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Cycloisomerization of γ- and δ-acetylenic acids catalyzed by gold(I) chloride

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Abstract—We have developed a gold(I)-catalyzed intramolecular cyclization of γ- and δ-alkyne acids in mild conditions yielding various alkylidene lactones. Whereas a slight electronic effect of the R group was observed on the regioselectivity, bulky substituents on the R group bearing the alkyne strongly modify the reactivity. The cycloisomerization of *o*-alkynylbenzoic methyl esters was achieved rather with $AuCl_3$ as catalyst owing the presence of water affording exclusively the isocoumarins.
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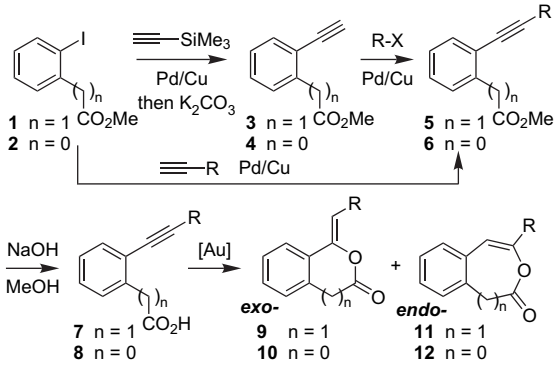
1. Introduction

Because of their wide range of biological properties and use as intermediates in the total synthesis of natural products, there is still significant interest in the preparation of alkylidene lactones.[1] Therefore many synthetic efforts have been directed toward synthesis to such derivatives.[2] Numerous methods reported consist of the use of transition metal,[3] electrophilic reagents[4] or organic acids, and bases[5] to catalyze or promote intramolecular addition of carboxylic acids (or esters) to alkynes. Although the usefulness of gold complexes for activation of alkynes was evidenced some years ago,[6] the catalytic activity of gold(I) chloride for cycloisomerization of acetylenic acids was described only recently,[7] which prompts us to report our results in the preparation of γ-alkylidene phthalides and alkylidene benzopyran-3-one from easily available γ- and δ-acetylenic acids, respectively.

As part of our ongoing interest in the potential photoprotective compounds,[8] we planned to synthesize various alkylidene lactones by varying the nature of the R group. Thus we expect to observe an impact on the profile of the UV spectra and to improve their photoprotective properties. A three step approach has been examined involving the preparation of *o*-(1-alkynyl)-benzoate esters **6** and *o*-(1-alkynyl)-phenylacetate esters **5** by a Sonogashira coupling reaction,[9] saponification, and gold-catalyzed ring-closure reaction (Scheme 1).



Scheme 1. Selected route to prepare various alkylidene lactones.

The intramolecular cyclization of γ- or δ-acetylenic acids can afford both the *exo*- and *endo*-derivatives. However, based on previously reported results,[7] we expected to obtain with high regioselectivity the *exo*-adduct without the influence of the R group.

2. Results and discussion

In order to examine the gold-catalyzed cycloisomerization to give alkylidene lactones, a variety of *o*-(1-alkynyl)-benzoate

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and *o*-(1-alkynyl)-phenylacetate methyl esters and their corresponding acids were synthesized and the results of these preparations are summarized in Table 1. The annulation precursors were prepared by a Sonogashira coupling reaction from **1** and **2** according to classical reaction conditions (see Section 4). The esters and the acids prepared after treatment with aq NaOH are isolated in good yields.

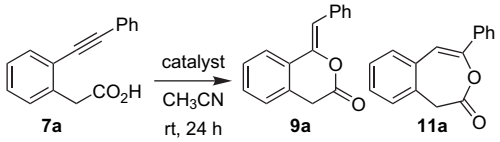
Table 1. Yield of formation of esters **5** and **6** and acids **7** and **8**

Entry	R	Ester	Procedure[a]	Yield (%)	Acid[b]	Yield (%)
1	Ph	**5a**	1	83	**7a**	93
2	*p*-$MeOC_6H_4$	**5b**	1	83	**7b**	90
3	*m*-FC_6H_4	**5c**	1	83	**7c**	80
4	2-Pyridinyl	**5d**	2	62	**7d**	52
5	2-Ethyl-6-methylphenyl	**5e**	1	52	**7e**	97
6	*o*-Tolyl	**5f**	1	75	**7f**	96
7	H	**3**	—	88	**7g**	97
8	Propyl	**5h**	2	92	**7h**	84
9	Ph	**6a**	1	93	**8a**	63
10	*p*-$MeOC_6H_4$	**6b**	1	84	**8b**	66
11	*m*-FC_6H_4	**6c**	1	89	**8c**	88
12	2-Pyridinyl	**6d**	2	86	**8d**	59
13	2-Ethyl-6-methylphenyl	**6e**	1	40	**8e**	99
14	*o*-Tolyl	**6f**	1	84[c]	**8f**	92
15	H	**4**	—	97	**8g**	99[d]
16	Propyl	**6h**	2	98	**8h**	86

[a] See Section. 4.
[b] NaOH (5%) of 1.3 equiv was used.
[c] P(*t*-Bu)$_3$ was used instead of PPh_3.
[d] NaOH (10%) of 12 equiv was used.

The search for optimal cycloisomerization conditions was conducted using δ-acetylenic acid **7a** as a model compound by varying the catalyst's system in acetonitrile (Table 2) and then the solvent. Best results giving the mixture of alkylidene lactones **9a/11a** were obtained by using identical conditions to those previously described by Pale (10 mol % AuCl in the presence of 10 mol % K_2CO_3).[7b] In the absence of K_2CO_3 (entry 2) we only observed the formation of traces of products contrary to the results reported by Genêt et al.[7a,c,10] No cycloisomerization occurred in the presence of $AuCl_3/K_2CO_3$ (entry 4) and only 50% conversion was noticed with the more elaborated Au[(*o*-biphenyl)P-(*t*-Bu)$_2$]Cl[11] (entry 5). Other electrophilic agents were evaluated and the use of silver salts as catalysts in the presence of potassium carbonate afforded the cycloisomerization in incomplete conversion after 24 h (entries 6 and 7). Various solvents were also tested with $AuCl/K_2CO_3$ as a catalytic system. Only in methylene chloride **7a** gave **9a/11a** without notable influence of the *exo*-selectivity. The acetylenic acid **7a** remained unchanged in THF, dioxane, toluene or DMF. It should be also pointed out that although the gold chloride is well known to promote hydratation of alkynes, this reaction could also be realized in wet acetonitrile[12] without the formation of the corresponding ketones and loss of reactivity.

Table 2. Lactonization of **7a** with various catalysts



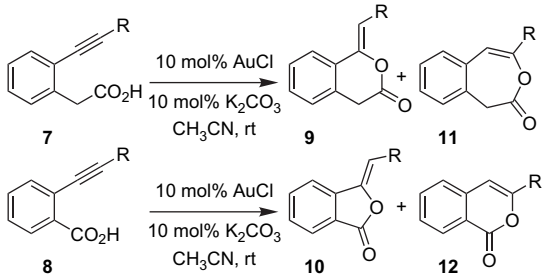
Entry	Catalyst (10 mol %)	Conversion[a,b] (%)
1	AuCl, K_2CO_3	100[c]
2	AuCl	5
3	K_2CO_3	NR
4	$AuCl_3$, K_2CO_3	NR
5	Au[(*o*-biphenyl)P(*t*-Bu)$_2$]Cl, K_2CO_3	50
6	AgOTf, K_2CO_3	80
7	$AgSbF_6$, K_2CO_3	80

[a] Based on the formation of the lactone, determined by ^{1}H NMR, *exo*/*endo* mixture.
[b] NR=no reaction.
[c] Complete conversion after 12 h.

Therefore we decided to use catalytic amount of gold(I) chloride and potassium carbonate in acetonitrile to prepare some γ-alkylidene phthalides and alkylidene benzopyran-3-one from γ- and δ-acetylenic acids, respectively. The substrates were chosen in order to examine the regioselectivity and the limitations of the present catalytic process. The results are reported in Table 3. Both chain length, and electronic and steric effects influenced the reactivity and the regiochemical outcome of the studied reaction.

Although some alkylidene lactones are not easy to purify, they are obtained with satisfactory yields as a mixture of *exo*- and *endo*-adducts. Baldwin's rules[13] indicate that both 5- or 6-*exo*-dig and 6- or 7-*endo*-dig cyclizations are favorable; however, the *exo*-dig mode of cyclization

Table 3. AuCl-catalyzed lactones formation in acetonitrile



Entry	Acid	R	*t* (h)	*exo*/*endo*[a]	Yield[b,c] (%)
1	**7a**	Ph	12	6/1	62
2	**7b**	*p*-$MeOC_6H_4$	12	2/1	54
3	**7c**	*m*-FC_6H_4	12	50/1	62
4	**7d**	2-Pyridinyl	72[d]	—	NR
5	**7e**	2-Ethyl-6-methylphenyl	24[d]	—	NR
6	**7f**	*o*-Tolyl	72[d]	8/1	30[e]
7	**7g**	H	12	12/1	74[f]
8	**7h**	Propyl	12	1/9	89
9	**8a**	Ph	2	10/1	82[g]
10	**8b**	*p*-$MeOC_6H_4$	2	1.5/1	78
11	**8c**	*m*-FC_6H_4	2	13/1	61[h]
12	**8d**	2-Pyridinyl	72[d]	—	NR
13	**8e**	2-Ethyl-6-methylphenyl	72	0/1	85
14	**8f**	*o*-Tolyl	18	1/1	85
15	**8g**	H	2	1/1	75
16	**8h**	Propyl	2	1.3/1	74

[a] Determined by ^{1}H NMR (average of two or three runs).
[b] Isolated yield (average of two or three runs) as an *exo*/*endo* mixture.
[c] NR=no reaction.
[d] 50 °C.
[e] Conversion determined by ^{1}H NMR.
[f] Isolated after a rapid filtration through Celite.
[g] Compound **13a** isolated in 4% yield.
[h] Compound **13c** isolated in 7% yield.

predominated affording the lactones **9** and **10** as major product and as a single stereoisomer *Z* (entries 1–3, 6, 7, 9–11, and 16). In most examples we could also notice a faster rate of cyclization for the γ-acetylenic acids **8**. The structures of the alkylidene lactones are confirmed not only by comparison with the known compounds but also with the crystal structure of **10a** determined by X-ray analysis (Fig. 1). No cyclization occurred when R is a 2-pyridinyl group and the starting material is totally recovered even after several days at 50 °C (entries 4 and 12). Surprisingly low amounts of the dimers **13a** and **13c** (entries 9 and 11) are isolated from the reaction mixture. The spectroscopic data collected are not enough to assess their structures without ambiguity (Fig. 2).[14]

Whereas a slight electronic effect of the R group was observed on the regioselectivity (for example, when R is an electron-rich aromatic group the *exo*-selectivity decreased leading to the lactones **9b** and **10b** in a moderate excess (entries 2 and 10)), the presence of substituents in the *ortho* position in the R group modifies dramatically the cyclization. The rate of the reaction is considerably slowed for the acids **7f** and **8f** and the *exo*-selectivity is also affected (entries 6 and 14). No cyclization occurred for the acetylenic acid **7e** and the cycloisomerization of **8e** needed 3 days at rt for a complete conversion leading only to the lactone **10e** (entries 5 and 13). The coordination of the carbon–carbon triple bond to the gold catalyst is probably most difficult in the presence of steric hindrance. Then the nucleophilic addition of the carboxylate to the triple bond was effected following the *endo*-mode to minimize the steric interactions.

We next examined the possibility of achieving the same cycloisomerization from esters. From the ester **6a** placed in the above described conditions (either in the presence of K_2CO_3 or not), no cyclization occurred and the starting material was totally recovered. On the other hand when reaction was tested in wet acetonitrile[12] (10 mol % AuCl, rt, 24 h), trace amounts of the lactone **12a** were observed. Contrary to the cycloisomerization of the acetylenic acids catalyzed with AuCl, a rapid optimization of the reaction conditions was shown and the best results were obtained with 10 mol % $AuCl_3$ and 2 equiv of H_2O in acetonitrile at 50 °C. Some examples of cycloisomerization of esters **6** are presented in Table 4. Whatever is the nature of the group R, only the isocoumarins **12** resulting from the 6-*endo*-cyclization are isolated. No 5-*exo*-product is formed during this reaction. This

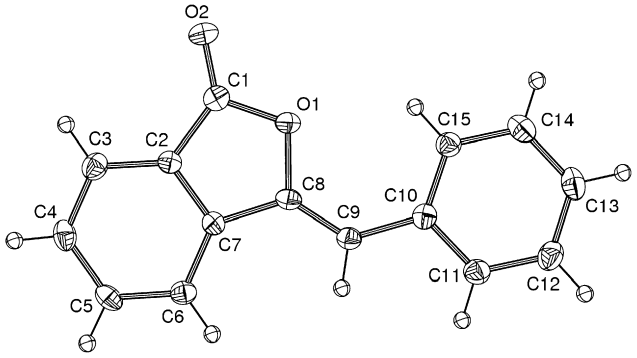


Figure 1. ORTEP representation of the X-ray structure of **10a**.

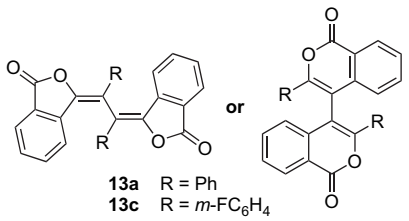
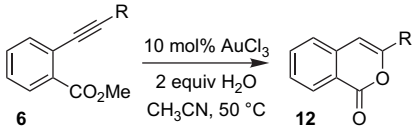


Figure 2. Possible structures of the side products **13**.

6-*endo* regioselectivity is probably due to a similar process of cyclization of γ-alkyne acid catalyzed under acidic conditions as described by Uchiyama.[5a] The presence of water seemed to be indispensable[18] for the success of the reaction (entries 1 and 2) and $AuCl_3$ appeared more active than AuCl (entries 4 and 5).

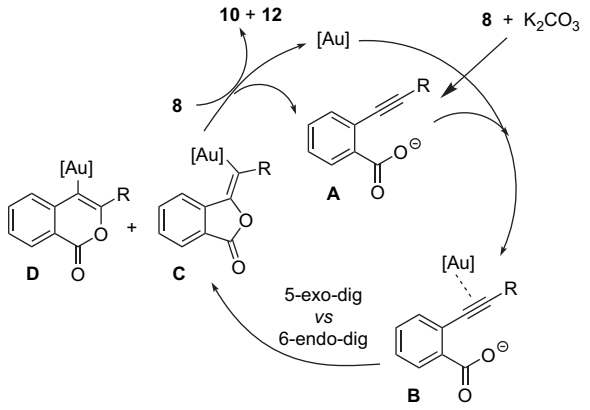
On the basis of the above observations we propose a plausible mechanism for the gold-catalyzed cyclization of acetylenic acids and esters (Scheme 2). In the case of the cycloisomerization of acetylenic acids the mechanism involved the initial formation of carboxylate **A** by deprotonation of the acid with K_2CO_3. The *anti*-nucleophilic attack of the carboxylate on the gold-activated ethylene led probably to the gold complexe **C** or **D**. Exchange of the proton of acetylenic acid with the organogold regenerated the gold(I) catalytic species, forming the carboxylate **A** and furnishing the lactone. For the cyclization of acetylenic esters, the methyl group being not transferred, the success of the catalytic process was only possible owing to the presence of water. In recent examples *tert*-butyl and methyl-allenoates were shown to lactonize under gold catalysis.[15] Shin and colleague.[15a] observed that $AuCl_3$ cleaves also the ester moiety. However the corresponding acid is slowly formed (low conversion after 48 h). In order to determine if in our reaction conditions the gold(III) catalyst promotes cleavage of methyl group, we realized a control experiment. Methyl benzoate was placed in acetonitrile in the presence of 10 mol % $AuCl_3$ and 2 equiv of water. After stirring for 48 h at 50 °C, no hydrolysis of ester was observed. Thus we believe that water could play a dual role: hydrolysis of methyl oxonium and gold–carbon bond of the intermediate **F** lead to the lactone and the gold catalyst.

Table 4. $AuCl_3$-catalyzed cycloisomerization of esters

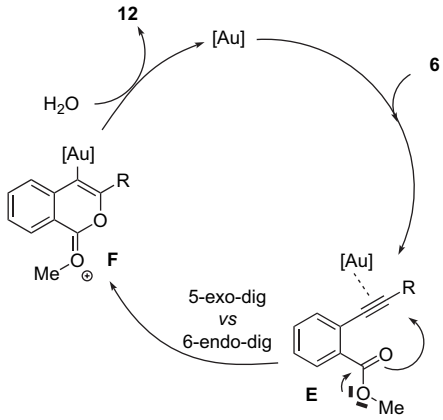


Entry	Ester	R	*t* (h)	Yield[a] (%)
1[b]	**6a**	Ph	24	Traces
2	**6a**	Ph	48	60[c]
3	**6b**	*p*-$MeOC_6H_4$	24	90
4	**6c**	*m*-FC_6H_4	48	—[d]
5	**6c**	*m*-FC_6H_4	48	75
6	**6h**	Propyl	24	60

[a] Isolated yield (average of two runs).
[b] Without H_2O.
[c] Conversion 83%.
[d] AuCl as catalyst, 60% conversion.



Cycloisomerization of acetylenic acids



Cycloisomerization of acetylenic esters

Scheme 2. Proposed catalytic cycles.

3. Conclusion

In summary, we have developed an efficient and mild gold-catalyzed cycloisomerization, which provides a rapid access to various new alkylidene lactones resulting from an intramolecular nucleophilic *exo*- and *endo*-additions of carboxylate to a carbon–carbon triple bond. Gratifyingly, the cyclization of γ-acetylenic esters is also possible in the presence of water yielding exclusively the isocoumarins. The detailed mechanism of this process and its application to the synthesis of natural products are currently under investigation. Toward the profiles of the UV spectra of the related lactones, a complete study of their photoprotective properties is undertaken and the results will be reported in due course.

4. Experimental part

4.1. General methods

Commercially available reagents were used as received. THF was freshly distilled from Na. Commercially available MeCN contained 0.2% of water. Commercially available anhydrous MeCN contained less than 0.02% of water. Concentration of water was determined by Karl Fisher method. Column chromatography was performed with silica gel (0.063–0.200 nm). Reactions were monitored by TLC inspection on silica gel 60 F_{254} plates. PTLC was performed with silica gel 60 PF_{254}. Melting points are uncorrected. NMR spectra were recorded on a 270 MHz spectrometer. Chemical shifts are reported relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) for ^1H, and chloroform (δ 77.0) for ^{13}C NMR. UV spectra were recorded between 200 and 400 nm in CH_2Cl_2.

4.1.1. Methyl 2-(2-iodophenyl)acetate (1).[16a] To a solution of 2-(iodophenyl)acetic acid (2.00 g, 7.63 mmol) in methanol (3 mL) was added sulfuric acid (97–98%, 1.10 mL). The solution was stirred for 2.5 h at 65 °C and methanol removed under reduced pressure. The residue was dissolved in H_2O (80 mL) and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to yield 2.09 g (quantitative, 7.63 mmol) of the ester as a colorless oil; R_f 0.40 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.72 (s, 3H), 3.81 (s, 2H), 6.96 (m, 1H), 7.26–7.35 (m, 2H), 7.85 (d, 1H, J=7.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 4 6.1, 52.2, 101.0, 128.4, 129.0, 130.6, 137.7, 170.9 ppm; IR (film) 1735 cm^{-1}.

4.1.2. Methyl 2-(2-(trimethylsilylethynyl)phenyl)acetate.[16b] To a solution of methyl 2-(2-iodophenyl)acetate **1** (2.60 g, 9.48 mmol) in anhydrous THF (15 mL) were added CuI (45 mg, 0.23 mmol, 0.025 equiv) and PPh_3 (60 mg, 0.23 mmol, 0.025 equiv). The mixture was degassed and filed with argon three times and then $PdCl_2(PPh_3)_2$ (332 mg, 0.47 mmol, 0.05 equiv), triethylamine (1.90 mL, 14.22 mmol, 1.5 equiv), and trimethylsilylacetylene (2.02 mL, 14.22 mmol, 1.5 equiv) were added to the solution. The reaction mixture was stirred for 12 h at rt and then filtered through a pad of silica and Celite®. The solvents were removed in vacuo and the crude oil obtained was purified by chromatography on silica gel, using a 10/90 mixture of Et_2O and pentane as the eluent to yield 2.11 g (90%, 8.56 mmol) of yellow oil; R_f 0.46 AcOEt/pentane (5/95); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.00 (s, 9H), 3.45 (s, 3H), 3.58 (s, 2H), 6.97–7.04 (m, 3H), 7.22 (d, 1H, J=7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 0.0, 39.9, 52.0, 99.2, 103.0, 123.5, 127.1, 128.8, 129.8, 132.4, 136.7, 171.6 ppm; IR (film) 2155, 1740 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{18}O_2Si$: 246.1076; found 246.1085.

4.1.3. Methyl 2-((trimethylsilyl)ethynyl)benzoate.[16c] By a similar procedure as outline above, methyl 2-((trimethylsilyl)ethynyl)benzoate was obtained from methyl 2-iodobenzoate **2** (2.00 g, 7.63 mmol). After purification by chromatography on silica gel, using a 10/90 mixture of Et_2O and pentane as the eluent, 1.81 g (quantitative, 7.78 mmol) of a yellow oil was isolated; R_f 0.66 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.00 (s, 9H), 3.65 (s, 3H), 7.08 (td, 1H, J=7.7, 1.4 Hz), 7.16 (td, 1H, J=7.7, 1.4 Hz), 7.30 (dd, 1H, J=7.7, 1.4 Hz), 7.62 (dd, 1H, J=7.7, 1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 0.0, 52.1, 99.7, 103.4, 123.3, 128.3, 130.3, 131.6, 134.6, 170.0 ppm; IR (film) 2159, 1734 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{16}O_2Si$: 232.0920; found 232.0913.

4.1.4. Methyl 2-(2-ethynylphenyl)acetate (3).[16b] Methyl 2-(2-(trimethylsilylethynyl)phenyl)acetate (1.20 g, 4.87 mmol) was dissolved in a mixture of MeOH (4 mL) and EtOH (2 mL). Then a catalytic quantity of K_2CO_3 was added to

the solution. After one night of stirring the mixture was concentrated under reduced pressure and CH_2Cl_2 was added and then washed with H_2O (20 mL), brine (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude oil obtained was purified by chromatography on silica gel, using a 10/90 mixture of Et_2O and pentane as the eluent to yield 0.75 g (88%, 4.30 mmol) of a colorless oil; R_f 0.44 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.28 (s, 1H), 3.70 (s, 3H), 3.86 (s, 2H), 7.22–7.36 (m, 3H), 7.51 (d, 1H, J=7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.5, 52.0, 81.5, 122.4, 127.1, 129.0, 129.8, 132.8, 136.6, 171.5 ppm; IR (film) 3282, 1735 cm^{-1}; HRMS (EI): calcd for $C_{11}H_{10}O_2$: 174.0681; found 174.0679.

4.1.5. Methyl 2-(ethynyl)benzoate (4).[16d] Methyl 2-((trimethylsilyl)ethynyl)benzoate (1.40 g, 6.02 mmol) was dissolved in a mixture of MeOH (4 mL) and EtOH (2 mL). Then a catalytic quantity of K_2CO_3 was added to the solution. After one night of stirring the mixture was concentrated under reduced pressure and CH_2Cl_2 was added and then washed with H_2O (20 mL), brine (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude oil obtained was purified by chromatography on silica gel, using a 10/90 mixture of Et_2O and pentane as the eluent to yield 0.94 g (97%, 5.87 mmol) of yellow oil; R_f 0.42 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.41 (s, 1H), 3.93 (s, 3H), 7.37–7.50 (m, 2H), 7.63 (d, 1H, J=7.7 Hz), 7.94 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 52.1, 82.0, 82.2, 122.6, 128.4, 130.2, 131.7, 134.9, 132.4, 166.4 ppm; IR (film) 3283, 1727 cm^{-1}; HRMS (EI): calcd for $C_{10}H_8O_2$: 160.0524; found 160.0530.

4.1.6. General procedure 1 for the Sonogashira coupling: coupling of methyl 2-(2-ethynylphenyl)acetate 3 and methyl 2-(ethynyl)benzoate 4. To a solution of **3** or **4** (1.15 mmol, 1.00 equiv) in anhydrous THF (2 mL) were added CuI (0.027 mmol, 0.025 equiv) and PPh_3 (0.027 mmol, 0.025 equiv). The mixture was degassed and filed with argon three times and then $PdCl_2(PPh_3)_2$ (0.055 mmol, 0.05 equiv), a iodo-compound (1.15 mmol, 1.00 equiv), and triethylamine (1.15 mmol, 1.00 equiv) were added to the solution. The reaction mixture was heated at 70 °C for 4 h and then filtered through a pad of silica and Celite®. After concentration under reduced pressure the residue was purified by column chromatography affording the desired compound.

4.1.7. General procedure 2 for the Sonogashira coupling: coupling of methyl 2-iodoacetate 1 and methyl 2-iodobenzoate 2. To a solution of the iodo-compound (1.82 mmol, 1.00 equiv) in anhydrous THF (5 mL) were added CuI (0.045 mmol, 0.025 equiv) and PPh_3 (0.085 mol, 0.025 equiv). The mixture was degassed and filed with argon three times and then $PdCl_2(PPh_3)_2$ (0.091 mmol, 0.05 equiv), alkyne (2.73 mmol, 1.50 equiv), and triethylamine (2.73 mmol, 1.50 equiv) were added to the solution. The reaction mixture was stirred for 24 h at rt and then filtered through a pad of silica and Celite®. After concentration under reduced pressure the residue was purified by column chromatography affording the desired compound.

4.1.8. General procedure for saponification. To a solution of the ester **5** or **6** (0.10 mmol, 1.00 equiv) in a mixture of methanol (2 mL) and ethanol (1 mL) was added NaOH (aq, 5%) (1.00 mL, 1.30 equiv). After 1 h of stirring at 75 °C the solution was concentrated under reduced pressure. The residue was dissolved in water (20 mL) and washed with Et_2O (2×15 mL). After acidification to pH=1–2, the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic layers were washed with H_2O, brine and dried (Na_2SO_4).

4.1.8.1. Methyl 2-(2-(phenylethynyl)phenyl)acetate (5a). Pale yellow oil; R_f 0.42 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.69 (s, 3H), 3.91 (s, 2H), 7.25–7.37 (m, 6H), 7.51–7.56 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 40.0, 52.1, 87.3, 94.0, 123.1, 123.5, 127.2, 128.3, 128.4, 128.5, 129.9, 131.5, 132.0, 136.2, 171,7 ppm; IR (film) 1736 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_2$: 250.0994; found 250.0987.

4.1.8.2. 2-(2-(Phenylethynyl)phenyl)acetic acid (7a). White solid; mp 153–155 °C; R_f 0.15 CH_2Cl_2+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.93 (s, 2H), 7.27–7.35 (m, 5H), 7.47–7.57 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.7, 87.1, 94.2, 123.0, 123.6, 128.3, 128.4, 128.5, 130.0, 131.5, 132.1, 135.4, 177.4 ppm; IR (KBr) 3033, 1707 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0826.

4.1.8.3. Methyl 2-(2-((4-methoxyphenyl)ethynyl)phenyl)acetate (5b). Pale yellow oil; R_f 0.48 Et_2O/pentane (20/80); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.69 (s, 3H), 3.84 (s, 3H), 3.90 (s, 2H), 6.88 (d, 2H, J=9.0 Hz), 7.25–7.30 (m, 3H), 7.45–7.53 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 40.1, 52.0, 55.3, 86.1, 94.1, 114.0, 115.3, 123.9, 127.1, 128.2, 129.8, 131.8, 133.0, 136.0, 159.7, 171.7 ppm; IR (film) 1736 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{16}O_3$: 280.1099; found 280.1086.

4.1.8.4. 2-(2-((4-Methoxyphenyl)ethynyl)phenyl)acetic acid (7b). White solid; mp 157–159 °C; R_f 0.20 CH_2Cl_2/MeOH (95/5)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.80 (s, 3H), 3.90 (s, 2H), 6.83 (d, 2H, J=7.7 Hz), 7.23–7.26 (m, 3H), 7.42 (d, 2H, J=7.7 Hz), 7.50 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.8, 55.3, 85.9, 94.3, 114.0, 124.0, 127.4, 128.2, 129.9, 133.0, 135.2, 159.7, 177.2 ppm; IR (KBr) 3961, 2211, 1697 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_3$: 266.0943; found 266.0953.

4.1.8.5. Methyl 2-(2-((2-fluorophenyl)ethynyl)phenyl)-acetate (5c). Colorless oil; R_f 0.39 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.64 (s, 3H), 3.85 (s, 2H), 7.00 (m, 1H), 7.16–7.26 (m, 6H), 7.48 (d, 1H, J=6.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.9, 52.0, 88.2, 92.6, 115.3 (d, J^2_{F-C}=21 Hz), 118.1 (d, J^2_{F-C}=22 Hz), 122.9, 124.9 (d, J^3_{F-C}=9 Hz), 127.2, 127.3 (d, J^3_{F-C}=3 Hz), 128.8, 129.8, 129.9, 132.1, 136.3, 162.3 (d, J^1_{F-C}=246 Hz), 171.4 ppm; IR (film) 2206, 1736 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{13}O_2F$: 268.0900; found 268.0900.

4.1.8.6. 2-(2-((3-Fluorophenyl)ethynyl)phenyl)acetic acid (7c). White solid; mp 106–108 °C; R_f 0.66 CH_2Cl_2/MeOH (95/5)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.86 (s, 2H), 6.98 (m, 1H), 7.12–7.26 (m,

6H), 7.49 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.8, 88.0, 92.8, 115.7 (d, J^2_{F-C}=21 Hz), 118.2 (d, J^2_{F-C}=23 Hz), 123.2, 124.8 (d, J^3_{F-C}=9 Hz), 127.4 (d, J^4_{F-C}=5 Hz), 127.4, 128.9, 129.9 (d, J^3_{F-C}=9 Hz), 130.1, 132.2, 135.5, 162.3 (d, J^1_{F-C}=246 Hz), 177.5 ppm; IR (KBr) 3012, 1701 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{11}O_2F$: 254.0743; found 254.0734.

4.1.8.7. Methyl 2-(2-(pyridin-2-ylethynyl)phenyl)acetate (5d). Brown oil; R_f 0.27 AcOEt/pentane (30/70); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.70 (s, 3H), 3.95 (s, 2H), 7.22–7.39 (m, 4H), 7.12–7.53 (m, 3H), 8.62 (d, 1H, J=4.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.9, 52.0, 87.1, 93.0, 122.5, 122.8, 127.2, 127.3, 129.2, 129.8, 132.6, 136.1, 136.6, 143.3, 150.0, 171.4 ppm; IR (film) 2219, 1736 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{13}NO_2$: 251.0946; found 251.0937.

4.1.8.8. 2-(2-(Pyridin-2-ylethynyl)phenyl)acetic acid (7d). Pale yellow solid; mp 159–161 °C; R_f 0.73 MeOH/CH_2Cl_2 (10/90)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 4.26 (s, 1H), 7.24–7.38 (m, 2H), 7.40–7.45 (m, 2H), 7.55 (d, 1H, J=7.7 Hz), 7.63 (d, 1H, J=7.7 Hz), 7.73 (td, 1H, J=7.7, 1.2 Hz), 8.73 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.3, 90.2, 122.1, 123.3, 127.0, 127.6, 129.8, 130.6, 132.8, 138.1, 138.2, 141.5, 148.2, 174.0 ppm; IR (film) 2474, 2217, 1696 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{11}NO_2$: 237.0790; found 237.0800.

4.1.8.9. Methyl 2-(2-((2-ethyl-6-methylphenyl)ethynyl)phenyl) acetate (5e). Colorless oil; R_f 0.43 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.29 (t, 3H, J=7.5 Hz), 2.51 (s, 3H), 2.89 (q, 2H, J=7.5 Hz), 3.66 (s, 3H), 3.94 (s, 2H), 7.06–7.20 (m, 2H), 7.24–7.34 (m, 3H), 7.57 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 14.8, 21.1, 28.0, 39.6, 51.9, 91.1, 95.4, 122.1, 124.2, 125.2, 126.8, 127.13, 128.1, 128.3, 129.8, 132.3, 135.4, 140.4, 146.3, 171.4 ppm; IR (film) 2206, 1736, 1736 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{20}O_2$: 292.1463; found 292.1459.

4.1.8.10. 2-(2-((2-Ethyl-6-methylphenyl)ethynyl)phenyl)acetic acid (7e). White solid; mp 133–135 °C; R_f 0.27 EtO_2/pentane (30/70)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.25 (t, 3H, J=7.6 Hz), 2.48 (s, 3H), 2.86 (q, 2H, J=7.6 Hz), 3.96 (s, 2H), 7.03–7.06 (m, 2H), 7.16 (t, 1H, J=7.6 Hz), 7.28–7.32 (m, 3H), 7.57 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 14.9, 21.2, 28.1, 39.5, 91.3, 95.2, 122.0, 124.4, 125.2, 126.8, 127.4, 128.2, 128.3, 129.9, 132.4, 134.6, 140.5, 146.4, 177.4 ppm; IR (KBr) 2966, 1706 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{18}O_2$: 278.1307; found 278.1288.

4.1.8.11. Methyl 2-(2-(*o*-tolylethynyl)phenyl)acetate (5f). Colorless oil; R_f 0.35 CH_2Cl_2/pentane (30/70); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.51 (s, 3H), 3.69 (s, 3H), 3.93 (s, 2H), 7.16–7.33 (m, 6 H), 7.49–7.58 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.7, 39.9, 52.0, 91.3, 92.8, 122.9, 123.9, 125.6, 127.2, 128.43, 129.5, 129.8, 132.0, 132.2, 135.8, 140.0, 171.6 ppm; IR (film) 2211, 1736 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{16}O_2$: 264.1150; found 264.1148.

4.1.8.12. 2-(2-(*o*-Tolylethynyl)phenyl)acetic acid (7f). White solid; mp 122–124 °C; R_f 0.13 EtO_2/pentane (50/50)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.47 (s, 3H), 3.94 (s, 2H), 7.13–7.30 (m, 6H), 7.48 (d, 1H, J=7.4 Hz), 7.56 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.7, 39.6, 91.0, 93.0, 122.8, 124.0, 125.6, 127.4, 128.5, 129.5, 129.9, 132.0, 132.3, 135.0, 140.0, 177.2 ppm; IR (KBr) 2917, 1709 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_2$: 250.0994; found 250.0987.

4.1.8.13. 2-(2-Ethynylphenyl)acetic acid (7g). White solid; mp 96–98 °C; R_f 0.38 CH_2Cl_2/MeOH (95/5)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.28 (s, 1H), 3.88 (s, 2H), 7.21–7.35 (m, 3H), 7.51 (d, 1H, J=7.6 Hz), 11.48 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 39.4, 81.4, 81.8, 122.6, 127.3, 129.0, 129.9, 132.8, 135.9, 177.4 ppm; IR (KBr) 3068, 1709 cm^{-1}; HRMS (EI): calcd for $C_{10}H_8O_2$: 160.0524; found 160.0515.

4.1.8.14. Methyl 2-(2-(pent-1-ynyl)phenyl)acetate (5h). Colorless oil; R_f 0.25 CH_2Cl_2/pentane (30/70); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.04 (t, 3H, J=7.2 Hz), 1.63 (sext, 2H, J=7.2 Hz), 2.40 (t, 2H, J=7.2 Hz), 3.69 (s, 3H), 3.82 (s, 1H), 7.18–7.27 (m, 3H), 7.41 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.5, 21.5, 22.2, 39.8, 51.9, 78.7, 95.0, 124.3, 127.0, 127.7, 129.6, 132.0, 135.9, 171.7 ppm; IR (film) 2235, 1736, 1736 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{16}O_2$: 216.1150; found 216.1150.

4.1.8.15. 2-(2-(Pent-1-ynyl)phenyl)acetic acid (7h). White solid; mp <50 °C; R_f 0.27 EtO_2/pentane (10/90)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.02 (t, 3H, J=7.2 Hz), 1.61 (sext, 2H, J=7.2 Hz), 2.39 (t, 2H, J=7.2 Hz), 3.85 (s, 2H), 7.21–7.25 (m, 3H), 7.42 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.5, 21.5, 22.1, 78.6, 95.4, 124.5, 127.2, 127.7, 129.7, 132.1, 135.2, 177.5 ppm; IR (KBr) 3025, 2235, 1707 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{14}O_2$: 202.0994; found 202.0988.

4.1.8.16. Methyl 2-(phenylethynyl)benzoate (6a).[16e] Colorless oil; R_f 0.52 Et_2O/pentane (10/90); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.88 (s, 3H), 7.27–7.32 (m, 4H), 7.40 (td, 1H, J=7.7, 0.6 Hz), 7.48–7.58 (m, 3H), 7.89 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 52.2, 88.2, 94.3, 123.3, 123.7, 127.9, 128.3, 128.5, 130.4, 131.7, 131.7, 134.0, 131.8, 166.7 ppm; IR (film) 2217, 1728 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0826.

4.1.8.17. 2-(Phenylethynyl)benzoic acid (8a). White solid; mp 127–129 °C (lit.[16f] mp 127–128 °C); R_f 0.64 CH_2Cl_2/MeOH (90/10)+0.1% CH_3COOH; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.17–7.65 (m, 8H), 8.08 (d, 1H, J=7.9 Hz), 10.71 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 88.0, 95.4, 123.1, 124.4, 128.0, 128.4, 128.6, 130.5, 131.4, 131.7, 132.6, 134.2, 171.4 ppm; IR (KBr) 2995, 2212, 1691 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{10}O_2$: 222.0681; found 222.0674.

4.1.8.18. Methyl 2-((4-methoxyphenyl)ethynyl)benzoate (6b).[16g] Yellow oil; R_f 0.51 Et_2O/pentane (30/70); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.83 (s, 3H), 3.96 (s, 3H), 6.88 (dd, 2H, J=7.0, 1.9 Hz), 7.35 (td, 1H, J=7.7, 1.2 Hz), 7.44–7.53 (m, 3H), 7.62 (d, 1H, J=7.7 Hz), 7.96 (dd, 1H, J=7.7, 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 52.1, 55.3,

87.1, 94.5, 114.0, 115.4, 124.1, 127.5, 130.4, 131.6, 133.7, 133.2, 159.8, 166.8 ppm; IR (film) 2214, 1727 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_3$: 266.0943; found 266.0944.

4.1.8.19. 2-((4-Methoxyphenyl)ethynyl)benzoic acid (8b). White solid; mp 133–135 °C; R_f 0.84 CH_2Cl_2/MeOH (90/10)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.79 (s, 3H), 6.83 (d, 2H, J=8.7 Hz), 7.39 (t, 1H, J=7.7 Hz), 7.50–7.56 (m, 3H), 7.62 (d, 1H, J=7.7 Hz), 8.12 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 55.2, 86.9, 95.8, 114.1, 115.2, 124.7, 127.6, 130.3, 131.4, 132.5, 133.3, 133.9, 159.9, 171.1 ppm; IR (KBr) 2962, 2219, 1707 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}O_3$: 252.0786; found 252.0791.

4.1.8.20. Methyl 2-((3-fluorophenyl)ethynyl)benzoate (6c). Yellow oil; R_f 0.48 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.87 (s, 3H), 6.97 (m, 1H), 7.16–7.34 (m, 4H), 7.42 (td, 1H, J=7.7, 1.3 Hz), 7.55 (d, 1H, J=7.7 Hz), 7.90 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 52.2, 89.0, 92.9, 115.8 (d, J^2_{F-C}= 21 Hz), 118.4 (d, J^2_{F-C}=23 Hz), 123.2, 125.1 (d, J^3_{F-C}= 9 Hz), 127.6 (d, J^4_{F-C}=3 Hz), 128.2, 129.9 (d, J^3_{F-C}=9 Hz), 130.5, 131.7, 134.0, 162.4 (d, J^1_{F-C}=247 Hz), 166.5 ppm; IR (film) 2206, 1728 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{11}O_2F$: 254.0743; found 254.0743.

4.1.8.21. 2-((3-Fluorophenyl)ethynyl)benzoic acid (8c). Rosy solid; mp 125–127 °C; R_f 0.52 Et_2O/pentane (50/50)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.01 (m, 1H), 7.20–7.28 (m, 2H), 7.34 (d, 1H, J=7.7 Hz), 7.42 (t, 1H, J=7.7 Hz), 7.55 (t, 1H, J=7.7 Hz), 7.67 (d, 1H, J=7.7 Hz), 8.14 (d, 1H, J=7.7 Hz), 11.83 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 88.9, 93.8 (d, J^4_{F-C}=3 Hz), 115.8 (d, J^2_{F-C}=21 Hz), 118.4 (d, J^2_{F-C}= 23 Hz), 124.2, 125.1 (d, J^3_{F-C}=9 Hz), 127.6 (d, J^4_{F-C}= 3 Hz), 128.2, 129.9 (d, J^3_{F-C}=9 Hz), 130.6, 131.4, 132.6, 134.2, 162.3 (d, J^1_{F-C}=246 Hz), 171.6 ppm; IR (KBr) 3071, 1702 cm^{-1}; HRMS (EI): calcd for $C_{15}H_9FO_2$: 240.0587; found 240.0593.

4.1.8.22. Methyl 2-(pyridin-2-ylethynyl)benzoate (6d). Brown oil; R_f 0.11 AcOEt/pentane (30/70); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.97 (s, 3H), 7.25 (m, 1H), 7.39–7.75 (m, 4H), 8.00 (dd, 1H, J=7.8, 1.0 Hz), 8.63 (d, 1H, J=7.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 52.2, 87.8, 93.2, 122.8, 127.4, 128.5, 130.4, 131.7, 132.1, 134.3, 136.0, 143.4, 150.0, 166.2 ppm; IR (film) 2221, 1726 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{11}NO_2$: 237.0790; found 237.0800.

4.1.8.23. 2-(Pyridin-2-ylethynyl)benzoic acid (8d). Yellow solid mp >250 °C; R_f 0.74 CH_2Cl_2/MeOH (90/10)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 6.91 (t, 1H, J=7.9 Hz), 7.49–7.52 (m, 2H), 7.61–7.63 (m, 2H), 7.79–7.84 (m, 2H), 8.61 (d, 1H, J=7.9 Hz), 14.71 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 97.5, 115.2, 120.3, 120.7, 120.8, 132.1, 132.4, 134.1, 139.4, 139.7, 141.1, 151.3, 190.1, 193.9 ppm; IR (KBr) 3024 cm^{-1}; HRMS (EI): calcd for $C_{14}H_9NO_2$: 223.0633; found 233.0624.

4.1.8.24. Methyl 2-((2-ethyl-6-methylphenyl)ethynyl)-benzoate (6e). Colorless oil; R_f 0.40 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.31 (t, 3H, J=7.6 Hz), 2.57 (s, 3H), 2.95 (q, 2H, J=7.6 Hz), 3.94 (s, 3H), 7.07–7.39 (m, 3H), 7.36 (td, 1H, J=7.7, 1.3 Hz), 7.49 (td, 1H, J=7.7, 1.3 Hz), 7.65 (dd, 1H, J=7.7, 1.3 Hz), 7.95 (dd, 1H, J=7.7, 1.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 15.0, 21.1, 27.9, 52.2, 92.1, 95.9, 122.2, 124.1, 125.2, 126.8, 127.6, 128.3, 130.4, 131.4, 131.5, 134.12, 140.9, 146.8, 166.8 ppm; IR (film) 2207, 1731 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{18}O_2$: 278.1307; found 278.1316.

4.1.8.25. 2-((2-Ethyl-6-methylphenyl)ethynyl)benzoic acid (8e). White solid; mp 121–123 °C; R_f 0.28 Et_2O/pentane (30/70)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.29 (t, 3H, J=7.6 Hz), 2.55 (s, 3H), 2.94 (q, 2H, J=7.6 Hz), 7.03–7.05 (m, 2H), 7.18 (t, 1H, J=7.6 Hz), 7.42 (td, 1H, J=7.7, 1.3 Hz), 7.56 (td, 1H, J=7.7, 1.3 Hz), 7.70 (d, 1H, J=7.7 Hz), 8.14 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 15.0, 21.1, 27.9, 93.5, 95.7, 122.1, 125.2, 126.8, 127.7, 128.5, 129.9, 131.3, 132.6, 134.4, 141.2, 147.1, 171.5 ppm; IR (KBr) 2930, 2204, 1709 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{16}O_2$: 264.1150; found 264.1148.

4.1.8.26. Methyl 2-(*o*-tolylethynyl)benzoate (6f). Colorless oil; R_f 0.40 CH_2Cl_2/pentane (30/70); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.56 (s, 3H), 3.95 (s, 3H), 7.14–7.28 (m, 3H), 7.37 (td, 1H, J=7.7, 1.4 Hz), 7.46–7.56 (m, 2H), 7.66 (dd, 1H, J=7.7, 1.4 Hz), 7.97 (dd, 1H, J=7.7, 1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.7, 52.2, 91.9, 93.4, 123.1, 123.9, 123.1, 123.9, 125.5, 127.7, 128.5, 129.5, 130.4, 131.6, 131.7, 132.2, 134.1, 140.4, 166.8 ppm; IR (film) 2212, 1728 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_2$: 250.0994; found 250.0987.

4.1.8.27. 2-(*o*-Tolylethynyl)benzoic acid (8f). White solid; mp 119–121 °C; R_f 0.16 Et_2O/pentane (50/50)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.54 (s, 3H), 7.13–7.23 (m, 3H), 7.41 (td, 1H, J=7.8, 1.3 Hz), 7.51–7.57 (m, 2H), 7.69 (dd, 1H, J=7.8, 1.3 Hz), 8.13 (dd, 1H, J=7.8, 1.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.6, 91.7, 94.6, 122.9, 124.8, 125.5, 127.8, 128.6, 129.5, 130.2, 131.3, 132.2, 132.5, 134.4, 140.7, 171.6 ppm; IR (KBr) 2988, 2212, 1692 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0826.

4.1.8.28. 2-Ethynylbenzoic acid (8g).[16h] White solid; mp 121–123 °C; R_f 0.18 Et_2O/pentane (30/70)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.46 (s, 1H), 7.45 (td, 1H, J=7.7, 1.4 Hz), 7.54 (td, 1H, J=7.7, 1.4 Hz), 7.67 (dd, 1H, J=7.7, 1.4 Hz), 8.10 (dd, 1H, J=7.7, 1.4 Hz), 11.83 ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 81.7, 83.3, 123.2, 128.6, 131.2, 132.6, 135.2, 171.3 ppm; IR (KBr) 3275, 3071, 1693 cm^{-1}; HRMS (EI): calcd for $C_9H_6O_2$: 146.0368; found 146.0363.

4.1.8.29. Methyl 2-(pent-1-ynyl)benzoate (6h).[16e] Colorless oil; R_f 0.46 CH_2Cl_2/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.07 (t, 3H, J=7.2 Hz), 1.66 (sext, 2H, J=7.2 Hz), 2.46 (t, 2H, J=7.2 Hz), 3.91 (s, 3H), 7.30 (td, 1H, J=7.6, 1.2 Hz), 7.41 (td, 1H, J=7.6, 1.2 Hz,), 7.51 (dd, 1H, J=7.6, 1.2 Hz), 7.88 (dd, 1H, J=7.6, 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.5, 21.7, 22.1, 51.9, 79.3, 95.7, 124.4, 127.0, 130.0, 131.3, 131.9, 134.11,

166.9 ppm; IR 2233, 1732 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{14}O_2$: 202.0994; found 202.00998.

4.1.8.30. 2-(Pent-1-ynyl)benzoic acid (8h).[16e] Colorless oil; R_f 0.72 Et_2O/pentane (30/70)+0.1% CH_3COOH; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.09 (t, 3H, J=7.2 Hz), 1.68 (sext, 2H, J=7.2 Hz), 2.48 (t, 2H, J=7.2 Hz), 7.36 (td, 1H, J=7.5, 1.4 Hz,), 7.45–7.57 (m, 2H), 8.07 (dd, 1H, J=7.5, 1.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.5, 21.8, 22.0, 79.2, 97.6, 124.6, 127.4, 130.7, 131.2, 132.3, 134.3, 170.6 ppm; IR 2961, 2234, 1693 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{12}O_2$: 188.0837; found 188.0836.

4.1.9. General procedure A for cyclization of γ- and δ-acetylenic acid catalyzed by AuCl. In a flask under argon containing acetylenic acid (1.00 equiv) and K_2CO_3 (0.10 equiv) was added acetonitrile (2 mL/0.4 mmol). The solution was purged with argon three times before charging with AuCl (0.10 equiv). After disappearance of the starting material reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure. The crude material was purified on silica gel.

4.1.10. General procedure B for cyclization of γ-acetylenic esters catalyzed by $AuCl_3$. In a flask under argon, γ-acetylenic ester (1.00 equiv) was dissolved in anhydrous acetonitrile (2 mL/0.4 mmol) and H_2O (2.00 equiv) was added by syringe. The solution was purged with argon three times before charging with $AuCl_3$ (0.10 equiv) and then heated at 50 °C. After disappearance of the starting material reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure. The crude material was purified on silica gel.

4.1.10.1. (*Z*)-1-Benzylideneisochroman-3-one (9a). Compound **9a** was obtained according to general procedure A from **7a** (120 mg, 0.51 mmol) in 24 h. Purification by column chromatography (Et_2O/pentane 30/70) gives 74 mg (62%, 0.32 mmol) of a mixture of **9a** and **11a**. Compound **9a** was isolated as a yellow oil; R_f 0.30 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.85 (s, 2H), 6.32 (s, 1H), 7.16–7.41 (m, 6H), 7.64 (m, 1H), 7.78 (dd, 2H, J=7.4, 1.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 35.1, 109.9, 124.2, 127.4, 127.7, 127.9, 128.4, 128.6, 128.7, 129.4, 129.7, 133.7, 146.7, 165.6 ppm; IR (film) 1761 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 229 (8000), 300 (16,300); HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0849.

4.1.10.2. (*Z*)-4-Phenylbenzo[*d*]oxepin-2(1*H*)-one (11a). As previously describe **11a** was isolated as a colorless oil; R_f 0.38 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.73 (s, 2H), 7.08 (s, 1H), 7.35–7.47 (m, 7H), 7.77 (dd, 2H, J=7.4, 1.8 Hz,) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 35.1, 110.7, 127.5, 128.0, 128.3, 128.7, 128.8, 129.2, 129.3, 129.6, 132.9, 134.3, 148.8, 167.0 ppm; IR (film) 1762 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0835.

4.1.10.3. (*Z*)-1-(4-Methoxybenzylidene)isochroman-3-one (9b). Compound **9b** was obtained according to general procedure A from **7b** (150 mg, 0.57 mmol) in 24 h. Purification by column chromatography (AcOEt/hexane 10/90) gives 82 mg (54%, 0.31 mmol) of a mixture of **9b** and **11b**. Compound **9b** was isolated as a yellow solid; mp 95–97 °C; R_f 0.61 AcOEt/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.85 (s, 5H), 6.28 (s, 1H), 6.93 (d, 2H, J=8.9 Hz), 7.18 (m, 1H), 7.32–7.37 (m, 2H), 7.62 (m, 1H), 7.76 (d, 2H, J=8.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 35.2, 55.3, 109.7, 114.1, 124.1, 126.5, 126.9, 127.4, 128.2, 129.1, 131.2, 145.2, 159.2, 165.9 ppm; IR (KBr) 1751 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_3$: 266.0943; found 266.0927.

4.1.10.4. (*Z*)-4-(4-Methoxyphenyl)benzo[*d*]oxepin-2(1*H*)-one (11b). As previously describe **11b** was isolated as a yellow solid; mp 99–101 °C; R_f 0.54 AcOEt/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.71 (s, 2H), 3.86 (s, 3H), 6.93–6.96 (m, 3H), 7.37 (s, 4H), 7.69 (d, 2H, J=9.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 41.3, 55.4, 109.0, 114.0, 126.9, 127.9, 128.1, 128.7, 128.8, 129.3, 133.1, 148.6, 160.5, 167.2 ppm; IR (KBr) 1752, 1262 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 230 (11,500), 300 (24,700); HRMS (EI): calcd for $C_{17}H_{14}O_3$: 266.0943; found 266.0953.

4.1.10.5. (*Z*)-1-(3-Fluorobenzylidene)isochroman-3-one (9c). Compound **9c** was obtained according to general procedure A from **7c** (100 mg, 0.39 mmol) in 24 h. Purification by column chromatography (Et_2O/pentane 20/80) gives 62 mg of **9c** (62%, 0.24 mmol) as a white solid; mp 100–102 °C; R_f 0.51 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.79 (s, 2H), 6.21 (s, 1H), 6.90 (m, 1H), 7.12 (m, 1H), 7.19–7.34 (m, 2H), 7.44–7.51 (m, 2H), 7.57 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 34.9, 108.5 (d, J^4_{F-C}=3 Hz), 114.4 (d, J^2_{F-C}=21 Hz), 116.1 (d, J^2_{F-C}=23 Hz), 124.2, 125.4 (d, J^4_{F-C}=3 Hz), 127.4, 127.9, 128.1, 128.4, 129.7, 129.8 (d, J^3_{F-C}=8 Hz), 135.7 (d, J^3_{F-C}=8 Hz), 147.5, 162.7 (d, J^1_{F-C}=244 Hz), 165.1 ppm; IR (KBr) 1754 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 230 (11,100), 302 (25,200); HRMS (EI): calcd for $C_{16}H_{11}O_2F$: 254.0743; found 254.0758.

4.1.10.6. (*Z*)-1-(2-Methylbenzylidene)isochroman-3-one (9f). Compound **9f** was obtained according to general procedure A from **7f** (100 mg, 0.39 mmol) in 72 h. Purification by PTLC (CH_2Cl_2/pentane 3/7) gives 16 mg of **9f** (16%, 0.06) as a pale yellow solid; mp 108–110 °C; R_f 0.34 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.41 (s, 3H), 3.85 (s, 2H), 6.49 (s, 1H), 7.19–7.29 (m, 4H), 7.36–7.41 (m, 2H), 7.67 (m, 1H), 7.97 (d, 1H, J=7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.4, 35.3, 107.7, 124.4, 126.1, 127.4, 127.7, 127.9, 128.5, 129.0, 129.4, 130.0, 130.1, 132.1, 136.4, 146.6, 165.8 ppm; IR (KBr) 1759 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{14}O_2$: 250.0994; found 250.0987.

4.1.10.7. (*Z*)-4-*o*-Tolylbenzo[*d*]oxepin-2(1*H*)-one (11f). As previously describe 4 mg of **11f** was obtained (4%, 0.01 mmol) as a pale yellow oil; R_f 0.45 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.47 (s, 3H), 3.80 (s, 2H), 6.64 (s, 1H), 7.25–7.32 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.7, 41.6, 114.5, 125.9, 127.98, 128.03, 128.8, 129.1, 129.3, 129.5, 130.8 ppm; HRMS (EI): calcd for $C_{17}H_{14}O_2$: 250.0994; found 250.0999.

4.1.10.8. 1-Methyleneisochroman-3-one (9g). Compound **9g** was obtained according to general procedure A

from **7g** (95 mg, 0.54 mmol) in 24 h. Compound **9g** (70 mg) was obtained (74%, 0.40 mmol) as a brown oil; R_f 0.32 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.83 (s, 2H), 5.02 (d, 1H, J=2.3 Hz), 5.13 (d, 1H, J=2.3 Hz), 7.18 (m, 1H), 7.29–7.40 (m, 2H), 7.59 (dd, 1H, J=7.6, 1.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 41.3, 94.8, 124.6, 127.3, 127.8, 128.5, 129.9, 132.8, 153.6, 166.0 ppm; IR (film) 1748 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 245 (3500).

4.1.10.9. (*Z*)-1-Butylideneisochroman-3-one (9h). Compound **9h** was obtained according to general procedure A from **7h** (145 mg, 0.72 mmol) in 12 h. Purification by PTLC (Et_2O/pentane 10/90) gives 129 mg (89%, 0.64 mmol) of a mixture of **9h** and **11h**. Compound **9h** was isolated as a colorless oil; R_f 0.29 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.98 (t, 3H, J=7.3 Hz), 1.51 (sext, 2H, J=7.3 Hz), 2.36 (q, 2H, J=7.3 Hz), 3.79 (s, 2H), 5.50 (t, 1H, 7.6 Hz), 7.15 (m, 1H), 7.29–7.34 (m, 2H), 7.5 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.8, 22.5, 26.9, 35.2, 112.0, 123.9, 127.1, 127.6, 128.0, 128.6, 128.9, 146.8, 166.64 ppm; HRMS (EI): calcd for $C_{13}H_{14}O_2$: 202.0994; found 202.0988.

4.1.10.10. (*Z*)-4-Propylbenzo[*d*]oxepin-2(1*H*)-one (11h).[17a] As previously described **11h** was isolated as a colorless oil; R_f 0.34 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (t, 3H, J=7.4 Hz), 1.67 (sext, 2H, J=7.4 Hz), 2.38 (t, 2H, J=7.4 Hz), 3.61 (s, 1H), 6.27 (s, 1H), 7.21–7.34 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.4, 20.5, 37.3, 41.2, 110.4, 127.4, 127.7, 128.4, 128.5, 129.3, 132.9, 152.2, 167.0 ppm; IR (film) 1757 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 229 (10,900), 252 (18,600); HRMS (EI): calcd for $C_{13}H_{14}O_3$: 202.0994; found 202.0988.

4.1.10.11. (*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-one (10a).[16f] Compound **10a** was obtained according to general procedure A from **8a** (150 mg, 0.67 mmol) in 2 h. Purification by column chromatography (AcOEt/pentane 10/90) gives 123 mg (82%, 0.55 mmol) of a mixture of **10a** and **12a**. Twelve milligram of dimer **13a** (4%, 0.03 mmol) was obtained. Compound **10a** was obtained as a pure white solid by purification on PTLC ($CHCl_3$/petroleum ether 1/1); mp 90–92 °C (lit.[17b] mp 100–101 °C); R_f 0.47 AcOEt/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.36 (s, 1H), 7.23–7.51 (m, 4H), 7.63–7.89 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 107.2, 112.0, 123.5, 125.7, 128.6, 128.9, 129.9, 130.3, 133.3, 134.7, 140.8, 144.8, 167.3 ppm; IR (KBr) 1774 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 239 (15,800), 297 (21,900), 309 (21,700), 338 (22,800); HRMS (EI): calcd for $C_{15}H_{10}O_2$: 222.0681; found 222.0674.

4.1.10.12. 3-Phenyl-1*H*-isochromen-1-one (12a). Compound **12a** was obtained according to general procedure B from **6a** (70 mg, 0.29 mmol) in 48 h at 80 °C. Purification by column chromatography (Et_2O/pentane 20/80) gives 38 mg of **12a** (60%, 0.17 mmol) as a white solid; mp 89–91 °C (lit.[17c] mp 87–89 °C); R_f 0.49 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.95 (s, 1H), 7.41–7.52 (m, 5H), 7.71 (t, 1H, J=7.8 Hz), 7.88 (dd, 2H, J=7.8, 1.8 Hz,), 8.31 (d, 1H, J=7.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 101.8, 120.6, 125.2, 125.9, 128.1, 128.8, 129.7, 129.9, 132.0, 134.8, 137.5, 153.7, 162.2 ppm; IR (KBr) 1720 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 235 (16,900), 298 (16,900), 311 (14,600), 340 (8100); HRMS (EI): calcd for $C_{15}H_{10}O_2$: 222.0681; found 222.0674.

4.1.10.13. (3*E*,3′*E*)-3,3′-(1,2-Diphenylethane-1,2-diylidene)diisobenzofuran-1(3*H*)-one (13a). Mp 228–230 °C; R_f 0.23 AcOEt/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.26–7.40 (m, 3H), 7.43–7.49 (m, 2H), 7.61 (m, 1H), 7.86–7.92 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 118.5, 123.7, 125.7, 127.6, 128.8, 129.0, 130.0, 130.3, 135.1, 135.6, 138.7, 145.1, 166.6 ppm; HRMS (EI): calcd for $C_{30}H_{18}O_4$: 442.1205; found 442.1195.

4.1.10.14. (*Z*)-3-(4-Methoxybenzylidene)isobenzofuran-1(*H*)-one (10b). Compound **10b** was obtained according to general procedure A from **8b** (43 mg, 0.17 mmol) in 2 h. Purification by column chromatography (AcOEt/pentane 10/90) gives 33 mg (78%, 0.13 mmol) of a mixture of **10b** and **12b**. Compound **10b** was obtained pure by purification on PTLC ($CHCl_3$/petroleum ether 2/1) as a yellow solid; mp 140–142 °C (lit.[17d] mp 139–140 °C); R_f 0.37 $CHCl_3$/petroleum ether (2/1); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.39 (s, 1H), 6.94 (d, 2H, J=8.6 Hz), 7.51 (m, 1H), 7.67–7.79 (m, 2H), 7.81 (d, 2H, J=8.6 Hz), 7.93 (d, 1H, J=7.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 55.3, 106.9, 114.3, 119.5, 123.1, 125.5, 125.9, 129.3, 131.7, 134.3, 140.8, 143.1, 159.8, 167.2 ppm; IR (KBr) 1787, 1261 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 359 (23,900), 322 (17,100), 310 (16,400), 239 (15,400); HRMS (EI): calcd for $C_{16}H_{12}O_3$: 252.0786; found 252.0791.

4.1.10.15. 3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (12b). Compound **12b** was obtained according to general procedure B from **6b** (100 mg, 0.37 mmol) in 24 h at 50 °C. Purification by column chromatography ($CHCl_3$/petroleum ether 50/50) gives 90 mg of **12b** (90%, 0.34 mmol) as a white solid; mp 120–122 °C (lit.[17e] mp 121 °C); R_f 0.37 $CHCl_3$/petroleum ether (50/50); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.88 (s, 1H), 6.84 (s, 1H), 6.98 (d, 2H, J=8.7 Hz), 7.44–7.50 (m, 2H), 7.70 (t, 1H, J=7.7 Hz), 7.84 (d, 2H, J=8.7 Hz), 8.30 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 55.4, 100.2, 114.2, 120.1, 124.5, 125.7, 126.8, 127.6, 129.6, 134.8, 137.9, 153.7, 161.1, 162.5 ppm; IR (KBr) 1740 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 230 (18,700), 250 (11,000), 257 (10,900), 307 (23,400), 346 (12,900); HRMS (EI): calcd for $C_{17}H_{14}O_3$: 266.0943; found 266.0953.

4.1.10.16. (*Z*)-3-(3-Fluorobenzylidene)isobenzofuran-1(3*H*)-one (10c). Compound **10c** was obtained according to general procedure A from **8c** (140 mg, 0.58 mmol) in 2 h. Purification by column chromatography (Et_2O/pentane 20/80) gives 86 mg of **10c** (61%, 0.34 mmol) as a white solid and 21 mg of dimer **12c** (7%, 0.04 mmol); mp 228–230 °C; R_f 0.46 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.37 (s, 1H), 6.99 (m, 1H), 7.30 (m, 1H), 7.53–7.62 (m, 3H), 7.70–7.78 (m, 2H), 7.93 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 105.6, 115.2 (d, J^2_{F-C}= 22 Hz,), 116.4 (d, J^2_{F-C}=22 Hz), 119.9, 123.4, 125.6, 125.7, 130.0, 134.6, 135.1 (d, J^3_{F-C}=8 Hz), 140.2, 145.3, 162.8 (d, J^1_{F-C}=245 Hz), 164.7 ppm; IR (KBr) 1766 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 231 (12,500), 296 (18,700), 307 (18,000), 338 (20,700); HRMS (EI): calcd for $C_{15}H_9O_2F$: 240.0587; found 240.0593.

4.1.10.17. 3-(3-Fluorophenyl)-1*H*-isochromen-1-one (12c).[17f] Compound **12c** was obtained according to general procedure B from **6c** (100 mg, 0.39 mmol) in 48 h at 50 °C. Purification by column chromatography (Et_2O/pentane 20/80) gives 75 mg of **12c** (75%, 0.31 mmol) as a white solid; mp 138–140 °C; R_f 0.40 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 6.96 (s, 1H), 7.12 (td, 1H, J=7.9, 2.6 Hz), 7.42 (m, 1H), 7.49–7.60 (m, 3H), 7.64–7.77 (m, 2H), 8.31 (d, 1H, J=7.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 102.6, 112.2 (d, J^2_{F-C}=24 Hz), 116.8 (d, J^2_{F-C}=22 Hz), 120.7, 120.8 (d, J^4_{F-C}=3 Hz), 126.1, 128.5, 129.7, 130.4 (d, J^3_{F-C}=9 Hz), 134.1 (d, J^3_{F-C}=8 Hz), 134.9, 137.1, 152.2, 161.8, 163.0 (d, J^1_{F-C}=245 Hz) ppm; IR (KBr) 1715 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 234 (16,600), 298 (17,500), 311 (15,800), 339 (8800); HRMS (EI): calcd for $C_{15}H_9O_2F$: 240.0587; found 240.0593.

4.1.10.18. (3*E*,3′*E*)-3,3′-(1,2-Bis(3-fluorophenyl)-ethane-1,2-diylidene)diisobenzofuran-1(3*H*)-one (13c). White solid; mp 200 °C (dec); R_f 0.30 Et_2O/pentane (20/80); ^1H NMR ($CDCl_3$, 270 MHz) δ 7.02 (m, 1H), 7.35 (m, 1H), 7.47–7.65 (m, 5H), 7.93 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 116.2 (d, J^2_{F-C}=22 Hz), 116.7 (d, J^2_{F-C}=24 Hz), 123.7, 124.8, 125.6, 130.1 (d, J^3_{F-C}=7 Hz), 130.8, 135.4, 135.9 (d, J^3_{F-C}=7 Hz), 138.3, 146.0, 162.9 (d, J^1_{F-C}=245 Hz), 166.1 ppm; IR (KBr) 1786, 1766 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 233 (24,300), 293 (21,600), 335 (22,600); HRMS (EI): calcd for $C_{30}H_{16}O_4F_2$: 478.1017; found 478.1010.

4.1.10.19. 3-(5-Ethyl-2-methylphenyl)-1*H*-isochromen-1-one (12e). Compound **12e** was obtained according to general procedure A from **8e** (130 mg, 0.49 mmol) in 48 h. Purification by column chromatography (Et_2O/pentane 10/90) gives 110 mg of **12e** (85%, 0.49 mmol) as a colorless oil; R_f 0.45 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.18 (t, 3H, J=7.6 Hz), 2.29 (s, 3H), 2.63 (q, 2H, J=7.6 Hz), 6.47 (s, 1H), 7.11 (d, 1H, J=7.7 Hz), 7.15 (d, 1H, J=7.7 Hz), 7.29 (m, 1H), 7.46 (d, 1H, J=7.7 Hz), 7.53 (t, 1H, J=7.7 Hz), 7.75 (t, 1H, J=7.7 Hz), 8.35 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 15.7, 20.1, 26.6, 107.0, 120.4, 125.7, 125.9, 127.5, 128.3, 129.7, 132.3, 134.8, 137.2, 137.4, 143.6, 154.0, 162.9 ppm; IR (film) 1721 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 231 (20,300), 268 (12,100), 276 (12,200), 325 (4100); HRMS (EI): calcd for $C_{18}H_{16}O_2$: 264.1150; found 264.1148.

4.1.10.20. (*Z*)-3-(2-Methylbenzylidene)isobenzofuran-1(3*H*)-one (10f). Compound **10f** was obtained according to general procedure A from **8f** (70 mg, 0.29 mmol) in 18 h. Purification by column chromatography (Et_2O/pentane 10/90) gives 60 mg (85%, 0.25 mmol) of a mixture of **10f** and **12f**. Compound **10f** was isolated as a white solid; mp 130–132 °C (lit.[17g] mp 130–131 °C); R_f 0.26 $CHCl_3$/petroleum ether (50/50); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.47 (s, 3H), 6.62 (s, 1H), 7.20–7.31 (m, 3H), 7.55 (t, 1H, J=7.6 Hz), 7.73 (t, 1H, J=7.6 Hz), 7.81 (d, 1H, J=7.6 Hz), 7.93 (d, 1H, J=7.6 Hz), 8.15 (d, 1H, J=7.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.2, 103.9, 119.8, 123.5, 125.5, 126.4, 128.3, 129.7, 130.3, 130.5, 131.4, 134.4, 136.6, 140.6, 144.7, 167.1 ppm; IR (KBr) 1719 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 237 (5000), 299 (6000), 340 (7000); HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0826.

4.1.10.21. 3-*o*-Tolyl-(1*H*)-isochromen-1-one (12f). As previously describe **12f** was isolated as a white solid; mp 85–87 °C (lit.[17h] mp 80–82 °C); R_f 0.20 $CHCl_3$/petroleum ether (50/50); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.51 (s, 3H), 6.61 (s, 1H), 7.24–7.38 (m, 3H), 7.46–7.55 (m, 3H), 7.74 (td, 1H, J=7.7, 1.0 Hz), 8.33 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 20.7, 105.8, 120.3, 125.8, 125.9, 128.2, 129.1, 129.5, 129.7, 131.0, 132.7, 134.8, 136.7, 137.4, 155.6, 162.5 ppm; IR (KBr) 1764 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 233 (28,500), 286 (13,600), 330 (6000); HRMS (EI): calcd for $C_{16}H_{12}O_2$: 236.0837; found 236.0826.

4.1.10.22. 3-Methyleneisobenzofuran-1(3*H*)-one (10g).[17i] Compound **10g** was obtained according to general procedure A from **8g** (50 mg, 0.34 mmol) in 2 h. Purification by column chromatography (Et_2O/pentane 20/80) gives 37 mg of **10g** (75%, 0.25 mmol) as a white solid; mp 61–63 °C; R_f 0.36 Et_2O/pentane (10/90); ^1H NMR ($CDCl_3$, 270 MHz) δ 5.23 (d, 2H, J=6.4 Hz), 7.58 (m, 1H), 7.70–7.74 (m, 2H), 7.89 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 91.1, 120.5, 125.1, 125.2, 130.4, 134.4, 138.9, 151.8, 166.7 ppm; IR (film) 1766 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 235 (13,400), 300 (3700); HRMS (EI): calcd for $C_9H_6O_2$: 146.0368; found 146.0363.

4.1.10.23. (*Z*)-3-Butylideneisobenzofuran-1(3*H*)-one (10h).[3b] Compound **10h** was obtained according to general procedure A from **8h** (55 mg, 0.29 mmol) in 2 h. Purification by PTLC ($CHCl_3$/petroleum ether 50/50) gives 40 mg (74%, 0.21 mmol) of a mixture of **10h** and **12h**. Compound **10h** was isolated as colorless oil; R_f 0.59 $CHCl_3$/petroleum ether (50/50); ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99 (t, 3H, J=7.4 Hz), 1.56 (sext, 2H, J=7.4 Hz), 2.46 (q, 2H, J=7.4 Hz), 5.65 (t, 1H, J=7.7 Hz), 7.50 (m, 1H), 7.51 (m, 2H), 7.89 (d, 1H, J=7.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.8, 22.5, 27.7, 109.4, 119.6, 124.4, 125.2, 129.3, 134.2, 139.6, 145.7, 167.1 ppm; IR (film) 1775 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 237 (14,300), 262 (15,800), 311 (5000); HRMS (EI): calcd for $C_{12}H_{12}O_2$: 188.0837; found 188.0836.

4.1.10.24. 3-Propyl-1*H*-isochromen-1-one (12h).[17i] Compound **12h** was obtained according to general procedure B from **6h** (127 mg, 0.63 mmol) in 12 h at 50 °C. Purification by column chromatography ($CHCl_3$/petroleum ether 1/2) gives 75 mg of **12h** (60%, 0.37 mmol) as a colorless oil; R_f 0.28 $CHCl_3$/petroleum ether (1/2); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.00 (t, 3H, J=7.4 Hz), 1.76 (sext, 2H, J=7.4 Hz), 2.51 (d, 2H, J=7.4 Hz), 6.26 (s, 1H), 7.35 (d, 1H, J=7.6 Hz), 7.45 (t, 1H, J=7.6 Hz), 7.67 (m, 1H), 8.25 (d, 1H, J=7.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 13.4, 20.2, 35.4, 103.0, 120.1, 125.0, 127.5, 129.5, 134.6, 137.6, 158.0, 163.0 ppm; IR (film) 1727 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 233 (21,600), 240 (19,600), 266 (12,000), 275 (9800), 327 (4500); HRMS (EI): calcd for $C_{12}H_{12}O_2$: 188.0837; found 188.0836.

4.2. Structure analysis for compound 10a

$C_{14}H_{10}O_2$, Mr=222.23, triclinic, *P*-1, a=6.9468(9) Å, b=8.5049(7) Å, c=9.1799(8) Å, α=94.029(7)°, β=93.450(9)°, γ=98.239(9)°, V=534.08(9) $Å^3$, Z=2, D_X=1.382 Mg m^{-3}, λ(Mo Kα)=0.71073 Å, μ=0.91 cm^{-1}, F(000)=232, T=110(1) K. The sample (0.24×0.22×0.08 mm) is studied on

an Oxford Diffraction Xcalibur Saphir 3 diffractometer with graphite monochromatized Mo Kα radiation. The data collection (Crysalis, 2004) ($2\theta_{max}$=54°, omega scan frames via 0.7° omega rotation and 20 s per frame, range HKL: H -10,10 K -12,12 L -5,13) gives 4668 reflections. The data leads to 3020 independent reflections from which 1547 with $I>2.0\sigma(I)$. The structure was solved with SIR-97 (Altomare et al., 1998), which reveals the non-hydrogen atoms of the molecule. After anisotropic refinement, all the hydrogen atoms are found with a Fourier difference. The whole structure was refined with SHELXL97 (Sheldrick, 1997) by the full-matrix least-square techniques (use of F square magnitude; x, y, z, β_{ij} for C and O atoms, x, y, z in riding mode for H atoms; 154 variables and 1547 observations with $I>2.0\sigma(I)$; calcd $w=1/[\sigma^2(F_0^2)+(0.089P)^2]$ where $P=(F_0^2+2F_c^2)/3$ with the resulting R=0.047, R_w=0.110, and S_w=0.687, $\Delta\rho<0.32$ eÅ^{-3} atomic scattering factors from International Tables for X-ray Crystallography (1992). ORTEP view realized with PLATON98 (Spek, 1998). The CIF file has been deposit at Cambridge Crystallographic Deposit Center with registry number CCDC 641686.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.066.

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18. The cycloisomerization of the ester **6b** was also performed in the presence of 2 equiv of D_2O. The product **12b** is isolated with deuterium at its olefinic position (>70% deuterium insertion). This experiment confirms the role played by the water.