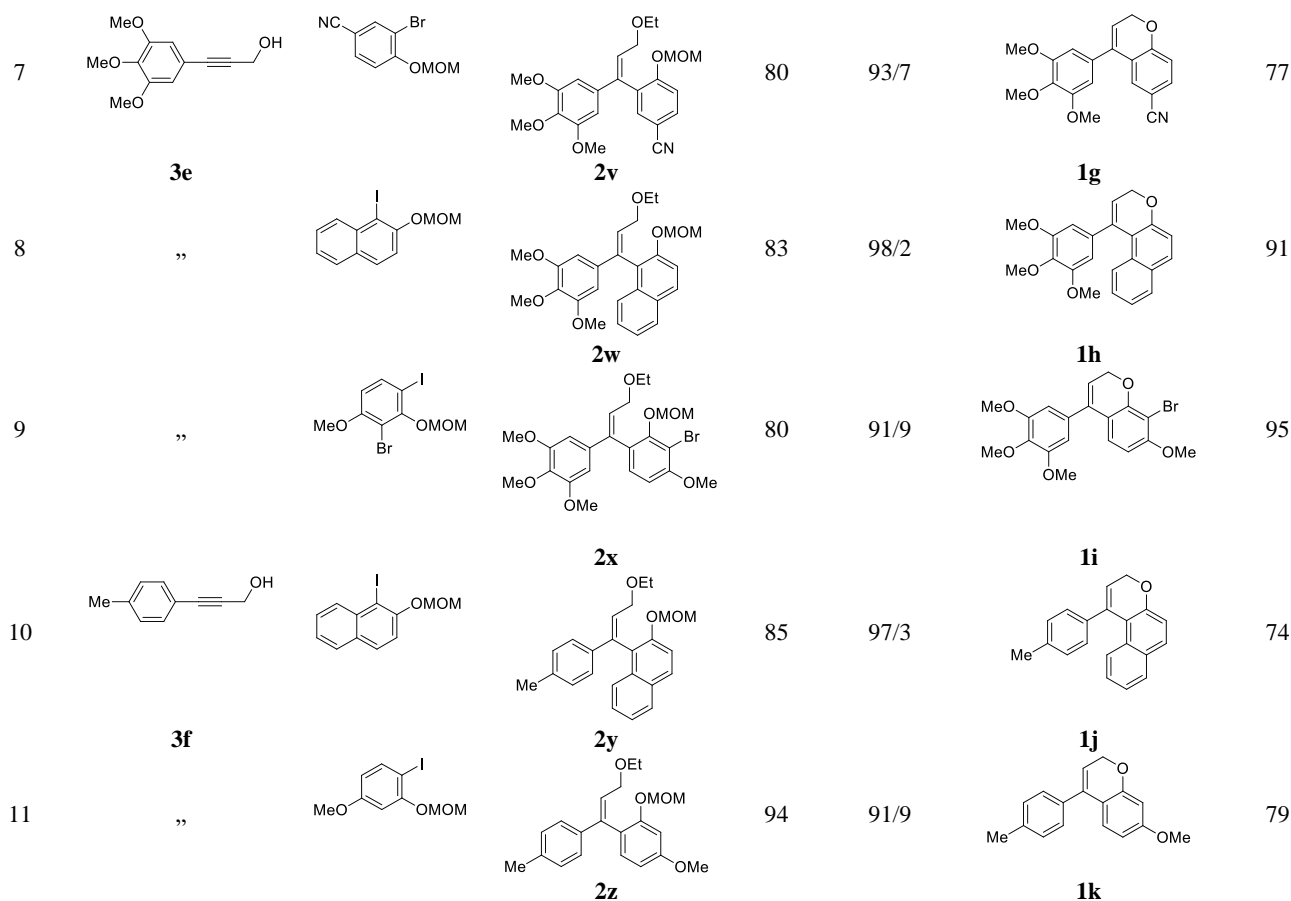
We next focused our attention on the preparation of olefins **2p-z** having an ortho-OMOM substituent, which could be further transformed into 4-aryl-2*H*-chromenes **1a-k** by an intramolecular cyclization. As depicted in Table 2, using the optimized conditions, olefins **2p-z** were obtained again with a pronounced *Z*-stereoselectivities ranging from *Z*/*E*: 90/10 to 99/1. One can note that this one-pot three-steps process worked well with various substituted aryl halides and resulted with no exception in the formation of the expected *Z*-olefins **2p-z** in good to excellent overall yields (50% to 94%) indicating that several groups (e.g.;

Me, OMe, OMOM, Cl, F, CN) are well tolerated. Having ortho OMOM diarylethylenes **2p-z** in hands, the cyclization reaction was attempted in refluxing EtOH in the presence of PTSA (3.0 equiv.). As expected, 4-aryl-2*H*-chromenes **1a-k** were obtained in good to excellent yields within a short reaction time of 1 h. Thus, a small library of 4-aryl-2*H*-chromenes was prepared rapidly from arylalkynols **3** with efficiency and a reduced number of purification steps. This success prompted us to extend the versatility of the method to the preparation of 5-aryl-2,3-dihydrobenzo[*b*] oxepine **4** (Scheme 2). Thus, starting from arylalkynol **3b** having a butynol chain, and using 1-iodo-2-methoxymethoxybenzene as coupling partner, the one-pot process led to *Z*-olefin **5** in a good 72% yield and high stereoselectivity (*Z*/*E*: 95/5). In the case of olefin **5**, TfOH was found to be superior to PTSA to achieve the cyclization reaction, providing the expected benzoxepine **4** in an acceptable 62% yield.

**Table 2.** Synthesis of 4-aryl-2*H*-chromenes **1a-k**

<div> <div> </div> </div>							
Entry	Alkyne <b>3</b>	Aryl iodide	<i>Z</i> -Olefin <b>2</b> <sup>a</sup>	Yield <sup>b</sup> (%)	<i>Z</i> / <i>E</i> ratio <sup>c</sup>	Chromene <b>1</b>	Yield <sup>d</sup> (%)
1	 <b>3a</b>	 	 <b>2p</b>	68	90/10	 <b>1a</b>	100
2		 	 <b>2q</b>	50	99/1	 <b>1b</b>	52
3		 	 <b>2r</b>	52	99/1	 <b>1c</b>	59
4		 	 <b>2s</b>	64	93/7	 <b>1d</b>	68
5		 	 <b>2t</b>	59	94/6	 <b>1e</b>	61
6		 	 <b>2u</b>	57	96/4	 <b>1f</b>	78





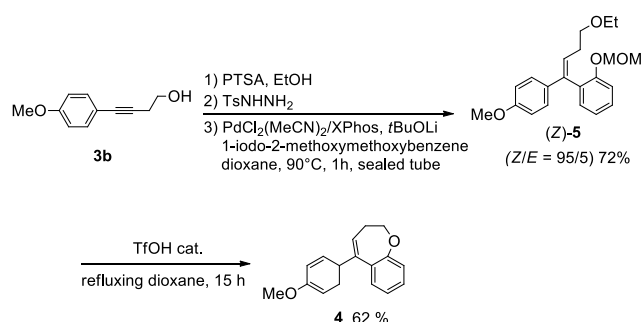
<sup>a</sup>The stereochemistry of the double bond was determined in all cases by NOESY experiments.

<sup>b</sup>Overall isolated yield based from arylalkynols **3a**, **3e** and **3f** for the three step-sequence.

<sup>c</sup>*Z/E* ratio was determined by <sup>1</sup>H NMR in the crude reaction mixture.

<sup>d</sup>Isolated yields of **1**.

## Scheme 2. Synthesis of **4** from alkynol **3b**.



## Conclusion

In summary, we have described a rapid and stereoselective access to *Z*-trisubstituted olefins **2** from arylalkynes using a one-pot three steps procedure based on alkyne hydration, *N*-tosylhydrazone *in situ* formation and subsequent Pd-coupling reactions with aryl halides. A remarkable to exclusive *Z*-selectivity in olefins **2** formation was observed with aryl halides as well as with arylalkynes having an ortho substituent. This protocol proved to be suitable for the synthesis of a series of olefins **2p-z**, having an ortho-OMOM substituent, which were next transformed into the corresponding 4-aryl-2*H*-chromenes **1a-k** in good to excellent yields using PTSA in refluxing EtOH.

Owing to its practical advantages and low environmental impact, the exploitation of this new procedure, in the context of our current medicinal program, will allow us to quickly prepare a small library of novel olefins of type **2**, as well as 4-aryl-2*H*-chromenes **1** bearing adequate decorations. These compounds which could be regarded as *isoCA-4* and restricted-*isoCA-4* analogues, respectively, are under investigation in our laboratory.

## Experimental Section

### General comments

All glasswares were oven-dried at 140 °C and all reactions were conducted under an argon atmosphere. Solvents: cyclohexane and ethyl acetate (EtOAc), for chromatography were technical grade. All new compounds were characterized by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and IR spectroscopy. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured in CDCl<sub>3</sub> with a Bruker Avance 300. <sup>1</sup>H 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), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), dt (doublet of triplet). <sup>13</sup>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<sup>-1</sup>). Analytical TLC was performed on Merck precoated silica gel 60 F-254 plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography. The plates were visualized by either UV light (254 nm), or by a solution of phosphomolybdic acid in ethanol. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected.

**Typical procedure for Sonogashira-Linstrumelle couplings:** A mixture of 4-iodoanisole (42.8 mmol, 1 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (2.14 mmol, 0.05 equiv.) and CuI (3.42 mmol, 0.08 equiv.) under argon atmosphere was



dissolved in anhydrous triethylamine (100 mL). Suitable alkyne (51.4 mmol, 1.2 equiv.) was then added dropwise. After being stirred at room temperature for 4 h, the solution was quenched with a saturated  $\text{NH}_4\text{Cl}$  solution and extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). Organic layers were then washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated *in vacuo* to give the crude product which was purified by flash chromatography.

#### 3-(4-Methoxyphenyl)prop-2-yn-1-ol (3a)

Yield: 99%; yellow solid;  $F = 66^\circ\text{--}69^\circ\text{C}$  ( $62.5^\circ\text{--}64.5^\circ\text{C}$ )<sup>[16]</sup>;  $R_f$ : 0.5 (EtOAc/c-hexane: 4/6); IR (v,  $\text{cm}^{-1}$ ) 3261, 2232, 1603, 1506, 1248, 1015, 835;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.37 (d, 2H,  $J = 8.8$  Hz), 6.84 (d, 2H,  $J = 8.8$  Hz), 4.48 (s, 2H), 3.81 (s, 3H), OH not seen;  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.7, 133.1 (2C), 114.6, 113.9 (2C), 85.8, 85.6, 55.2, 51.7; MS (APCI+)  $m/z$  163.0 ( $\text{MH}^+$ ). The spectral data above are in accordance with the literature data.<sup>[17]</sup>

#### 4-(4-Methoxyphenyl)but-3-yn-1-ol (3b)

Yield: 89%; yellow solid;  $F = 60^\circ\text{--}61^\circ\text{C}$  ( $61^\circ\text{C}$ )<sup>[18]</sup>;  $R_f$ : 0.5 (EtOAc/c-hexane: 4/6); IR (v,  $\text{cm}^{-1}$ ) 2836, 1674, 1602, 1573, 1509, 1463, 1440, 1242, 1029, 830;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.35 (d, 2H,  $J = 8.8$  Hz), 6.82 (d, 2H,  $J = 8.8$  Hz), 3.80 (m, 5H), 2.67 (t, 2H,  $J = 6.2$  Hz), OH not seen;  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.3, 132.9 (2C), 115.4, 113.8 (2C), 84.7, 82.2, 61.2, 55.2, 23.8; MS (APCI+)  $m/z$  177.2 ( $\text{MH}^+$ ). The spectral data above are in accordance with the literature data.<sup>[19]</sup>

#### 1-Methoxy-4-(oct-1-yn-1-yl)benzene (3c)

Yield: 100%; brown oil;  $R_f$ : 0.5 (EtOAc/c-hexane: 5/95); IR (v,  $\text{cm}^{-1}$ ) 2934, 2197, 1509, 1246, 904, 831, 729, 620;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.32 (d, 2H,  $J = 8.0$  Hz), 6.81 (d, 2H,  $J = 8.0$  Hz), 3.79 (s, 3H), 2.38 (t, 2H,  $J = 6.9$  Hz), 1.60 – 1.31 (m, 8H), 0.90 (t, 3H,  $J = 6.3$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.1, 133.0 (2C), 116.4, 113.9 (2C), 88.9, 80.3, 55.3, 31.5, 29.0, 28.8, 22.7, 19.5, 14.2; MS (APCI+)  $m/z$  217.5 ( $\text{MH}^+$ ). The spectral data above are in accordance with the literature data.<sup>[20]</sup>

#### 3-(2-Methoxyphenyl)prop-2-yn-1-ol (3d)

Yield: 87%; light yellow oil;  $R_f$ : 0.3 (EtOAc/c-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2136, 1509, 1467, 1246, 904, 825, 755, 729;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.35 (dd, 1H,  $J = 7.2, 2.9$  Hz), 7.22 (m, 1H), 6.85 – 6.70 (m, 2H), 4.48 (d, 2H,  $J = 6.8$  Hz), 3.8 (s, 3H), 2.23 (t, 1H,  $J = 6.8$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.9, 133.7, 129.9, 120.5, 111.7, 110.6, 91.5, 81.8, 55.8, 51.7; MS (ESI+)  $m/z$  163.2 ( $\text{MH}^+$ ). The spectral data above are in accordance with the literature data.<sup>[21]</sup>

#### General procedure for the synthesis of trisubstituted olefins:

To an Emrys Optimizer 0.5–2 mL pyrex reaction vessel were added alkyne (1.2 mmol, 1 equiv.) and PTSA. $\text{H}_2\text{O}$  (0.24 mmol, 0.20 equiv.) in EtOH (1 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature, 120  $^\circ\text{C}$ ; time, 30 min; fixed hold time, on; sample absorption, high; pre-stirring, 60 s. After cooling to room temperature, suitable sulfonhydrazide (1.35 mmol, 1.1 equiv.) was added and the reaction vessel was exposed once again to microwave irradiation according to the following specifications: temperature, 50  $^\circ\text{C}$ ; time, 15 min; fixed hold time, on; sample absorption, high; pre-stirring, 60 s. After cooling to room temperature,  $\text{PdCl}_2(\text{MeCN})_2$  (0.12 mmol, 0.10 equiv.), Xphos (0.24 mmol, 0.20 equiv.),  $t\text{BuOLi}$  (6 mmol, 5 equiv.) and dioxane (1 mL) were added, and the mixture was stirred at room temperature. After 3 min, the aryl halide (1.5 mmol, 1.25 equiv.) was finally added, the vessel was sealed and the mixture was stirred at 90  $^\circ\text{C}$  for 1 h. After cooling to room temperature,  $\text{H}_2\text{O}$  was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 2 mL). Organic layers were dried, concentrated, and the crude product was purified by column chromatography on silica gel. All the compounds gave satisfactory spectroscopic data.

#### 4,4'-(3-Ethoxyprop-1-ene-1,1-diyl)bis(methoxybenzene) (2a)

Yield: 63%; colorless oil;  $R_f$ : 0.67 (EtOAc/c-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2972, 2836, 2228, 2066, 2033, 2011, 1606, 1575, 1510, 1463, 1418, 1374, 1286, 1244, 1174, 1098, 1034, 835, 779, 737;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.20 (d, 2H,  $J = 8.8$  Hz), 7.10 (d, 2H,  $J = 8.7$  Hz), 6.90 (d, 2H,  $J = 8.7$  Hz), 6.81 (d, 2H,  $J = 8.8$  Hz), 6.09 (t, 1H,  $J = 6.7$  Hz), 4.03 (d, 2H,  $J = 6.7$  Hz), 3.84 (s, 3H), 3.80 (s, 3H), 3.47 (q, 2H,  $J = 7.0$  Hz), 1.20 (t, 3H,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.1, 158.9, 143.7, 134.9, 131.8 (2C), 130.9 (2C), 128.8, 123.7, 113.4 (4C), 68.4, 65.6, 55.2 (2C), 15.3; MS (APCI+)  $m/z$  299.6 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3$ : C, 76.48; H, 7.43, found: C, 76.41; H, 7.38.

#### (Z)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-3-methoxybenzene (2b)

Yield: 78%; colorless oil;  $R_f$ : 0.33 (EtOAc/c-hexane: 4/6); IR (v,  $\text{cm}^{-1}$ ) 2972, 2836, 2228, 2066, 2033, 1510, 1463, 1418, 1374, 1286, 1244, 1174, 936, 835, 779, 737;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 65/35 complicates the spectrum] major *Z* isomer 7.93 – 7.12 (m, 3H), 7.76 – 7.00 (m, 5H), 6.29 – 6.15 (m, 1H), 4.01 (d, 2H,  $J = 6.7$  Hz), 3.90 (s, 6H), 3.53 (q, 2H,  $J = 7.0$  Hz), 1.23 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.29 – 6.15 (m, 1H), 4.06 (d, 2H,  $J = 6.7$  Hz), 3.84 (s, 3H), 3.76 (s, 3H), 3.50 – 3.43 (m, 2H), 1.24 – 1.18 (m, 3H);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ); major *Z* isomer 159.5, 159.3, 143.9, 141.1, 134.4, 129.2, 128.7 (2C), 124.1, 122.4, 115.3, 113.6 (2C), 113.1, 68.5, 65.8, 55.4 (2C), 15.4; minor *E* isomer [only the most significant signals are listed] 159.09, 144.0, 143.9, 131.6, 131.1 (2C), 125.8, 120.5, 113.5, 113.0, 68.5, 65.87, 55.4 (2C), 15.44; MS (APCI+)  $m/z$  299.8 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3$ : C, 76.48; H, 7.43, found: C, 76.24; H, 7.21.

#### (Z)-2-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-6-methoxy naphthalene (2c)

Yield: 97%; yellow oil;  $R_f$ : 0.6 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2931, 2339, 2136, 1509, 1467, 1410, 1334, 1238, 1197, 1153, 1128, 1104, 1047, 1013, 924, 750, 646;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 55/45 complicates the spectrum] Major *Z* isomer 7.74 – 7.59 (m, 3H), 7.48 (dd, 1H,  $J = 8.6, 1.8$  Hz), 7.30 – 7.10 (m, 4H), 6.95 (q, 2H,  $J = 8.8$  Hz), 6.31 (t, 1H,  $J = 6.8$  Hz), 4.13 (d, 2H,  $J = 6.8$  Hz), 3.92 (s, 3H), 3.88 (s, 3H), 3.53 (t, 2H,  $J = 7.0$  Hz), 1.25 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.24 (t, 1H,  $J = 6.8$  Hz), 4.09 (d, 2H,  $J = 6.8$  Hz), 3.96 (s, 3H), 3.81 (s, 3H), 3.48 (q, 2H,  $J = 7.0$  Hz), 1.22 (t, 3H,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) major *E* isomer 159.1, 157.9, 144.2, 137.7, 134.1, 133.9, 131.8, 131.2 (2C), 128.8, 128.7, 126.9, 126.3, 125.3, 118.9, 113.6 (2C), 105.7, 68.6, 65.8, 55.5, 55.4, 15.4; minor *Z* isomer 159.3, 158.0, 144.2, 126.3, 134.8, 134.8, 134.1, 133.9, 129.0 (2C), 128.8, 128.7, 124.3, 119.1, 113.6 (2C), 105.8, 68.6, 65.8, 55.5, 55.4, 15.4. MS (APCI+)  $m/z$  349.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{24}\text{O}_3$ : C, 79.28; H, 6.94, found: C, 79.12; H, 6.81.

#### (Z)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-2-methoxybenzene (2d)

Yield: 77%; brownish oil;  $R_f$ : 0.45 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2836, 2228, 2033, 2011, 1606, 1510, 1463, 1418, 1415, 1374, 1286, 1174, 1098, 1034, 779, 735;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.33 (m, 1H), 7.19 (d, 2H,  $J = 8.9$  Hz), 7.09 (dd, 1H,  $J = 7.4, 1.8$  Hz), 7.02 – 6.85 (m, 2H), 6.79 (d, 2H,  $J = 8.9$  Hz), 6.25 (t, 1H,  $J = 6.5$  Hz), 3.91 (d, 2H,  $J = 6.5$  Hz), 3.78 (s, 3H), 3.70 (s, 3H), 3.42 (q, 2H,  $J = 7.0$  Hz), 1.17 (t, 3H,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 158.9, 157.0, 139.4, 133.7, 131.2, 128.9, 128.2, 127.1 (2C), 124.1, 120.5, 113.4 (2C), 111.1, 68.6, 65.4, 55.6, 55.2, 15.3; MS (ESI+)  $m/z$  321.1 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3$ : C, 76.48; H, 7.43, found: C, 76.33; H, 7.27.

#### (Z)-1-(benzyloxy)-2-(3-ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)benzene (2e)

Yield: 51%; brownish oil;  $R_f$ : 0.45 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2053, 1606, 1374, 1286, 1244, 1098, 1072, 1036, 837, 803, 749, 648;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) Only the major *Z* isomer is described 7.39 – 7.17 (m, 7H), 7.13 – 7.08 (m, 2H), 7.03 (m, 2H), 6.84 (d, 2H,  $J = 8.6$  Hz), 6.26 (t, 1H,  $J = 6.5$  Hz), 4.99 (s, 2H), 3.98 (d, 2H,  $J = 6.5$  Hz), 3.83 (s, 3H), 3.45 (q, 2H,  $J = 7.0$  Hz), 1.18 (t, 3H,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 159.1, 156.2, 140.2, 137.2, 134.3, 131.6, 129.0, 128.8, 128.4 (2C), 127.9 (2C), 127.6, 127.0 (2C), 124.9, 120.8, 113.6 (2C), 112.9, 70.1, 68.8, 65.6, 55.4, 15.4; MS (APCI+)  $m/z$  375.4 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{26}\text{O}_3$ : C, 80.18; H, 7.00, found: C, 79.67; H, 6.79.

#### (Z)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-4-methoxy-2-nitrobenzene (2f)

Yield: 97%; brownish oil;  $R_f$ : 0.63 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2972, 1606, 1529, 1510, 1462, 1353, 1246, 1181, 1099, 1032, 827, 804;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.56 (d, 1H,  $J = 2.4$  Hz), 7.31 – 7.21 (m, 2H), 7.16 (d, 2H,  $J = 8.9$  Hz), 6.81 (d, 2H,  $J = 8.9$  Hz), 6.25 (t, 1H,  $J = 6.8$  Hz), 3.93 (s, 3H), 3.88 (d, 2H,  $J = 6.8$  Hz), 3.79 (s, 3H), 3.43 (q, 2H,  $J = 7.0$  Hz), 1.18 (t, 3H,  $J = 7.0$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 159.5, 159.4, 149.7, 139.9, 133.4, 132.6, 127.9 (2C), 127.5, 124.9, 119.6, 113.8 (2C), 109.3, 68.1, 65.7, 55.4, 55.0, 15.3; MS (APCI-)  $m/z$  342 ( $\text{M-H}^-$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_5$ : C, 66.46; H, 6.16; N, 4.08, found: C, 66.11; H, 6.01; N, 3.97.



*(Z)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-2,3-dimethylbenzene (2g)*

Yield: 88%; yellow oil;  $R_f$ : 0.8 (EtOAc/c-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2930, 1606, 1510, 1460, 1291, 1248, 1177, 1099, 1037, 910, 826, 793, 730;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 95/5 complicates the spectrum] major *Z* isomer 7.17 (d, 2H,  $J = 8.9$  Hz), 7.15 – 7.07 (m, 2H), 6.93 (dd, 1H,  $J = 6.7, 2.3$  Hz), 6.79 (d, 2H,  $J = 8.9$  Hz), 6.26 (t, 1H,  $J = 6.4$  Hz), 3.91 – 3.81 (m, 2H), 3.78 (s, 3H), 3.41 (q, 2H,  $J = 7.0$  Hz), 2.30 (s, 3H), 2.00 (s, 3H), 1.17 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 5.78 (t, 1H,  $J = 6.4$  Hz), 4.19 (d, 1H,  $J = 6.4, 5.5$  Hz), 3.53 (q, 2H,  $J = 7.0$  Hz), 2.24 (s, 3H), 1.98 (s, 3H), 1.23 (t, 3H,  $J = 7.0$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 159.2, 142.8, 138.7, 137.0, 134.8, 133.3, 129.1, 127.6, 127.7 (2C), 125.3, 123.7, 113.6 (2C), 68.7, 65.6, 55.2, 20.4, 16.2, 15.2; MS (ESI+)  $m/z$  319.1 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_2$ : C, 81.04; H, 8.16, found: C, 80.89; H, 8.05.

*(Z)-2-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-1,3,5-trimethylbenzene (2h)*

Yield: 71%; colorless oil;  $R_f$ : 0.5 (EtOAc/c-hexane: 4/6); IR (v,  $\text{cm}^{-1}$ ) 2962, 2219, 2186, 2053, 1606, 1510, 1461, 1249, 1180, 1099, 1037, 828, 652, 617;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.16 (d, 2H,  $J = 8.6$  Hz), 6.90 (m, 2H), 6.78 (d, 2H,  $J = 8.6$  Hz), 6.33 (t, 1H,  $J = 6.3$  Hz), 3.77 (m, 5H), 3.40 (q, 2H,  $J = 7.0$  Hz), 2.32 (s, 3H), 2.05 (s, 6H), 1.16 (t, 3H,  $J = 7.0$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 159.2, 140.3, 136.7, 136.1 (2C), 135.3, 132.1, 128.3 (2C), 127.2 (2C), 123.6, 113.9 (2C), 69.0, 66.1, 55.4, 21.2, 19.9 (2C), 15.4; MS (ESI+)  $m/z$  311.2 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_2$ : C, 81.25; H, 8.44, found: C, 81.00; H, 8.19.

*(Z)-2-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-1,3,5-triisopropylbenzene (2i)*

Yield: 27%; colorless oil;  $R_f$ : 0.73 (EtOAc/c-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2925, 2187, 1607, 1510, 1249, 1180, 1100, 1036, 827;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 94/6 complicates the spectrum] major *Z* isomer 7.20 (d, 2H,  $J = 9.0$  Hz), 7.03 (s, 2H), 6.78 (d, 2H,  $J = 9.0$  Hz), 6.45 (t, 1H,  $J = 6.5$  Hz), 3.82 – 3.72 (m, 5H), 3.41 (q, 2H,  $J = 7.0$  Hz), 3.00 – 2.81 (m, 3H), 1.30 (d, 6H,  $J = 6.9$  Hz), 1.17 (t, 3H,  $J = 7.0$  Hz), 1.12 (d, 6H,  $J = 6.8$  Hz), 0.95 (d, 6H,  $J = 6.9$  Hz); minor *E* isomer [only the most significant signals are listed] 5.68 (t, 1H,  $J = 6.6$  Hz), 4.33 (d, 2H,  $J = 6.6$  Hz), 3.52 (q, 3H,  $J = 7.0$  Hz), 3.15 – 3.00 (m, 3H);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 158.9, 147.9, 146.3, 139.7, 132.9, 132.3, 127.3 (2C), 123.2, 120.9 (2C), 113.4 (2C), 69.3, 65.9, 55.1, 34.3, 30.4 (2C), 34.6, 24.5 (2C), 24.4 (2C), 24.1 (2C), 15.3. Anal. Calcd for  $\text{C}_{27}\text{H}_{38}\text{O}_2$ : C, 82.18; H, 9.71, found: C, 82.01; H, 9.66.

*(Z)-1-(4-Ethoxy-1-(4-methoxyphenyl)but-1-en-1-yl)-2-(methoxymethoxy)naphthalene (2j)*

Yield: 58%; yellow oil;  $R_f$ : 0.47 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2939, 1658, 1596, 1509, 1226, 1143, 1099, 837, 803, 749;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.90 – 7.69 (m, 3H), 7.49 (d, 1H,  $J = 9.1$  Hz), 7.40 – 7.31 (m, 2H), 7.21 (d, 2H,  $J = 8.9$  Hz), 6.76 (d, 2H,  $J = 8.9$  Hz), 6.48 (t, 1H,  $J = 7.2$  Hz), 5.20 (d, 1H,  $J = 6.8$  Hz), 5.12 (d, 2H,  $J = 6.8$  Hz), 3.74 (s, 3H), 3.49 – 3.30 (m, 7H), 2.25 – 2.08 (m, 2H), 1.13 (t, 3H,  $J = 7.0$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 158.8, 151.7, 136.1, 133.9, 133.2, 129.9, 129.1, 128.0, 127.2 (2C), 126.6, 125.7, 125.4, 124.1, 116.7, 113.7 (2C), 94.9, 69.9, 66.1, 56.1, 55.3, 30.8, 27.0, 15.3; MS (APCI+)  $m/z$  393.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{28}\text{O}_4$ : C, 76.50; H, 7.19, found: C, 76.34; H, 7.07.

*(Z)-2-(4-ethoxy-1-(4-methoxyphenyl)but-1-en-1-yl)phenyl(methyl)sulfane (2k)*

Yield: 55%; brownish oil;  $R_f$ : 0.75 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2972, 1606, 1509, 1434, 1375, 1289, 1245, 1180, 1107, 1035, 828, 793, 742, 633;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.38 – 7.12 (m, 5H), 7.09 (dd, 1H,  $J = 7.4, 1.3$  Hz), 6.80 (d, 2H,  $J = 8.9$  Hz), 6.20 (t, 1H,  $J = 7.4$  Hz), 3.77 (s, 3H), 3.54 – 3.40 (m, 4H), 2.35 (s, 3H), 2.24 (m, 2H), 1.19 (t, 3H,  $J = 7.0$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 158.9, 140.2, 138.2 (2C), 133.2, 130.3, 127.9, 127.4 (2C), 125.3, 124.5 (2C), 113.7 (2C), 70.1, 66.1, 55.3, 30.6, 15.3, 15.3; MS (APCI+)  $m/z$  329.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_2\text{S}$ : C, 73.13; H, 7.36, found: C, 73.00; H, 7.19.

*(Z)-1-(4-Ethoxy-1-(4-methoxyphenyl)but-1-en-1-yl)-4-methoxy-2-nitrobenzene (2l)*

Yield: 65%; brown oil;  $R_f$ : 0.63 (EtOAc/c-hexane: 4/6); IR (v,  $\text{cm}^{-1}$ ) 2972, 1606, 1509, 1434, 1375, 1289, 1245, 1180, 1107, 1035, 828, 793, 742, 633;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.53 (d, 1H,  $J = 2.4$  Hz), 7.25 (d, 1H,  $J = 8.4$  Hz), 7.19 (dd, 1H,  $J = 8.4, 2.4$  Hz), 7.12 (d, 2H,  $J = 8.9$  Hz), 6.78 (d,

2H,  $J = 8.9$  Hz), 6.09 (t, 1H,  $J = 7.5$  Hz), 3.90 (s, 3H), 3.77 (s, 3H), 3.47 – 3.42 (m, 4H), 2.22 (m, 2H), 1.18 (t, 3H,  $J = 7.0$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 159.3, 159.1, 149.7, 138.6, 133.3, 133.7, 127.7 (2C), 127.4, 125.0, 113.8 (2C), 119.8, 109.3, 69.9, 66.3, 55.9, 55.4, 30.8, 15.3; MS (APCI+)  $m/z$  358.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_5$ : C, 67.21; H, 6.49; N, 3.92, found: C, 67.05; H, 6.30; N, 3.68.

*(Z)-4-Methoxy-2-(methoxymethoxy)-1-(1-(4-methoxyphenyl)oct-1-en-1-yl)benzene (2m)*

Yield: 72%; colorless oil;  $R_f$ : 0.58 (EtOAc/c-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2978, 1514, 1434, 1375, 1183, 1107, 1035, 913, 828, 793, 742, 650;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.16 (d, 2H,  $J = 8.6$  Hz), 6.99 (d, 1H,  $J = 8.3$  Hz), 6.80 – 6.73 (m, 3H), 6.59 (dd, 1H,  $J = 8.3, 2.4$  Hz), 6.07 (t, 1H,  $J = 7.3$  Hz), 4.99 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.25 (s, 3H), 1.99 (q, 2H,  $J = 7.3$  Hz), 1.47 – 1.14 (m, 8H), 0.85 (t, 3H,  $J = 6.8$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 160.1, 155.8, 158.6, 136.9, 135.4, 132.1, 129.3, 127.4 (2C), 122.8, 113.5 (2C), 106.7, 102.3, 94.7, 55.9, 55.5, 55.4, 31.9, 30.1, 29.8, 29.2, 22.8, 14.2; MS (APCI+)  $m/z$  385.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{32}\text{O}_4$ : C, 74.97; H, 8.39, found: C, 74.89; H, 8.27.

*(Z)-4-Methoxy-1-(1-(4-methoxyphenyl)oct-1-en-1-yl)-2-nitrobenzene (2n)*

Yield: 52%; colorless oil;  $R_f$ : 0.64 (EtOAc/c-hexane: 5/5); IR (v,  $\text{cm}^{-1}$ ); 2972, 1701, 1606, 1509, 1434, 1289, 1180, 999, 802; [the presence of an inseparable impurity complicates the spectrum]  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) 7.52 (d, 1H,  $J = 1.9$  Hz), 7.20 (d, 1H,  $J = 8.1$  Hz), 7.17 (dd, 1H,  $J = 8.1, 1.9$  Hz), 7.11 (d, 2H,  $J = 8.5$  Hz), 6.78 (d, 2H,  $J = 8.5$  Hz), 3.91 (s, 3H), 3.77 (s, 3H), 1.95–1.84 (q, 2H,  $J = 6.9$  Hz), 1.43–1.33 (m, 2H), 1.29–1.11 (m, 4H), 0.85 (t, 3H,  $J = 6.9$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) 159.2, 158.9, 149.9, 136.7, 133.7, 133.6, 129.5, 127.8 (2C), 127.7, 113.7 (2C), 119.7, 109.1, 56.9, 55.4, 31.8, 30.0, 29.6, 29.1, 22.7, 14.2; MS (APCI+)  $m/z$  370.6 ( $\text{MH}^+$ ).

*(Z)-1-(3-Ethoxy-1-(3-methoxyphenyl)prop-1-en-1-yl)-2-methoxybenzene (2o)*

Yield: 32%; yellow oil;  $R_f$ : 0.23 (EtOAc/c-hexane: 5/95); IR (v,  $\text{cm}^{-1}$ ) 2924, 2834, 1597, 1578, 1482, 1469, 1434, 1373, 1335, 1294, 1244, 1169, 1130, 1096, 1049, 1026, 907, 883, 785, 751, 661, 631;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 96/4 complicates the spectrum] major *Z* isomer 7.33 (ddd, 1H,  $J = 8.2, 7.4, 1.9$  Hz), 7.16 (t, 1H,  $J = 8.2$  Hz), 7.09 (dd, 1H,  $J = 7.4, 1.9$  Hz), 6.99 (dd, 1H,  $J = 7.4, 1.1$  Hz), 6.94 (d, 1H,  $J = 8.2$  Hz), 6.88 – 6.81 (m, 2H), 6.77 (ddd, 1H,  $J = 8.2, 2.5, 1.1$  Hz), 6.34 (t, 1H,  $J = 6.4$  Hz), 3.93 (d, 2H,  $J = 6.4$  Hz), 3.76 (s, 3H), 3.70 (s, 3H), 3.43 (q, 2H,  $J = 7.0$  Hz), 1.17 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.03 (t, 1H,  $J = 6.6$  Hz), 4.15 (d, 2H,  $J = 6.6$  Hz);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 159.6, 157.2, 142.8, 139.9, 131.3, 129.1 (2C), 128.0, 127.0, 120.6, 119.4, 112.7, 112.4, 111.2, 68.8, 65.7, 55.7, 55.3, 15.4; MS (APCI+)  $m/z$  299.0 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{22}\text{O}_3$ : C, 76.48; H, 7.43, found: C, 76.30; H, 7.26.

*(Z)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-2-(methoxymethoxy)benzene (2p)*

Yield: 68%; colorless oil;  $R_f$ : 0.34 (EtOAc/c-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2930, 2149, 2010, 1606, 1510, 1487, 1450, 1373, 1246, 1198, 1180, 1152, 1076, 1036, 995, 906, 825, 755, 729;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 9/1 complicates the spectrum] major *Z* isomer 7.43 – 7.04 (m, 6H), 6.78 (d, 2H,  $J = 8.9$  Hz), 6.25 (t, 1H,  $J = 6.6$  Hz), 5.02 (s, 2H), 3.95 (d, 2H,  $J = 6.6$  Hz), 3.77 (s, 3H), 3.43 (q, 2H,  $J = 7.0$  Hz), 3.26 (s, 3H), 1.17 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.83 (d, 2H,  $J = 8.9$  Hz), 5.95 (t, 1H,  $J = 6.6$  Hz), 4.88 (s, 2H), 4.18 (d, 2H,  $J = 6.6$  Hz), 3.79 (s, 3H), 3.51 (q, 2H,  $J = 7.0$  Hz), 3.16 (s, 3H);  $\delta_C$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 158.9, 154.7, 139.8, 133.9, 131.4, 129.3, 128.9, 127.7 (2C), 124.7, 121.9, 115.2, 113.6 (2C), 94.4, 68.7, 65.6, 55.9, 55.2, 15.3; minor *E* isomer [only the most significant signals are listed] 131.2, 130.2, 129.1, 113.2, 94.5, 68.4, 55.8; MS (APCI+)  $m/z$  329.6 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_4$ : C, 73.15; H, 7.37, found: C, 72.97; H, 7.08.

*(Z)-2-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-1-(methoxymethoxy)-4-methylbenzene (2q)*

Yield: 50%; yellow oil;  $R_f$ : 0.38 (EtOAc/c-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2918, 1606, 1511, 1494, 1464, 1292, 1248, 1230, 1199, 1179, 1147, 1098, 1072, 1036, 1010, 985, 922, 823, 806, 732;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.22 (d, 2H,  $J = 8.9$  Hz), 7.11 (dd, 1H,  $J = 8.4, 2.2$  Hz), 7.05 (d, 1H,  $J = 8.4$  Hz), 6.93 (d, 1H,  $J = 2.2$  Hz), 6.80 (d, 2H,  $J = 8.9$  Hz), 6.24 (t, 1H,  $J = 6.5$  Hz), 4.99 (s, 2H), 3.96 (d, 2H,  $J = 6.5$  Hz), 3.78



(s, 3H), 3.45 (q, 2H,  $J = 7.0$  Hz), 3.27 (s, 3H), 2.30 (s, 3H), 1.19 (t, 3H,  $J = 7.0$  Hz);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 158.9, 152.5, 139.7, 133.9, 131.7, 131.2, 129.3, 129.0, 127.7 (2C), 124.5, 115.3, 113.4 (2C), 94.7, 68.7, 65.6, 55.8, 55.2, 20.5, 15.3; MS (ESI<sup>+</sup>)  $m/z$  365.2 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_4$ : C, 73.66; H, 7.65, found: C, 73.37; H, 7.31.

(*Z*)-3-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-4-(methoxy methoxy)benzonitrile (**2r**)

Yield: 52%; yellow oil;  $R_f$ : 0.53 (EtOAc/*c*-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2926, 2227, 1600, 1511, 1491, 1244, 1148, 1078, 1035, 923, 822, 785, 734, 669, 648;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.62 (dd, 1H,  $J = 8.6$ , 2.2 Hz), 7.44 (d, 1H,  $J = 2.2$  Hz), 7.22 (d, 1H,  $J = 8.6$  Hz), 7.13 (d, 2H,  $J = 8.9$  Hz), 6.80 (d, 2H,  $J = 8.9$  Hz), 6.28 (t, 1H,  $J = 6.6$  Hz), 5.09 (s, 2H), 3.87 (d, 2H,  $J = 6.6$  Hz), 3.78 (s, 3H), 3.42 (q, 2H,  $J = 7.0$  Hz), 3.22 (s, 3H), 1.18 (t, 3H,  $J = 7.0$  Hz);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 159.4, 158.1, 138.1, 135.2, 133.6, 132.8, 130.3, 127.6 (2C), 125.9, 119.0, 115.0, 113.8 (2C), 105.2, 94.1, 68.5, 65.9, 56.4, 55.4, 15.4; MS (ESI<sup>+</sup>)  $m/z$  376.1 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{23}\text{NO}_4$ : C, 71.37; H, 6.56; N, 3.96, found: C, 71.09; H, 6.37; N, 3.78.

(*Z*)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-4-methoxy-2-(methoxymethoxy)benzene (**2s**)

Yield: 64%; brown oil;  $R_f$ : 0.4 (EtOAc/*c*-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2835, 1605, 1575, 1510, 1464, 1442, 1395, 1289, 1245, 1216, 1152, 1097, 1071, 1036, 1004, 992, 923, 825, 805, 731;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 93/7 complicates the spectrum] major *Z* isomer 7.20 (d, 2H,  $J = 8.9$  Hz), 7.01 (d, 1H,  $J = 8.4$  Hz), 6.78 (d, 2H,  $J = 8.9$  Hz), 6.74 (d, 1H,  $J = 2.5$  Hz), 6.59 (dd, 1H,  $J = 8.4$ , 2.5 Hz), 6.21 (t, 1H,  $J = 6.5$  Hz), 4.99 (s, 2H), 3.95 (d, 2H,  $J = 6.5$  Hz), 3.83 (s, 3H), 3.77 (s, 3H), 3.43 (q, 2H,  $J = 7.0$  Hz), 3.25 (s, 3H), 1.17 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 7.08 (d, 1H,  $J = 8.4$  Hz), 6.53 (dd, 1H,  $J = 8.4$ , 2.5 Hz), 5.91 (t, 1H,  $J = 6.5$  Hz), 4.86 (s, 2H), 4.14 (d, 2H,  $J = 6.5$  Hz), 3.79 (s, 3H), 3.14 (s, 3H);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 160.3, 158.9, 155.6, 139.5, 134.2, 131.7, 127.7 (2C), 124.6, 121.5, 113.4 (2C), 106.5, 101.9, 94.5, 68.8, 65.5, 55.9, 55.3, 55.2, 15.3; minor *E* isomer [only the most significant signals are listed] 130.1, 126.9, 112.9, 106.1; MS (APCI<sup>+</sup>)  $m/z$  359.3 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_5$ : C, 70.37; H, 7.31, found: C, 70.25; H, 7.20.

(*Z*)-2-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-4-fluoro-1-(methoxy methoxy)benzene (**2t**)

Yield: 59%; colorless oil;  $R_f$ : 0.47 (EtOAc/*c*-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 1512, 1485, 1286, 1248, 903, 806, 792, 731, 649, 634, 619;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 94/6 complicates the spectrum] major *Z* isomer 7.18 (d, 2H,  $J = 8.8$  Hz), 7.14 – 7.07 (m, 1H), 7.04 – 6.95 (m, 1H), 6.88 – 6.83 (m, 1H), 6.80 (d, 2H,  $J = 8.8$ ), 6.25 (t, 1H,  $J = 6.6$  Hz), 4.95 (s, 2H), 3.93 (d, 2H,  $J = 6.6$  Hz), 3.78 (s, 3H), 3.43 (q, 2H,  $J = 7.0$  Hz), 3.27 (s, 3H), 1.18 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 5.96 (t, 1H,  $J = 6.2$  Hz), 4.79 (s, 2H), 4.15 (d, 2H,  $J = 6.5$  Hz), 3.19 (s, 3H);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 158.4, 156.7 (d,  $J$  231 Hz), 149.9, 137.8, 132.3, 126.8 (2C), 124.3, 116.9 (d,  $J$  22.6 Hz), 115.9 (d,  $J$  8.0 Hz), 114.3 (d,  $J$  22.7 Hz), 112.7 (2C), 94.3, 67.7, 64.9, 55.1, 54.4, 14.4. (one C missing);  $\delta_F$  (376 MHz,  $\text{CDCl}_3$ ) major *Z* isomer -122.0; MS (APCI<sup>+</sup>)  $m/z$  347.6 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{20}\text{H}_{23}\text{FO}_4$ : C, 69.35; H, 6.69, found: C, 69.32; H, 6.66.

(*Z*)-1-(3-Ethoxy-1-(4-methoxyphenyl)prop-1-en-1-yl)-2-(methoxy methoxy)naphthalene (**2u**)

Yield: 57%; yellow oil;  $R_f$ : 0.57 (EtOAc/*c*-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2939, 1658, 1596, 1509, 1487, 1462, 1450, 1373, 1246, 1226, 1143, 1099, 837, 803, 749, 728, 648;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.87 (d, 1H,  $J = 9.0$  Hz), 7.85 – 7.80 (m, 1H), 7.80 – 7.71 (m, 1H), 7.50 (d, 1H,  $J = 9.0$  Hz), 7.44 – 7.31 (m, 2H), 7.25 (d, 2H,  $J = 8.4$  Hz), 6.78 (d, 2H,  $J = 8.4$  Hz), 6.59 (t, 1H,  $J = 6.2$  Hz), 5.20 (d, 1H,  $J = 6.9$  Hz), 5.14 (d, 1H,  $J = 6.9$  Hz), 3.87 (dd, 1H,  $J = 12.9$ , 6.1 Hz), 3.80 – 3.72 (m, 4H), 3.38 – 3.29 (m, 5H), 1.11 (t, 3H,  $J = 7.0$  Hz);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 159.1, 151.6, 136.3, 133.1, 132.9, 129.8, 129.4, 128.0, 127.4 (2C), 126.8, 126.2, 125.3, 124.2, 116.6, 113.7 (2C), 94.9, 69.1, 65.8, 56.1, 55.2, 27.0, 15.23; MS (APCI<sup>+</sup>)  $m/z$  379.2 ( $\text{MH}^+$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{26}\text{O}_4$ : C, 76.17; H, 6.92, found: C, 76.01; H, 6.70.

(*Z*)-3-(3-Ethoxy-1-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)-4-(methoxy methoxy)benzonitrile (**2v**)

Yield: 83%; brown oil;  $R_f$ : 0.26 (EtOAc/*c*-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2226, 1581, 1490, 1411, 1343, 1241, 1125, 1077, 923, 821;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 93/7 complicates the

spectrum] major *Z* isomer 7.62 (dd, 1H,  $J = 8.7$ , 2.1 Hz), 7.44 (d, 1H,  $J = 2.1$  Hz), 7.21 (d, 1H,  $J = 8.7$  Hz), 6.39 (s, 2H), 6.30 (t, 1H,  $J = 6.5$  Hz), 5.09 (s, 2H), 3.86 (d, 2H,  $J = 6.5$  Hz), 3.79 (s, 3H), 3.74 (s, 6H), 3.42 (q, 2H,  $J = 7.0$  Hz), 3.19 (s, 3H), 1.16 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.99 (t, 1H,  $J = 6.8$  Hz), 5.00 (s, 2H), 4.11 (d, 2H,  $J = 6.8$  Hz), 3.09 (s, 3H);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 157.9, 153.1 (2C), 138.3, 138.0, 136.0, 135.0, 133.8, 129.8, 127.4, 118.8, 114.9, 105.1, 103.9 (2C), 93.9, 68.4, 66.1, 60.8, 56.2, 56.1 (2C), 15.2; MS (ESI<sup>+</sup>)  $m/z$  436.3 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{27}\text{NO}_6$ : C, 66.81; H, 6.58; N, 3.39, found: C, 66.75; H, 6.50; N, 3.29.

(*Z*)-1-(3-Ethoxy-1-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)-2-(methoxy methoxy)naphthalene (**2w**)

Yield: 83%; brownish oil;  $R_f$ : 0.43 (EtOAc/*c*-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2931, 2339, 2136, 2020, 1704, 1664, 1593, 1509, 1467, 1410, 1334, 1238, 1197, 1170, 1153, 1128, 1104, 1084, 1047, 1013, 924, 809, 750, 664, 646;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 7.86 (d, 1H,  $J = 9.2$  Hz), 7.85 – 7.71 (m, 2H), 7.49 (d, 1H,  $J = 9.0$  Hz), 7.43 – 7.32 (m, 2H), 6.62 (t, 1H,  $J = 6.0$  Hz), 6.54 (s, 2H), 5.17 (d, 1H,  $J = 6.9$  Hz), 5.11 (d, 1H,  $J = 6.9$  Hz), 3.89 – 3.71 (m, 2H), 3.80 (s, 3H), 3.69 (s, 6H), 3.34 (s, 3H), 3.31 (q, 2H,  $J = 7.0$  Hz), 1.09 (t, 3H,  $J = 7.0$  Hz);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) only the major *Z* isomer is described 150.7 (2C), 136.7, 136.2, 135.7, 132.0, 128.8, 128.4, 128.1 (2C), 127.1, 126.3, 125.8, 125.2 (2C), 124.4, 123.3, 122.4, 115.6, 93.9, 68.1, 64.9, 55.2 (2C), 20.2, 14.3; MS (ESI<sup>+</sup>)  $m/z$  461.3 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{30}\text{O}_6$ : C, 71.21; H, 6.90, found: C, 71.00; H, 6.71.

(*Z*)-2-Bromo-4-(3-ethoxy-1-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)-1-methoxy-3-(methoxymethoxy)benzene (**2x**)

Yield: 80%; yellow oil;  $R_f$ : 0.31 (EtOAc/*c*-hexane: 3/7); IR (v,  $\text{cm}^{-1}$ ) 2935, 1581, 1462, 1415, 1285, 1239, 1126, 1006;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 91/9 complicates the spectrum] major *Z* isomer 7.02 (d, 1H,  $J = 8.7$  Hz), 6.72 (d, 1H,  $J = 8.7$  Hz), 6.50 (s, 2H), 6.26 (t, 1H,  $J = 6.2$  Hz), 4.97 (s, 2H), 3.94 – 3.81 (m, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.76 (s, 6H), 3.49 – 3.43 (m, 5H), 1.19 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 7.06 (d, 1H,  $J = 8.7$  Hz), 6.65 (d, 1H,  $J = 8.7$  Hz), 6.44 (s, 2H), 6.05 (t, 1H,  $J = 6.2$  Hz), 5.00 (s, 2H), 4.11 (d, 2H,  $J = 6.2$  Hz), 3.78 (s, 6H), 3.52 (s, 3H);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 156.9, 153.6, 153.1 (2C), 138.9, 138.0, 136.9, 130.8, 127.2, 126.3, 107.7, 107.4, 104.6 (2C), 99.1, 69.0, 66.3, 61.0, 57.9, 56.6, 56.3 (2C), 15.4; minor *E* isomer [only the most significant signals are listed] 128.9, 106.7, 99.4, 68.2, 66.1, 61.0; MS (ESI<sup>+</sup>)  $m/z$  520.6 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{29}\text{BrO}_7$ : C, 55.54; H, 5.88, found: C, 55.27; H, 5.36.

(*Z*)-1-(3-ethoxy-1-(*p*-tolyl)prop-1-en-1-yl)-2-(methoxymethoxy)naphthalene (**2y**)

Yield: 85%; pale yellow oil;  $R_f$ : 0.43 (EtOAc/*c*-hexane: 1/9); IR (v,  $\text{cm}^{-1}$ ) 2931, 2339, 2136, 2020, 1704, 1664, 1593, 1509, 1467, 1410, 1334, 1238, 1197, 1170, 1153, 1128, 1104, 1084, 1047, 1013, 924, 809, 750, 664, 646;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 97/3 complicates the spectrum] major *Z* isomer 7.86 (d, 1H,  $J = 9.1$  Hz), 7.84 – 7.78 (m, 1H), 7.75 – 7.69 (m, 1H), 7.48 (d, 1H,  $J = 9.0$  Hz), 7.39 – 7.32 (m, 2H), 7.18 (d, 2H,  $J = 8.0$  Hz), 7.02 (d, 2H,  $J = 8.0$  Hz), 6.62 (t, 1H,  $J = 6.0$  Hz), 5.17 (d, 1H,  $J = 6.9$  Hz), 5.11 (d, 1H,  $J = 6.9$  Hz), 3.85 (dd, 1H,  $J = 13.0$ , 6.0 Hz), 3.74 (dd, 1H,  $J = 13.0$ , 6.0 Hz), 3.33 (s, 3H), 3.31 (q, 2H,  $J = 7.0$  Hz), 2.28 (s, 3H), 1.09 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 5.89 (t, 1H,  $J = 6.0$  Hz), 4.39 (d, 2H,  $J = 6.0$  Hz);  $\delta_c$  (75 MHz,  $\text{CDCl}_3$ ) major *Z* isomer 150.7, 136.7, 136.2, 135.7, 132.0, 128.8, 128.4, 128.1 (2C), 127.1, 126.3, 125.8, 125.2 (2C), 124.4, 123.3, 122.4, 115.6, 93.9, 68.1, 64.9, 55.2, 20.2, 14.3; MS (ESI<sup>+</sup>)  $m/z$  385.3 ( $\text{MNa}^+$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{26}\text{O}_3$ : C, 79.53; H, 7.23, found: C, 79.39; H, 7.10.

(*Z*)-1-(3-Ethoxy-1-(*p*-tolyl)prop-1-en-1-yl)-4-methoxy-2-(methoxy methoxy)benzene (**2z**)

Yield: 94%; brown oil;  $R_f$ : 0.66 (EtOAc/*c*-hexane: 2/8); IR (v,  $\text{cm}^{-1}$ ) 2973, 2362, 1607, 1576, 1509, 1466, 1441, 1396, 1374, 1298, 1248, 1217, 1153, 1118, 1097, 1072, 1039, 1005, 924, 831, 810, 729, 629;  $\delta_H$  (300 MHz,  $\text{CDCl}_3$ ) [the presence of *Z/E* isomers in a ratio of 91/9 complicates the spectrum] major *Z* isomer 7.17 (d, 2H,  $J = 8.2$  Hz), 7.05 (d, 2H,  $J = 8.2$  Hz), 7.01 (d, 1H,  $J = 8.4$  Hz), 6.75 (d, 1H,  $J = 2.3$  Hz), 6.59 (dd, 1H,  $J = 8.4$ , 2.3 Hz), 6.27 (t, 1H,  $J = 6.5$  Hz), 4.99 (s, 2H), 3.97 (d, 2H,  $J = 6.5$  Hz), 3.83 (s, 3H), 3.44 (q, 2H,  $J = 7.0$  Hz), 3.25 (s, 3H), 2.31 (s, 3H), 1.18 (t, 3H,  $J = 7.0$  Hz); minor *E* isomer [only the most significant signals are listed] 6.53 (dd, 1H,  $J = 8.4$ , 2.4 Hz), 5.95 (t, 1H,  $J = 6.6$  Hz), 4.85 (s, 2H), 4.15 (d, 2H,  $J = 6.6$  Hz), 3.79 (s, 3H), 3.14 (s, 3H), 2.33 (s, 3H);  $\delta_c$  (75



MHz, CDCl<sub>3</sub>) 160.4, 155.8, 140.0, 138.9, 137.0, 132.0, 128.9 (2C), 126.6 (2C), 125.8, 121.7, 106.6, 102.1, 94.7, 68.9, 65.7, 56.0, 55.5, 21.2, 15.4; MS (ESI<sup>+</sup>) *m/z* 365 (MNa<sup>+</sup>). Anal. Calcd for C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>: C, 73.66; H, 7.65, found: C, 73.54; H, 7.54.

**(Z)-1-(4-Ethoxy-1-(4-methoxyphenyl)but-1-en-1-yl)-2-(methoxy methoxy)benzene (5)**

Yield: 71%; yellow oil; R<sub>f</sub>: 0.76 (EtOAc/c-hexane: 8/2); IR (v, cm<sup>-1</sup>) 2939, 1658, 1509, 1487, 1462, 1450, 1373, 1226, 1143, 837, 803, 749, 648; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) [the presence of Z/E isomers in a ratio of 95/5 complicates the spectrum] major Z isomer 7.32 – 7.25 (m, 1H), 7.18 (d, 2H, J = 8.7 Hz), 7.15 – 7.10 (m, 2H), 7.08 – 7.00 (m, 1H), 6.79 (d, 2H, J = 8.7 Hz), 6.16 (t, 1H, J = 7.3 Hz), 5.03 (s, 2H), 3.77 (s, 3H), 3.51 – 3.39 (m, 4H), 3.27 (s, 3H), 2.30 (q, 2H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz); minor E isomer [only the most significant signals are listed] 5.90 (t, 1H, J = 7.4 Hz), 4.98 (s, 2H), 2.66 (q, 2H, J = 7.1 Hz); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) major Z isomer 158.7, 154.8, 139.1, 134.6, 131.7, 130.0, 128.7, 127.5 (2C), 124.5, 121.9, 115.3, 113.5 (2C), 94.5, 70.3, 66.2, 55.9, 55.3, 30.8, 15.3; MS (APCI<sup>+</sup>) *m/z* 343.5 (MH<sup>+</sup>). Anal. Calcd for C<sub>21</sub>H<sub>26</sub>O<sub>4</sub>: C, 73.66; H, 7.65, found: C, 73.27; H, 7.39.

**General procedure for PTSA assisted cyclisation:** An ethanolic (8 mL) solution of trisubstituted olefin **2** (0.5 mmol) and PTSA (171 mg, 1.5 mmol) was refluxed for 1 h. After cooling to room temperature, water was added (10 mL) and the media was extracted with EtOAc (3 x 10 mL). The organic layers were then washed with brine, dried over Na<sub>2</sub>SO<sub>3</sub>, concentrated and the crude product was purified by column flash chromatography on silica gel.

**4-(4-Methoxyphenyl)-2H-chromene (1a)<sup>[10]</sup>**

Yield: 100%; yellow oil; R<sub>f</sub> (30% AcOEt/Cyclohexane) 0.58; IR (v, cm<sup>-1</sup>) 2040, 1609, 1226, 1143, 1099, 1029, 994, 907, 618; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.27 (dd, 2H, J = 11.1, 3.5 Hz), 7.16 (td, 1H, J = 8.1, 1.6 Hz), 7.03 (dd, 1H, J = 7.7, 1.5 Hz), 6.93 (d, 2H, J = 8.8 Hz), 6.97 – 6.80 (m, 2H), 5.76 (t, 1H, J = 4.0 Hz), 4.84 (d, 2H, J = 4.0 Hz), 3.85 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 159.3, 154.8, 136.7, 130.7, 129.7 (2C), 129.2, 125.9, 123.9, 121.1, 119.2, 116.2, 113.8 (2C), 65.3, 55.3; MS (APCI<sup>+</sup>) *m/z* 239 (MH<sup>+</sup>).

**4-(4-Methoxyphenyl)-6-methyl-2H-chromene (1b)**

Yield: 52%; yellow oil; R<sub>f</sub>: 0.75 (EtOAc/c-hexane: 3/7); IR (v, cm<sup>-1</sup>) 2928, 2040, 1609, 1511, 1490, 1462, 1342, 1293, 1247, 1229, 1177, 1125, 1035, 838, 805, 612; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.26 (d, 2H, J = 8.9 Hz), 6.99 – 6.90 (m, 3H), 6.80 (d, 2H, J = 8.9 Hz), 5.75 (t, 1H, J = 3.9 Hz), 4.79 (d, 2H, J = 3.9 Hz), 3.86 (s, 3H), 2.20 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 158.4, 139.9, 135.9, 129.5, 128.9 (2C), 128.7, 125.4, 122.9, 118.5, 115.0, 112.9 (2C), 109.6, 64.3, 54.5, 19.9; MS (APCI<sup>+</sup>) *m/z* 253.1 (MH<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>: C, 80.93; H, 6.39, found: C, 80.74; H, 6.28.

**4-(4-Methoxyphenyl)-2H-chromene-6-carbonitrile (1c)**

Yield: 59%; yellow oil; R<sub>f</sub>: 0.7 (EtOAc/c-hexane: 3/7); IR (v, cm<sup>-1</sup>) 2935, 2224, 1609, 1512, 1488, 1344, 1243, 1177, 1122, 1061, 1034, 904, 838, 809, 729, 649; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.42 (dd, 1H, J = 8.4, 2.0 Hz), 7.29 (d, 1H, J = 2.0 Hz), 7.22 (d, 2H, J = 8.7 Hz), 6.96 (d, 2H, J = 8.7 Hz), 6.90 (d, 1H, J = 8.4 Hz), 5.79 (t, 1H, J = 3.8 Hz), 4.97 (d, 2H, J = 3.8 Hz), 3.86 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 158.4, 139.9, 135.9, 129.5, 128.9 (2C), 128.7, 125.4, 122.9, 118.5, 115.0, 112.9 (2C), 109.6, 64.3, 54.5, 19.9; MS (APCI<sup>+</sup>) *m/z* 264.1 (MH<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>13</sub>NO<sub>2</sub>: C, 77.55; H, 4.98; N, 5.32, found: C, 77.41; H, 4.79; N, 5.12.

**7-Methoxy-4-(4-methoxyphenyl)-2H-chromene (1d)**

Yield: 68%; colorless oil; R<sub>f</sub>: 0.4 (EtOAc/c-hexane: 2/8); IR (v, cm<sup>-1</sup>) 2020, 1704, 1636, 803, 781, 749, 728, 698, 612; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.26 (d, 2H, J = 2H, J = 8.8 Hz), 6.96 – 6.89 (m, 3H), 6.48 – 6.39 (m, 2H), 5.60 (t, 1H, J = 4.0 Hz), 4.79 (d, 2H, J = 4.0 Hz), 3.83 (s, 3H), 3.78 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 160.5, 159.3, 156.2, 136.5, 130.9, 130.0, 126.8, 117.2, 116.3, 113.8, 106.9, 102.0, 65.6, 55.4, 55.3 (2C missing); MS (ESI<sup>+</sup>) *m/z* 269.2 (MH<sup>+</sup>). The spectral data above are in accordance with the literature data<sup>[7]</sup>.

**6-Fluoro-4-(4-methoxyphenyl)-2H-chromene (1e)**

Yield: 61%; yellow oil; R<sub>f</sub>: 0.45 (EtOAc/c-hexane: 1/9); IR (v, cm<sup>-1</sup>) 1512, 1485, 1248, 903, 806, 731, 649, 619; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.26 (d, 2H, J = 8.4 Hz), 6.94 (d, 2H, J = 8.4 Hz), 6.86 – 6.69 (m, 3H), 5.82 (t, 1H, J = 3.9 Hz), 4.80 (d, 2H, J = 3.9 Hz), 3.85 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 159.7, 159.1, 153.4 (d, J = 383.8 Hz), 136.4, 130.2, 129.8 (2C), 125.3, 120.5, 117.1 (d, J = 8.1 Hz), 115.3 (d, J = 23.4 Hz), 114.1 (2C), 112.5 (d, J = 24.8 Hz), 65.5, 55.5, (1C missing); δ<sub>F</sub> (175 MHz, CDCl<sub>3</sub>) -122.3 (td, J = 9.3, 6.6 Hz);

MS (APCI<sup>+</sup>) *m/z* 257.0 (MH<sup>+</sup>). Anal. Calcd for C<sub>16</sub>H<sub>13</sub>FO<sub>2</sub>: C, 74.99; H, 5.11, found: C, 74.78; H, 4.99.

**1-(4-Methoxyphenyl)-3H-benzof[chromene (1f)**

Yield: 78%; yellow oil; R<sub>f</sub>: 0.75 (EtOAc/c-hexane: 1/8); IR (v, cm<sup>-1</sup>) 1658, 1596, 1509, 1462, 1246, 1226, 1143, 1099, 1029, 994, 907, 837, 803, 781, 749, 728, 648, 615; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.77 (d, 2H, J = 8.5 Hz), 7.34 – 7.06 (m, 6H), 6.88 (d, 2H, J = 8.5 Hz), 5.96 (t, 1H, J = 4.9 Hz), 4.68 (d, 2H, J = 4.9 Hz), 3.84 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 159.0, 155.1, 137.6, 133.6, 130.35, 130.3, 130.1, 128.8 (2C), 128.4, 126.6, 125.2, 123.3, 119.1, 117.75, 117.7, 113.8 (2C), 64.5, 55.3; MS (ESI<sup>+</sup>) *m/z* 311.02 (MNa<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>: C, 83.31; H, 5.59, found: C, 83.00; H, 5.32. The spectral data above are in accordance with the literature data<sup>[10]</sup>.

**1-(3,4,5-Trimethoxyphenyl)-2H-chromene-6-carbonitrile (1g)**

Yield: 77%; colorless oil; R<sub>f</sub>: 0.51 (EtOAc/c-hexane: 4/6); IR (v, cm<sup>-1</sup>) 2224, 1580, 1507, 1488, 1409, 1355, 1240, 1123, 1063, 1005, 943, 825, 733; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.43 (dd, 1H, J = 8.4, 2.0 Hz), 7.30 (d, 1H, J = 2.0 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.48 (s, 2H), 5.83 (t, 1H, J = 3.7 Hz), 4.98 (d, 2H, J = 3.7 Hz), 3.91 (s, 3H), 3.86 (s, 6H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 158.4, 153.6 (2C), 138.3, 135.7, 133.6, 132.6, 129.9, 124.3, 121.1, 119.3, 117.4, 105.7 (2C), 104.6, 66.1, 61.1, 56.4 (2C); MS (APCI<sup>+</sup>) *m/z* 324.3 (MH<sup>+</sup>). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>: C, 70.58; H, 5.30; N, 4.33, found: C, 70.25; H, 5.18; N, 4.29.

**1-(3,4,5-Trimethoxyphenyl)-3H-benzof[chromene (1h)**

Yield: 91%; colorless oil; R<sub>f</sub>: 0.72 (EtOAc/c-hexane: 3/7); IR (v, cm<sup>-1</sup>) 2930, 1580, 1508, 1464, 1414, 1343, 1232, 1126, 997, 815, 732; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.74 (m, 2H), 7.25 – 7.06 (m, 4H), 6.40 (s, 2H), 6.01 (t, 1H, J = 4.8 Hz), 4.69 (d, 2H, J = 4.8 Hz), 3.89 (s, 3H), 3.70 (s, 6H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 154.1, 152.3 (3C), 137.2, 135.9, 129.71, 129.4, 129.1, 127.4, 125.6, 124.4, 122.5, 118.8, 116.8, 116.6, 104.3 (2C), 63.6, 60.2, 55.3 (2C); MS (APCI<sup>+</sup>) *m/z* 349.3 (MH<sup>+</sup>). Anal. Calcd for C<sub>22</sub>H<sub>20</sub>O<sub>4</sub>: C, 75.84; H, 5.79, found: C, 75.75; H, 5.70.

**8-Bromo-7-methoxy-4-(3,4,5-trimethoxyphenyl)-2H-chromene (1i)**

Yield: 95%; colorless oil; R<sub>f</sub>: 0.24 (EtOAc/c-hexane: 3/7); IR (v, cm<sup>-1</sup>) 3663, 3324, 2974, 2224, 2012, 1608, 1511, 1487, 1442, 730, 700; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 6.96 (d, 1H, J = 8.6 Hz), 6.52 (s, 2H), 6.43 (d, 1H, J = 8.6 Hz), 5.70 (t, 1H, J = 3.9 Hz), 4.93 (d, 2H, J = 3.9 Hz), 3.88 (s, 6H), 3.84 (s, 6H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 157.0, 153.3 (2C), 153.2, 136.9, 138.8, 125.3, 119.6, 118.3, 117.5, 105.8 (2C), 104.1, 100.3, 66.3, 61.0, 56.5, 56.3 (2C); MS (APCI<sup>+</sup>) *m/z* 407.2, 409.1 (MH<sup>+</sup>). Anal. Calcd for C<sub>19</sub>H<sub>19</sub>BrO<sub>5</sub>: C, 56.03; H, 4.70, found: C, 55.80; H, 4.63.

**1-p-Tolyl-3H-benzof[chromene (1j)**

Yield: 74%; colorless oil; R<sub>f</sub>: 0.68 (EtOAc/c-hexane: 5/95); IR (v, cm<sup>-1</sup>) : 2934, 1672, 1579, 1499, 1410, 1374, 1335, 1235, 1168, 1124, 1031, 1007, 910, 835, 789, 730; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.74 (d, 2H, J = 8.6 Hz), 7.26 – 7.04 (m, 8H), 5.96 (t, 1H, J = 4.9 Hz), 4.68 (d, 2H, J = 4.9 Hz), 2.38 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 155.1, 138.5, 138.0, 137.0, 130.5, 130.3, 130.2, 128.5, 129.3 (2C), 127.8 (2C), 126.8, 125.3, 123.4, 119.8, 117.9, 117.8, 64.7, 21.4; MS (APCI<sup>+</sup>) *m/z* 273.4 (MH<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>16</sub>O: C, 88.20; H, 5.92, found: C, 87.79; H, 5.62.

**7-Methoxy-4-p-tolyl-2H-chromene (1k)**

Yield: 79%; colorless oil; R<sub>f</sub>: 0.55 (EtOAc/c-hexane: 1/9); IR (v, cm<sup>-1</sup>) 2955, 1612, 1567, 1502, 1376, 1346, 1309, 1281, 1195, 1160, 1128, 1115, 1034, 973, 805, 741; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.23 – 7.19 (m, 4H), 6.95 (d, 1H, J = 8.5 Hz), 6.50 (d, 1H, J = 2.4 Hz), 6.42 (dd, 1H, J = 8.5, 2.4 Hz), 5.64 (t, 1H, J = 3.9 Hz), 4.83 (d, 2H, J = 3.9 Hz), 3.80 (s, 3H), 2.40 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 160.7, 156.2, 137.6, 137.0, 135.7, 129.2 (2C), 128.6 (2C), 126.9, 117.2, 116.7, 106.9, 102.0, 65.7, 55.5, 21.4; MS (APCI<sup>+</sup>) *m/z* 253.0 (MH<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>: C, 80.93; H, 6.36, found: C, 80.74; H, 6.30.

**5-(4-methoxycyclohexa-2,4-dien-1-yl)-2,3-dihydrobenzo[b]oxepine (4)**

Yield: 64%; colorless oil; R<sub>f</sub>: 0.66 (EtOAc/c-hexane: 2/8); IR (v, cm<sup>-1</sup>) 2933, 2238, 2163, 2012, 1608, 1511, 1487, 1442, 1248, 1180, 1036, 825, 760; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.24 – 7.18 (m, 3H), 7.10 (d, 1H, J = 7.8 Hz), 7.03 – 6.98 (m, 2H), 6.86 (d, 2H, J = 8.8 Hz), 6.26 (t, 1H, J = 6.2 Hz), 4.50 (t, 2H, J = 6.2 Hz), 3.83 (s, 3H), 2.47 (q, 2H, J = 6.2 Hz); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 159.1, 158.0, 141.2, 135.4, 133.1, 131.3, 129.8 (2C), 128.5, 127.2, 123.3, 122.0, 113.7 (2C), 78.0, 55.4, 30.0; MS (APCI<sup>+</sup>) *m/z* 237.0 (MH<sup>+</sup>). Anal. Calcd for C<sub>17</sub>H<sub>18</sub>O<sub>2</sub>: C, 80.28; H, 7.13, found: C, 80.12; H, 6.97.



## Acknowledgments

The CNRS is gratefully acknowledged for financial support of this research. We thank the MNRES for a financial fellowship to E.R. and ICSN for a doctoral fellowship to B.T. Our laboratory BioCIS-UMR 8076 is a member of the Laboratory of Excellence LERMIT supported by a grant from ANR (ANR-10-LABX-33).

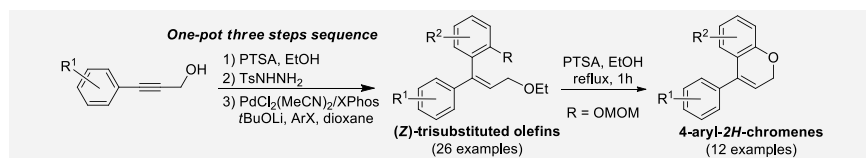
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Received: ((will be filled in by the editorial staff))  
Published online: ((will be filled in by the editorial staff))



## Entry for the Table of Contents

### Layout 2:



A one pot three-steps synthesis of (Z)-trisubstituted olefins from arylalkynols is presented. Olefins having an ortho-OMOM substituent were successfully transformed into 4-aryl-2H-chromenes using PTSA in EtOH in good to excellent yields.

(Heterocycle synthesis)

Evelia Rasolofonjatovo, Bret Tréguier,  
Olivier Provot,\* Abdallah Hamze, Jean-  
Daniel Brion and Mouâd Alami\* Page  
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A one pot three-steps synthesis of Z-trisubstituted olefins from arylalkynes and their cyclization into 4-aryl-2H-chromenes

Keywords: (Alkyne hydration/ Olefin / Chromene / N-tosylhydrazone/ Palladium)



