Pergamon

Tetrahedron 58 (2002) 5023–5038

TETRAHEDRON

New procedures for the selective synthesis of 2(2*H*)-pyranone derivatives and 3-aryl-4-iodoisocoumarins

Matteo Biagetti,* Fabio Bellina, Adriano Carpita, Paolo Stabile and Renzo Rossi*

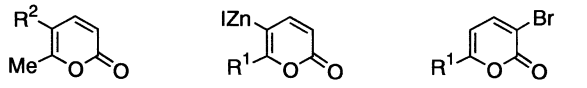
Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, I-56126 Pisa, Italy

Received 4 March 2002; revised 5 April 2002; accepted 2 May 2002

Abstract—5-Iodo-2(2*H*)-pyranone derivatives have been selectively synthesized by reaction of stereodefined methyl 2-en-4-ynoates with iodine in MeCN, CH_2Cl_2 or C_6H_6 at 20°C (Method C) or by treatment of these esters with ICl in CH_2Cl_2 at 20°C (Method B). Methods B and C proved also to be suitable for the preparation of 3-aryl-4-iodoisocoumarins from the corresponding methyl 2-(arylethynyl)benzoates. Interestingly, the high selectivity of iodolactonization of stereodefined methyl 2-en-4-ynoates by Method B allowed preparation in moderate yields of 2(2*H*)-pyranone derivatives by a one-pot sequence of iodolactonization and Stille-type reactions.

1. Introduction

Iodolactonization of alkynoic acids[1] is a process much less investigated and employed in synthetic organic chemistry than iodolactonization of alkenoic acids[2] or alkyl alkenoates.[3] Nevertheless, it has found utility in the preparation of five-membered halolactone analogues of α-aminoacids that have value as inhibitors of serine proteases.[4] On the other hand, until a few years ago no data were available on iodolactonization of stereodefined enynoic acids, but recently, in the course of our studies on the synthesis of biologically active, naturally-occurring oxygen-containing heterocycles and their analogues,[5] we developed convenient protocols for the synthesis of natural and unnatural 5,6-disubstituted and 6-substituted 2(2*H*)-pyranones, **7** and **8**, which involved iodolactonization of 5-substituted (*Z*)-2-en-4-ynoic acids **1** (Scheme 1).[6,7] In particular, we found that reaction of compounds **1** with 3.0 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in MeCN at 20°C (Method A) or with 1.0 equiv. of ICl in CH_2Cl_2 at 20°C (Method B) provides mixtures of (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones **3** and 6-substituted 5-iodo-2(2*H*)-pyranones **4** in which these last compounds are the major products (Scheme 1).[6] We also found that compounds **4**, which are available in 63–72% yield by chromatographic separation from iodides **3**, are able to undergo Stille-type reactions with a variety of organotin derivatives to give 5,6-disubstituted 2(2*H*)-pyranones **7** in moderate to good yields (Scheme 1).[6] One of these compounds, i.e. 5-(1-butynyl)-6-methyl-2(2*H*)-pyranone (**7a**), was then used as a direct precursor to two substances produced by fungal culture LL-11G219, which function as androgen ligands, i.e. (*Z*)-5-(1-butenyl)-6-methyl-2(2*H*)-pyranone (**11**) and 5-butyl-6-methyl-2(2*H*)-pyranone (**12**).[6]



7a: R^2 = Et-C≡C
11: R^2 = (*Z*)-Et-CH=CH
12: R^2 = *n*-Bu

13: R^1 = alkyl

14: R^1 = alkyl, aryl

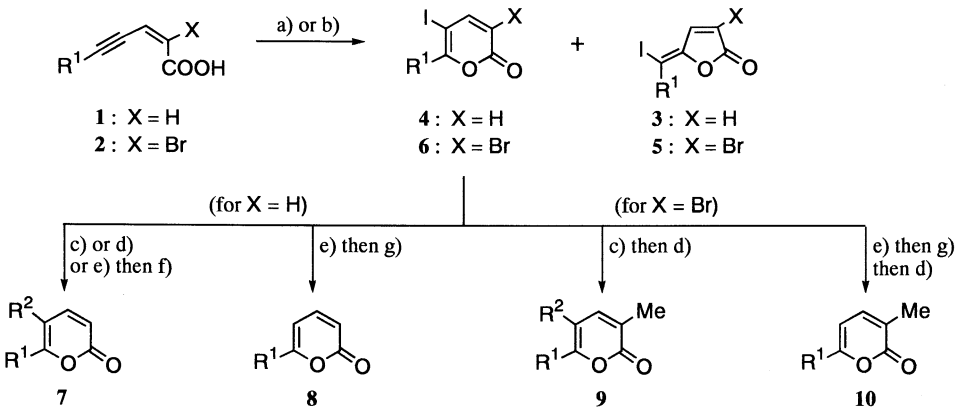
In continuation of these investigations we then discovered that 6-alkyl-5-iodozinc-2(2*H*)-pyranones **13**, which are easily available from iodides **4** by insertion of activated zinc metal on their carbon-iodine bond, undergo Pd-catalyzed reaction either with activated alkenyl halides or with activated and deactivated (hetero)aryl halides to provide compounds **7** in fair to good yields (Scheme 1).[7] Moreover, we observed that acidic hydrolysis of the above-mentioned organozinc derivatives gave in satisfactory yields 6-substituted 2(2*H*)-pyranones **8** including two natural products (Scheme 1).[7]

More recently, we examined the possibility of accessing 3,5,6-trisubstituted and 3,6-disubstituted 2(2*H*)-pyranones of general formula **9** and **10**, respectively, starting from 5-substituted (*E*)-2-bromo-2-en-4-ynoic acids **2** by a chemistry similar to that successfully used to prepare compounds **7** and **8** and we found that iodolactonization of carboxylic acids **2** using Methods A or B allows preparation of 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranones **6** in yields ranging from 30 to 75%.[8] These dihalides were then converted into compounds **9** by two consecutive Stille-type reactions (Scheme 1).[8] On the other hand, selective reduction of dihalides **6** to the corresponding 6-substituted 3-bromo-2(2*H*)-pyranones **14** followed by a

Keywords: iodine heterocycles; pyrones; isocoumarins; Stille coupling; palladium catalysis.

* Corresponding authors. Tel.: +39-50-918214; fax: +39-50-918260; e-mail: rossi@dcci.unipi.it

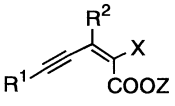
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00469-6



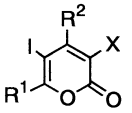
Scheme 1. (a) I_2 (3.0 equiv), $NaHCO_3$ (3.0 equiv.), MeCN, rt, 1.5 h; (b) ICl (1.0 equiv.), CH_2Cl_2, rt, 1 h; (c) R^2–SnR_3 (R^2=Ar, CH2=CH–) (1.2 equiv.), $PdCl_2(PhCN)_2$ (5 mol%), $AsPh_3$ (10 mol%), NMP, 50°C, 6.5–23 h, or R^2SnR_3 (R^2=1-alkynyl) (1.2 equiv.), $PdCl_2(PPh_3)_2$ (3 mol%), THF, 50°C, 6–21 h; (d) Me_4Sn (3.0 equiv.), $PdCl_2(PhCN)_2$ (5 mol%), CuI (10 mol%), $AsPh_3$ (10 mol%), NMP, 80°C, 22 h; (e) activated Zn dust (3–5 equiv.), THF, rt, 3–3.5 h; (f) R^2–X (R^2=alkenyl, (hetero)aryl; X=Br, I) (0.83–1.41 equiv.), $Pd_2(dba)_3$ (2 mol%), PPh_3 (8 mol%), THF, 20–70°C, 15–44 h; (g) H_3O^+, 0°C.

Pd/Cu-catalyzed reaction with tetramethyltin provided selectively compounds **10** (Scheme 1).[8]

Even though these results were satisfactory, we decided to search for a new, more direct and, possibly, more efficient route to 5-iodo-2(2*H*)-pyranones of general formula **17**, which did not involve the preparation of stereodefined 2-en-4-ynoic acids of general formula **16** from the corresponding methyl esters **15** and was also amenable to preparation of iodides **17** with selectivity higher than that obtained in the preparation of compounds **4** and **6** by iodolactonization of carboxylic acids **1** and **2**, respectively.[6–8]

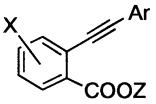


15 : R^1 = alkyl, alkenyl; R^2 = H, alkyl
X = H, Br; Z = Me
16 : R^1 = alkyl, alkenyl; R^2 = H, alkyl
X = H, Br; Z = H

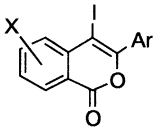


17 : R^1 = alkyl, alkenyl;
R^2 = H, alkyl; X = H, Br

We now wish to report that compounds **17** can be synthesized in satisfactory yields by treatment of methyl esters **15** with iodine in MeCN, CH_2Cl_2 or C_6H_6 at room temperature (rt) (Method C) and that the selectivity of this reaction is comparable with that of iodolactonization of carboxylic acids **16** by Method A. We also show that compounds **17** can be alternatively prepared in satisfactory yields by iodocyclization of **15** with ICl[9] (Method B) and that the selectivity of this last procedure is higher than that observed either using Method C or when carboxylic acids **16** undergo iodolactonization according to Method A. Moreover, we report that: (i) Methods B and C are also suitable for preparation of 3-aryl-4-iodoisocoumarins **20a–d** from the corresponding methyl 2-(arylethynyl)-benzoates **18a–d**, and that (ii) iodolactonization of **18a** and **d** by Method C is more selective than that of the corresponding carboxylic acids **19a** and **c**, respectively, by Method A.

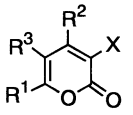


18a : X = 4-MeO; Ar = 4-$MeOC_6H_4$; Z = Me
18b : X = 6-MeO; Ar = 3,4-$(MeO)_2C_6H_3$; Z = Me
18c : X = 6-MeO; Ar = C_6H_5; Z = Me
18d : X = H; Ar = C_6H_5; Z = Me
19a : X = 4-MeO; Ar = 4-$MeOC_6H_4$; Z = H
19b : X = 6-MeO; Ar = 3,4-$(MeO)_2C_6H_3$; Z = H
19c : X = H; Ar = C_6H_5; Z = H



20a : X = 4-MeO; Ar = 4-$MeOC_6H_4$
20b : X = 6-MeO; Ar = 3,4-$(MeO)_2C_6H_3$
20c : X = 6-MeO; Ar = C_6H_5
20d : X = H; Ar = C_6H_5

Finally, we describe the results of some attempts to convert methyl esters **15** into 2(2*H*)-pyranone derivatives of general formula **21** and **22** by a one-pot sequence of iodolactonization and Stille-type reactions.[10]



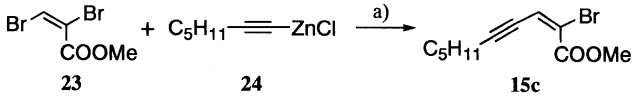
21 : R^1 = alkyl; R^2 = H, alkyl; R^3 = aryl, 1-alkynyl; X = H, Br
22 : R^1 = alkyl; R^2 = H; R^3 = 1-alkynyl; X = Me

2. Results and discussion

2.1. Iodolactonization of stereodefined methyl 2-en-4-ynoates and methyl 2-(arylethynyl)benzoates

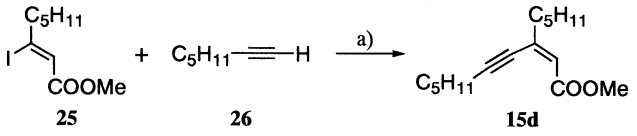
The stereodefined methyl 2-en-4-ynoates, which we used in this study, were compounds **15a–d**.

Compounds **15a** and **b** were prepared according to the



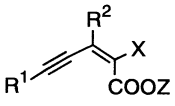
23 24 15c

Scheme 2. (a) **24** (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF, 0°C, 5 h, (78%).



25 26 15d

Scheme 3. (a) **26** (1.2 equiv.), $Pd(PPh_3)_4$ (3 mol%), CuI (9 mol%), Et_3N (3.0 equiv.), C_6H_6, rt, 19 h, (94%).



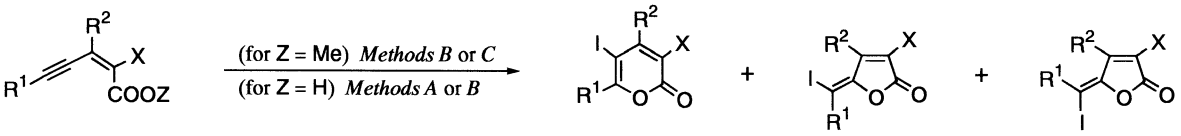
15a: R^1 = C_5H_{11}; R^2 = X = H; Z = Me
15b: R^1 = (*Z*)-MeCH=CMe; R^2 = H; X = Br; Z = Me
15c: R^1 = C_5H_{11}; R^2 = H; X = Br; Z = Me
15d: R^1 = R^2 = C_5H_{11}; X = H; Z = Me
16a: R^1 = C_5H_{11}; R^2 = X = H; Z = H
16b: R^1 = (*Z*)-MeCH=CMe; R^2 = H; X = Br; Z = H

literature[6,8] and compounds **15c** and **d** were synthesized as shown in Schemes 2 and 3, respectively. In particular, according to the general procedure which we previously developed for the synthesis of stereoisomerically pure alkyl (*E*)-2-bromo-2-en-4-ynoates,[11] methyl (*E*)-2,3-dibromopropenoate (**23**)[12] was reacted with 1.3 equiv. of 1-heptynylzinc chloride (**24**) in THF at 0°C in the presence of 5 mol% $Pd(PPh_3)_4$ to give **15c** in 78% yield (Scheme 2).

On the other hand, the Sonogashira reaction[13] between methyl (*Z*)-3-iodo-2-octenoate (**25**)[14] and 1.2 equiv. of 1-heptyne (**26**) gave compound **15d** in 94% yield (Scheme 3).

At the beginning of our investigations on iodolactonization of compounds **15a–d** we found that these esters can be converted in satisfactory yields into the corresponding 5-iodo-2(2*H*)-pyranones **17a–d** by treatment with 3.0 equiv. of iodine in MeCN, CH_2Cl_2 or C_6H_6 at rt for 1 h (Method C). A comparison of the results of iodolactonization of **15a–d** in MeCN according to this method with those obtained using CH_2Cl_2 or C_6H_6 as solvent is reported in Table 1. This table also summarizes the

Table 1. Iodolactonization of methyl 2-en-4-ynoates **15** and 2-en-4-ynoic acids **16**



15: Z = Me
16: Z = H

17 (*E*)-**27** (*Z*)-**27**

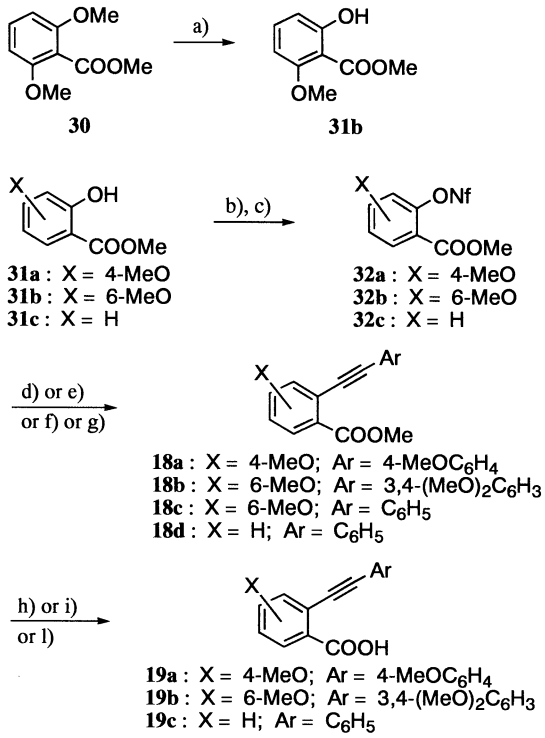
Entry	Substrate					Method for iodolactonization[a] (solvent)	Products		
	15 or **16**	R^1	R^2	X	Z		**17**+(*E*)-**27**+(*Z*)-**27**	**17**/(*E*)-**27**/(*Z*)-**27** molar ratio[b]	Yield (%) of **17**[c]
1	**15a**	C_5H_{11}	H	H	Me	*C*(MeCN)	**17a**+(*E*)-**27a**+(*Z*)-**27a**	70/14/16	(59)
2	**15a**	C_5H_{11}	H	H	Me	*C* (CH_2Cl_2)	**17a**+(*E*)-**27a**+(*Z*)-**27a**	86/6/8	80[d]
3	**15a**	C_5H_{11}	H	H	Me	*C* (C_6H_6)	**17a**+(*E*)-**27a**+(*Z*)-**27a**	83/7/10	(70)
4	**15a**	C_5H_{11}	H	H	Me	*B* (CH_2Cl_2)	**17a**	100/0/0	72
5[e]	**16a**	C_5H_{11}	H	H	H	*A* (MeCN)	**17a**+(*E*)-**27a**	69/31/0	65[e]
6	**15b**	(*Z*)-MeCH=CMe	H	Br	Me	*C* (MeCN)	**17b**+(*E*)-**27b**	95/5/0	(64)
7	**15b**	(*Z*)-MeCH=CMe	H	Br	Me	*C* (CH_2Cl_2)	**17b**+(*E*)-**27b**	>99/<1/0	64
8	**15b**	(*Z*)-MeCH=CMe	H	Br	Me	*C* (C_6H_6)	**17b**+(*E*)-**27b**	>98/<2/0	(64)
9	**15b**	(*Z*)-MeCH=CMe	H	Br	Me	*B* (CH_2Cl_2)	**17b**	100/0/0	62
10[f]	**16b**	(*Z*)-MeCH=CMe	H	Br	H	*A* (MeCN)	**17b**+(*E*)-**27b**	97/3/0	75[f]
11	**16b**	(*Z*)-MeCH=CMe	H	Br	H	*B* (CH_2Cl_2)	**17b**+(*E*)-**27b**	>99/<1/0	52[f]
12	**15c**	C_5H_{11}	H	Br	Me	*C* (MeCN)	**17c**+(*E*)-**27c**+(*Z*)-**27c**	58/20/22	46[g]
13	**15c**	C_5H_{11}	H	Br	Me	*C* (CH_2Cl_2)	**17c**+(*E*)-**27c**+(*Z*)-**27c**	69/12/19	n.d.
14	**15c**	C_5H_{11}	H	Br	Me	*C* (C_6H_6)	**17c**+(*E*)-**27c**+(*Z*)-**27c**	70/14/16	59
15	**15c**	C_5H_{11}	H	Br	Me	*B* (CH_2Cl_2)	**17c**+(*E*)-**27c**+(*Z*)-**27c**	94/4/2	51
16	**15d**	C_5H_{11}	C_5H_{11}	H	Me	*C* (MeCN)	**17d**+(*E*)-**27d**+(*Z*)-**27d**	82/13/5	(65)
17	**15d**	C_5H_{11}	C_5H_{11}	H	Me	*C* (CH_2Cl_2)	**17d**+(*E*)-**27d**+(*Z*)-**27d**	87/10/3	76[h]
18	**15d**	C_5H_{11}	C_5H_{11}	H	Me	*C* (C_6H_6)	**17d**+(*E*)-**27d**+(*Z*)-**27d**	86/9/5	(71)
19	**15d**	C_5H_{11}	C_5H_{11}	H	Me	*B* (CH_2Cl_2)	**17d**	100/0/0	63

[a] Two methods were used for iodoloactonization of compounds **15**. Method C involved treatment of **15** with 3.0 equiv. of iodine in MeCN, CH_2Cl_2 or C_6H_6 at rt for 1 h. Method B involved reaction of **15** with 1.0 equiv. of ICl in CH_2Cl_2 at rt for 5 h. Iodolactonization of compounds **16** was carried out by treatment of these compounds with 3.0 equiv. of iodine and with 3.0 equiv. of $NaHCO_3$ in MeCN at rt for 1.5 h (Method A) or by reaction of these acids with 1.0 equiv. of ICl in CH_2Cl_2 at 0°C for 1 h.
[b] Molar ratio in the crude reaction mixture.
[c] Isolated yields based on **15** or **16**. Values in parentheses refer to GLC yields.
[d] MPLC on silica gel of the crude reaction mixture also allowed isolation of (*E*)-**27a** in 5% yield.
[e] Ref. 6.
[f] Ref. 8.
[g] MPLC on silica gel of the crude reaction mixture also allowed isolation of (*E*)- and (*Z*)-**27c** in 17 and 19% yield, respectively.
[h] MPLC on silica gel of the crude reaction mixture also allowed isolation of (*E*)- and (*Z*)-**27d** in 9 and 2% yield, respectively.

previously obtained results,[6,8] regarding iodolactonization (according to Method A) of the carboxylic acids corresponding to **15a** and **b**, i.e. **16a** and **b**, respectively.

As shown in Table 1 iodolactonization of esters **15a**,**c** and **d** by Method C provided mixtures of (*E*)- and (*Z*)-5-(1-iodoylidene)-2(5*H*)-furanones **27** and 5-iodo-2(2*H*)-pyranones **17** in which these last compounds were the major products and both stereoisomers of iodides **27** were present in combined yields ranging from 13 to 42%. However, iodolactonization of **15b** in MeCN, CH_2Cl_2 or C_6H_6 furnished crude reaction mixtures in which iodide **17b** was contaminated by very small amounts of (*E*)-**27b** (entries 6–8, Table 1). On the other hand, the selectivity of iodolactonization of compounds **15** by this protocol proved to depend not only on the structure of these esters, but also on the solvent of the reaction. In fact, a comparison of the results of entries 2 and 3 with those of entry 1, of those of entries 13 and 14 with those of entry 12, and of those of entries 17 and 18 with those of entry 16 of Table 1 shows that the selectivity of the reactions carried out in CH_2Cl_2 was comparable with that obtained for iodocyclization of the same substrates in C_6H_6, but higher than that of the reactions performed in MeCN. Moreover, the selectivity of iodolactonization of esters **15** in MeCN according to Method C was comparable with that observed when the acids corresponding to **15** underwent iodolactonization by Method A.[6,8] In fact, whereas, iodocyclization of **15a** in MeCN according to Method C gave a mixture of **17a**, (*E*)- and (*Z*)-**27a** in a 70:14:16 molar ratio, respectively (entry 1, Table 1), iodolactonization of **16a** according to Method A provided a mixture of **17a** and (*E*)-**27a** in a 69:31 molar ratio, respectively (entry 5, Table 1).[6] Analogously, iodolactonization of **15b** in MeCN by Method C furnished a crude mixture in which **17b** and (*E*)-**27b** were in a 95:5 molar ratio, respectively (entry 6, Table 1) and iodolactonization of **16b** according to Method A gave these same iodo derivatives in a 97:3 molar ratio, respectively (entry 10, Table 1). It should also be noted that we previously observed that the selectivity of iodolactonization by Method A of compounds **16** in which X=H is similar to that obtained when these carboxylic acids undergo iodolactonization by Method B.[6,15] Finally, it is worth mentioning that the yields of compounds **17**, which were obtained by iodolactonization of esters **15** using Method C, proved to be satisfactory (46–80%) and comparable with those obtained when carboxylic acids **16** underwent iodocyclization by Method A (Table 1, compare entries 2 and 7 with entries 5 and 10, respectively).

These results were quite satisfactory. Nevertheless, we continued our investigations in order to develop a more selective procedure for the synthesis of iodides **17**. Thus, we examined iodolactonization of **15a–d** using ICl as a source of I^+ and found that treatment of these esters with 1.0 equiv. of ICl in CH_2Cl_2 at rt provides with high selectivity compounds **17a–d** in 72, 62, 51 and 63% yield, respectively (entries 4, 9, 15 and 19, Table 1). These yields, in the case of entries 4, 9 and 19, were lower than those obtained for the same compounds prepared by iodolactonization of **15a**,**b** and **d** according to Method C (entries 2, 7, and 17, Table 1), but the isolation of the desired 5-iodo-2(2*H*)-pyranones from their crude reaction mixtures was

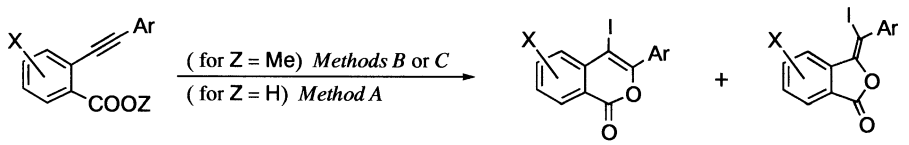


Scheme 4. (a) BCl_3 (3.0 equiv.), CH_2Cl_2, 0°C, 2.15 h then H_2O, (90%). (b) NaH (1.50 equiv.), DMF, 40 min at 0°C then 1 h at rt. (c) $C_4F_9SO_2F$ (1.15 equiv.), 3 h, rt, (94–96%). (d) (for **32a**) 4-$MeOC_6H_4$–C≡C–ZnCl (**33**) (1.20 equiv.), $Pd_2(dba)_3$ (1 mol%), dppf (2 mol%), THF, 60°C, 2 h, (87%). (e) (for **32b**) 3,4-$(MeO)_2C_6H_3$–C≡C–ZnCl (**34**) (1.25 equiv.), $Pd_2(dba)_3$ (1 mol%), dppf (2 mol%), THF, 60°C, 4.5 h, (86%). (f) (for **32b**) C_6H_5–C≡C–ZnCl (**35**) (1.20 equiv.), $Pd_2(dba)_3$ (1 mol%), dppf (2 mol%), THF, 60°C, 21 h, (90%). (g) (for **32c**) **35** (1.20 equiv.), $Pd_2(dba)_3$ (1 mol%), dppf (2 mol%), THF, 60°C, 5 h, (85%). (h) (for **18a**) KOH (10.8 equiv.), EtOH, H_2O, rt, 18 h then Amberlite IRC-76, 0°C, (99%) (i) (for **18b**) the reaction conditions, which were used for **18a** or for **18b**, did not furnish **19b**. (l) (for **18d**) KOH (10.8 equiv.), EtOH, H_2O, rt, 18 h then 5% H_2SO_4, 0°C (93%).

generally simpler than that of the same iodides prepared using this last protocol. In fact, iodolactonization of **15a**,**b** and **d** according to Method B (entries 4, 9, 19, Table 1) furnished compounds **17a**,**b** and **d**, respectively, which were free from the corresponding isomers of general formula (*E*)- and (*Z*)-**27**. Interestingly, in this case the yield of **17b** (entry 9, Table 1) proved to be higher than that previously obtained by iodolactonization of **16b** according to Method B (entry 11, Table 1).[8] Nevertheless, iodocyclization of **15c** by Method B (entry 15, Table 1) provided a crude reaction mixture which contained **17c**, (*E*)- and (*Z*)-**27c** in a 94:4:2 molar ratio, respectively. This crude mixture also contained either ca. 11 and 5% of two compounds, which likely corresponded to the two stereoisomers of compound **28**, or ca. 1% of a substance, which had GLC retention time lower than that of **15c** and a mass spectrum very similar to that of this compound. This substance likely corresponded to the (*Z*)-stereoisomer of **15c**. Fortunately, iodide **17c** was easily separated chromatographically from this last methyl ester and compounds (*E*)- and (*Z*)-**27c** and **28**.

It is also worth mentioning that the crude reaction mixture derived from iodolactonization of **15d** by Method B was contaminated by ca. 6 and 1% of two compounds

Table 2. Iodolactonization of compounds **18a–d** and **19a,c**



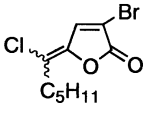
18a-d : Z = Me
19a,c : Z = H

20a-d **39a-d**

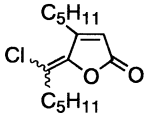
Entry	Substrate				Method for iodolactonization[a,b]	Products			
	18 or **19**	Ar	X	Z		**20**+**39**	**20/39** molar ratio[c]	Yield (%) of **20**	Yield (%) of **39**
1	**18a**	4-$MeOC_6H_4$	4-MeO	Me	*C*	**20a**	100/0	98	–
2	**18b**	3,4-$(MeO)_2C_6H_3$	6-MeO	Me	*C*	**20b**	100/0	89	–
3	**18c**	C_6H_5	6-MeO	Me	*C*	**20c**+**39c**	30/70	26	66
4	**18d**	C_6H_5	H	Me	*C*	**20d**+**39d**	98/2	83	n.d.
5	**18d**	C_6H_5	H	Me	*B*	**20d**+**39d**	99/1	81	n.d.
6	**18a**	4-$MeOC_6H_4$	4-MeO	Me	*C*[d]	**20a**	100/0	80	–
7[e]	**18b**	3,4-$(MeO)_2C_6H_3$	6-MeO	Me	*C*[d]	**20b**[e]	100/0	24[e]	–
8	**19a**	4-$MeOC_6H_4$	4-MeO	H	*A*	**20a**+**39a**	85/15	18[f]	n.d.
9	**18c**	C_6H_5	6-MeO	Me	*B*	**20c**+**39c**	55/45	47	38
10	**19c**	C_6H_5	H	H	*A*	**20d**+**39d**	95/5	88	n.d.

[a] Methods B and C were used for iodolactonization of **18a–d**. Method C involved treatment of these esters with 3.0 equiv. of iodine in MeCN at rt for 3 h. Method B involved treatment of compounds **18** with 1.0 equiv. of ICl in CH_2Cl_2 at rt for 3.5 h.
[b] Iodolactonization of **19a** and **c** was carried out using Method A,which involved treatment of these carboxylic acids with 3.0 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in MeCN at rt for 1.5 h.
[c] This molar ratio was evaluated by glc analysis of the crude reaction mixtures.
[d] This reaction was performed in MeCN at 52–57°C for 1.5 h.
[e] Purification by MPLC on silica gel of the crude reaction mixture, which was obtained from this reaction, also allowed isolation of 8-methoxy-3-(3,4-dimethoxyphenyl)isocoumarin (**40**) in 4% yield.
[f] This compound had 90% chemical purity.

structurally related to **28**. These byproducts, which had very similar mass spectra, likely corresponded to the two stereoisomers of **29**.



28

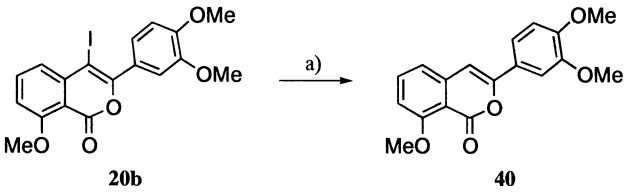


29

Taking into account these results we then thought it right to further test the scope of iodolactonization of methyl esters of acetylenic carboxylic acids and thus we investigated the electrophilic ring closure either of methyl 2-(arylethynyl)-benzoates **18a–d** by Method C or of **18c** and **d** by Method B to the corresponding 3-aryl-4-iodoisocoumarins of general formula **20**. We also compared the results of iodocyclization of **18a** and **d** by Method C with those obtained by iodocyclization of the corresponding carboxylic acids, i.e. **19a** and **c**, respectively, by *Method A*.

The reaction sequence, which was used to prepare compounds **18a–d**, **19a** and **c** is reported in Scheme 4. Thus, according to the general procedure which we previously developed for the synthesis of methyl 2-(1-ynyl)-benzoates from the corresponding methyl 2-hydroxybenzoates,[16] commercially available **31a** and **c** and compound **31b**, which was prepared in 90% yield by treatment of commercially available **30** with 3.0 equiv. of BCl_3 in CH_2Cl_2 at 0°C followed by hydrolysis, were converted in 96, 96 and 94% yield into the corresponding nonaflates, **32a–c**, respectively, by reaction with NaH in DMF at 0°C followed by treatment with perfluoro-1-butanesulfonyl fluoride. Compounds **32a–c** were then reacted with a molar excess of 4-methoxyphenylethynylzinc chloride (**33**), 3,4-dimethoxyphenylethynylzinc chloride (**34**) and phenylethynylzinc chloride (**35**), respectively, in THF at 60°C in the presence of 1 mol% $Pd_2(dba)_3$ and 2 mol% 1,1′-bis(diphenylphosphino)ferrocene (dppf) to give **18a**,**b** and **d** in 87, 86 and 85% yield, respectively. On the other hand, reaction between **32b** and **35** under similar experimental conditions furnished **18c** in 90% yield (Scheme 4).

Compounds **18a** and **d** were then converted into the corresponding carboxylic acids **19a** and **c**, respectively. However, unexpectedly the procedure used to prepare **19c** from **18d**, which consisted of a saponification reaction with KOH in EtOH and water at rt followed by acidification with dilute H_2SO_4 at 0°C, did not allow preparation of pure **19a** from **18a**. On the other hand, pure **19a** was obtained when the reaction mixture, which was derived from saponification of **18a** at rt, was neutralized at 0°C with Amberlite IRC-76. However, when we attempted to prepare **19b** from **18b** using the reaction conditions which we employed to prepare **19a** or **c**, we obtained a complex reaction mixture which did not contain **19b** in a significant amount. It should also be noted that whereas the organozinc derivatives **33** and **35**, which were used to synthesize compounds **18a**, **c** and **d** (Scheme 4), were prepared from commercially available 1-ethynyl-4-methoxybenzene and phenylacetylene, respectively, 1-ethynyl-3,4-dimethoxybenzene (**38**), which we used in the synthesis of **18b** via Pd-catalyzed reaction of **32b** with **34**, was prepared according to the literature[17] by conversion of 3,4-dimethoxybenzaldehyde (**36**) into 1,1-dibromo-2-(3,4-dimethoxyphenyl)ethene (**37**) and treatment



Scheme 5. (a) $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), Et_3N (3.0 equiv.), HCOOH (2.0 equiv.), DMF, 60°C, 5 h, (93%).

of this dibromide with butyllithium followed by hydrolysis. The overall yield was 78%.

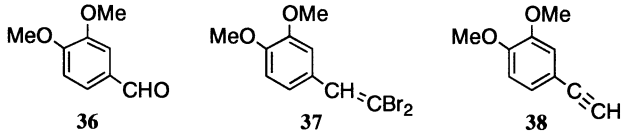
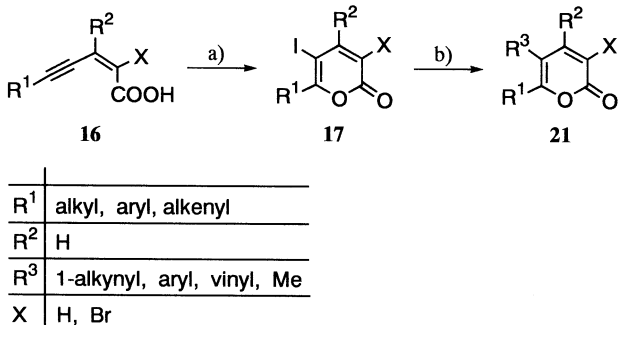


Table 2 summarizes the results of the iodocyclization reaction of esters **18a–d** in MeCN according to Method C and those obtained by iodocyclization either of **18c** and **d** using Method B or of **19a** and **c** using *Method A*.[18]

Several aspects of these results merit comment. Firstly, iodolactonization of **18a**,**b** and **d** by Method C occurred selectively at rt and afforded the desired isomerically pure 3-aryl-4-iodoisocoumarins **20a**,**b** and **d**, respectively in high yields (entries 1, 2 and 4, Table 2). However, iodolactonization of **18c** under similar experimental conditions provided a crude reaction mixture which contained **20c** and the corresponding (*E*)-configured 3-[(1-aryl-1-iodo)methylidene]phthalide **39c** in a ca. 30:70 molar ratio, respectively. Compound **20c** was isolated from this mixture in 26% yield (entry 3, Table 2). Thus, these results indicate that the selectivity and the yields of the iodolactonization reactions of the methyl 2-(arylethynyl)benzoates **18** by Method C are significantly affected by the nature of these compounds. Moreover, the yields of iodocyclization of esters **18** according to Method C proved to be dependent not only on the structure of these compounds but also on the reaction temperature. In fact, when iodocyclization of **18a** and **b** was carried out at 52–57°C for 1.5 h, compounds **20a** and **b** were isolated in yields lower than those obtained for the same reactions performed at rt (Table 2, compare entries 6 and 7 with entries 1 and 2, respectively). It should also be noted that purification by MPLC on silica gel of the crude reaction product, which was derived from iodolactonization of **18b** at 52–57°C according to Method C (entry 7, Table 2), also allowed isolation in 4% yield of an unexpected compound, which had spectral properties in agreement either with those reported in the literature for 3-(3,4-dimethoxyphenyl)-8-methoxyisocoumarin (**40**)[17] or with those found for the same compound, which we synthesized in 93% yield by Pd-catalyzed triethylammonium formate reduction[19] of **20b** (Scheme 5).



Scheme 6. (a) Iodolactonization according to Method A. (b) Stille-type reaction.

Secondly, also Method B proved to be unsuitable for the highly selective synthesis of **20c** from **18c** (entry 9, Table 2). However, it furnished **20c** in a yield (47%) higher than that (26%) which was obtained using Method C (entry 3, Table 2) or the selective synthesis of **20d** from **18d** in high yield (entry 5, Table 2). Finally, it should be noted that the selectivity of iodolactonization of **18a** in MeCN at rt by Method C (entry 1, Table 2) was significantly different from that of iodolactonization of **19a** by Method A (entry 8, Table 2). In fact, whereas the first procedure furnished isomerically pure **20a**, this last reaction provided a mixture of **20a** and **39a** in ca. 85:15 molar ratio, respectively. Purification of this crude mixture by MPLC on silica gel allowed isolation of 90% pure **20a** in 18% yield. On the other hand, iodolactonization of **18d** by Method C was more selective than that of **19c** by Method A (compare entries 4 and 10, Table 2).

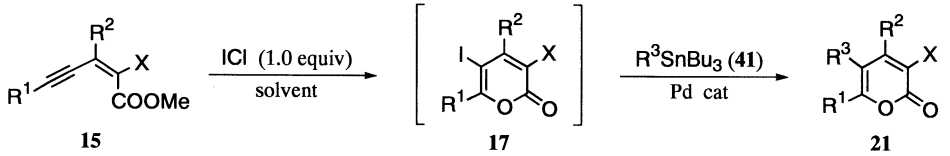
2.2. Synthesis of 2(2*H*)-pyranone derivatives from stereodefined methyl 2-en-4-ynoates by a one-pot sequence of iodolactonization–Stille-type reactions

Recently, we reported that compounds of general formula **21** in which R^2=H are accessible from 2-en-4-ynoic acids **16** via the two-step sequence reported in Scheme 6, which involves a Pd-catalyzed reaction between iodides **17** and organotin derivatives.[6,8,20]

Since we showed that iodocyclization of esters **15** by Method B provides iodides **17** with high selectivity, we wondered if compounds **21** could be more conveniently prepared from **15** by a one-pot sequence of iodolactonization and Stille-type reactions. Thus, in a test experiment we reacted **15c** with 1.0 equiv. of ICl in CH_2Cl_2 at rt and, after completion of the reaction, we treated the reaction mixture with 1.25 equiv. of 1-hexynyltributyltin (**41a**) and 3 mol% $PdCl_2(PPh_3)_2$ at 40°C for 65 h. This one-pot sequence of reactions furnished compound **21a** in 38% yield (entry 1, Table 3).

However, since the step of this sequence which involved the Stille-type reaction required a long reaction time, probably due to the low reaction temperature, we thought it right to perform the synthesis of other compounds of general formula **21** from esters **15** switching to 1,2-dichloroethane as the solvent and performing the Pd-catalyzed cross-coupling step at 60–90°C. Using this modification, which did not cause any variation in the selectivity of the iodolactonization reaction, we synthesized compounds **21b–d** in 52, 43 and 30% yield starting from **15c** and the organotin derivatives **41b–d**, respectively (entries 2, 3 and 4, Table 3). It should be noted that whereas the Stille-type reaction involving **41b** was performed using $PdCl_2(PPh_3)_2$ as the catalyst, the cross-coupling reactions involving **41c** and **d** were carried out in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$. This last catalyst system

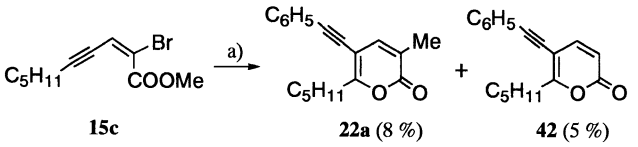
Table 3. One-pot sequence of iodolactonization and Stille-type reactions



Entry	Methyl ester **15**	Solvent	Organotributyltin			Palladium catalyst[a]	Reaction conditions (h/°C)	Products					
			41	R^3	Equiv.			**21**	R^1	R^2	R^3	X	Isolated yield (%)
1	**15c**	CH_2Cl_2	**41a**	C_4H_9–C≡C	1.25	A	65/40	**21a**	C_5H_{11}	H	C_4H_9–C≡C	Br	38
2	**15c**	$ClCH_2CH_2Cl$	**41b**	C_6H_5–C≡C	1.25	A	18/60	**21b**	C_5H_{11}	H	C_6H_5–C≡C	Br	52
3	**15c**	$ClCH_2CH_2Cl$	**41c**	C_6H_5	1.10	B	41/70	**21c**	C_5H_{11}	H	C_6H_5	Br	43
4	**15c**	$ClCH_2CH_2Cl$	**41d**	4-ClC_6H_4	1.10	B	63/70	**21d**	C_5H_{11}	H	4-ClC_6H_4	Br	30
5	**15d**	$ClCH_2CH_2Cl$	**41c**	C_6H_5	1.10	B	144/90	**21e**	C_5H_{11}	C_5H_{11}	C_6H_5	H	38

Compounds **15** were reacted with ICl (1.0 equiv.) in CH_2Cl_2 or $ClCH_2CH_2Cl$ at rt. After completion of the reactions the mixtures were treated with an organotin derivative **41** (1.10–1.25 equiv.) and the Pd catalyst and the resulting mixtures were heated to 40–90°C until one of the reagents was completely consumed or the reaction did not proceed.

[a] Two type of catalysts systems (A and B) were used for these reactions. The reactions involving 1-alkynyltributyltin derivatives were performed in the presence of 5 mol% $PdCl_2(PPh_3)_2$ (catalyst A). On the other hand, those involving aryltributyltin derivatives were performed in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% $AsPh_3$ and 10 mol% CuI (catalyst B).



15c **22a** (8 %) **42** (5 %)

Scheme 7. (a) ICl (1.0 equiv.), 1,2-dichloroethane, rt, 6 h, then C_6H_5–C≡C–$SnBu_3$ (**41b**) (1.25 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), 16 h, 70°C, then Me_4Sn (3.0 equiv.), 90°C, 48 h.

was also used to synthesize **21e** from **15d** and **41c** in 38% yield (entry 5, Table 3). It is also worth mentioning that, in contrast with what was reported on homocoupling of organotin derivatives in 1,2-dichloroethane in the presence of catalytic amounts of $PdCl_2$ and $AsPh_3$ or of $PdCl_2(PhCN)_2$,[21] we did not observe the presence of significant amounts of the homocoupling products derived from **41b**–**d** in the crude reaction mixtures, which were obtained in entries 2–5 of Table 3.

Finally, we also perfomed an exploratory test to establish if 3,5,6-trisubstituted 2(2*H*)-pyranones of general formula **22** might be synthesized by a one-pot procedure involving the selective iodolactonization reaction of methyl (*E*)-2-bromo-2-en-4-ynoates followed by two sequential Stille-type reactions.[22] Thus, 3.0 equiv. of tetramethyltin were added to the crude mixture, which was obtained by reaction of **15c** with 1.0 equiv. of ICl in 1,2-dichloroethane at rt followed by treatment with 1.25 equiv. of **41b** and 5 mol% $PdCl_2(PPh_3)_2$ at 70°C for 16 h. The resulting mixture was then stirred at 90°C for 48 h (Scheme 7). Purification by MPLC on silica gel of the crude reaction mixture, which was obtained after usual workup, allowed isolation of compounds **22a** and **42** in 8 and 5% yield, respectively. Compound **42** derived from the unexpected reduction in the last step of the sequence of bromide **21b**, which was an intermediate of this procedure.

However, the low yield of **22a** prompted us to drop the idea to synthesize other compounds of general formula **22** by an approach similar to that used to prepare **22a**.

3. Conclusions

In this study we have developed two new and convenient procedures for the regiocontrolled synthesis of 5-iodo-2(2*H*)-pyranones of general formula **17**. The first of these (Method C), which involves treatment of stereodefined methyl 2-en-4-ynoates **15** with a molar excess of iodine in MeCN, or preferably in CH_2Cl_2 or C_6H_6 at rt, affords reaction mixtures in which compounds **17** are the major products. Interestingly, the yields of these iodides were satisfactory (46–80%) and comparable with those obtained by iodolactonization of carboxylic acids **16** with molar excesses of iodine and $NaHCO_3$ in MeCN at rt (Method A).[6,8] The second procedure (Method B) involves reaction of esters **15** with ICl in CH_2Cl_2 at rt and provides iodides **17** with very high selectivity.

We have also found that Method C is suitable for the highly selective synthesis of three 3-aryl-4-iodoisocoumarins, i.e. compounds **20a**,**b** and **d**, from the corresponding methyl 2-(arylethynyl)benzoates, i.e. **18a**,**b** and **d**, respectively, but that it gives an unsatisfactory result when used for the synthesis of **20c** from **18c**. However, **20c** has been prepared in a satisfactory yield by treatment of **18c** according to Method B.

Finally, we have shown that the high selectivity of the iodolactonization reaction of methyl esters **15** by Method B allows preparation, although in modest to moderate yields, of 2(2*H*)-pyranone derivatives of general formula **21** by a one-pot sequence of iodolactonization and Stille-type reactions.

4. Experimental

4.1. General

Melting points and boiling points are uncorrected. Precoated aluminium silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani Data Station DDS 1000. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040 mm) were performed on a Büchi B-680 system using a Knauer K-2400 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas-chromatograph. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or on a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. The structure of compound **39c** was assigned on the basis of its ^1H NMR and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of NMR techniques which included ^1H–^1H COSY, NOESY (mixing time: 400 ms), heteronuclear multiple quantum Coherence (HMQC) and heteronuclear multiple bond correlation (HMBC). All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of nitrogen or argon using standard syringe, cannula and septa techniques. Solvents were dried and distilled before use. The following compounds were prepared by published procedures: $Pd(PPh_3)_4$,[23] $PdCl_2(PhCN)_2$,[24] $PdCl_2(PPh_3)_2$,[25] methyl (*E*)-2,3-dibromopropenoate (**23**)[12], methyl (*Z*)-2-decen-4-ynoate (**15a**),[6] (*Z*)-2-decen-4-ynoic acid (**16a**),[6] methyl (2*E*,6*Z*)-2-bromo-6-methyl-2,6-octadien-4-ynoate (**15b**),[8] (2*E*,6*Z*)-2-bromo-6-methyl-2,6-octadien-4-ynoic acid (**16b**),[8] methyl (*Z*)-3-iodo-2-octenoate (**25**),[13] 1-hexynyltributyltin (**41a**),[26] 4-chlorophenyltributyltin (**41d**),[27] 1,1-dibromo-2-(3,4-dimethoxyphenyl)ethene (**37**)[28] and 1-ethynyl-3,4-dimethoxybenzene (**38**).[28] (4-Methoxyphenyl)ethynylzinc chloride (**33**), (3,4-dimethoxyphenyl)ethynylzinc chloride (**34**) and phenylethynylzinc chloride (**35**) were synthesized by conversion of the corresponding 1-alkynes into 1-alkynylmagnesium bromides followed by transmetalation with dry $ZnCl_2$.

4.1.1. Methyl (*E*)-2-bromo-2-decen-4-ynoate (15c). A THF solution of 1-heptynylmagnesium bromide (1.07 M, 100 ml, 0.107 mol) was added dropwise to a slurry of dry $ZnCl_2$ (17.4 g, 0.128 mol) in THF (100 ml), which was stirred under argon at 0°C. After stirring for an additional

15 min at 0°C a solution of **23** (20.0 g, 0.082 mol) in THF (50 ml) and $Pd(PPh_3)_4$ (4.74 g, 4.10 mmol) were sequentially added and the resulting mixture was stirred at 0°C for 5 h. It was then poured into a saturated aqueous NH_4Cl solution (300 ml) and extracted with Et_2O (4×100 ml). The organic extract was washed with brine (100 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with a mixture of petroleum ether and toluene (40:60) (300 ml) and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using a mixture of petroleum ether and toluene (60:40) as eluant, to give **15c** (16.6 g, 78% yield) as a pale yellow liquid. MS, *m/z* (%): 260 (5), 258 (5), 188 (26), 186 (26), 62 (87), 61 (40), 50 (100). IR (film): ν 2213, 1727, 1338, 1222, 1031, 1008, 762 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.65 (1H, t, J=2.5 Hz), 3.84 (3H, s), 2.39 (2H, dt, J=6.5 and 2.5 Hz), 1.64–1.24 (6H, m), 0.90 ppm (3H, t, J=7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.0, 124.7, 121.3, 104.0, 77.5, 52.9, 30.9, 27.9, 22.1, 20.0, 13.9 ppm. Anal. Calcd for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 51.05; H, 5.92.

4.1.2. Methyl (*Z*)-3-pentyl-2-decen-4-ynoate (15d). 1-Heptyne (**26**) (4.40 ml, 33.5 mmol) was added to a stirred mixture of **25** (7.88 g, 27.9 mmol), $Pd(PPh_3)_4$ (0.97 g, 0.84 mmol), CuI (0.48 g, 2.52 mmol), Et_3N (11.7 ml, 83.9 mmol) and benzene (30 ml) and the resulting mixture was maintained for 19 h at rt. It was then poured into a saturated aqueous NH_4Cl solution (100 ml) and the resulting mixture was stirred open to the atmosphere until the aqueous phase became deep blue. The mixture was then extracted with Et_2O (4×60 ml) and the organic extract was washed with water (50 ml), 5% H_2SO_4 (20 ml) and water (30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with toluene (30 ml) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using toluene as eluant, to give **15d** (6.57 g, 94% yield) as a pale yellow liquid. MS, *m/z* (%): 250 (1), 206 (25), 179 (62), 150 (22), 90 (34), 58 (35), 54 (100). IR (film): ν 2220, 1730, 1708, 1615, 1217, 1153, 859 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.90 (1H, br s), 3.71 (3H, s), 2.46 (2H, t, J=7.0 Hz), 2.45 (2H, dt, J=7.5 and 1.0 Hz), 1.68–1.25 (12H, m), 0.91 (3H, t, J=7.0 Hz), 0.89 ppm (3H, t, J=6.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.7, 141.0, 122.0, 103.6, 78.9, 51.1, 39.4, 31.1, 31.0, 28.2, 27.7, 22.4, 22.2, 20.0, 14.0 ppm (2C). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.46. Found: C, 76.79; H, 10.71.

4.2. General procedures for iodolactonization of esters *15*. Synthesis of 5-iodo-2(2*H*)-pyranones 17 and the corresponding 5-[(*E*)-1-iodoylidene]- and 5-[(*Z*)-1-iodoylidene]-2(5*H*)-furanones, (*E*)- and (*Z*)-27, respectively

Iodolactonization of esters **15** was perfomed according to two different procedures (Methods B and C).

Method B: To a deaerated solution of an ester **15** (2.89 mmol) in dry CH_2Cl_2 (15 ml) was added a solution of ICl (474 mg, 2.92 mmol) in dry CH_2Cl_2 (15 ml) and the mixture was stirred in the dark under nitrogen for 5 h at rt. It was then poured into a cold 10% aqueous $NaHCO_3$ solution (35 ml) and extracted with CH_2Cl_2 (3×20 ml). The organic extract was washed with a 10% aqueous $Na_2S_2O_3$ solution (15 ml) and water (15 ml), dried over Na_2SO_4, analyzed by GLC and GLC/MS and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was used for iodolactonization of **15a–d**. As shown in Table 1, where the products of these reactions and the yields of 5-iodo-2(2*H*)-pyranones **17** are reported, whereas iodolactonization of **15a**,**b** and **d** furnished compounds **17a**,**b** and **d** free from the corresponding isomers of general formula (*E*)- and (*Z*)-**27** (entries 4, 9 and 19, Table 1), iodolactonization of **15c** according to this procedure provided a mixture of **17c**, (*E*)- and (*Z*)-**27c** in a 94:4:2 molar ratio, respectively (entry 15, Table 1).

Method C: This procedure was used for iodolactonization of **15a–d**. In particular, to a deaerated solution of an ester **15** (21.2 mmol) in MeCN, CH_2Cl_2 or C_6H_6 (175 ml) was added iodine (16.16 g, 63.7 mmol) and the resulting mixture was stirred in the dark under nitrogen at rt for 1 h, at which time the reaction was complete as shown by TLC and GLC analyses. The reaction mixture was then diluted with AcOEt (200 ml) and washed with 10% aqueous $Na_2S_2O_3$ solution (50 ml) and water (50 ml). The organic phase was dried over Na_2SO_4, analyzed by GLC and GLC/MS and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. Compound **17a** and the corresponding 5-[(*E*)-1-iodoylidene]-2(5*H*)-furanone, (*E*)-**27a**, were isolated from the crude reaction mixture derived from iodolactonization of **15a** by this procedure in CH_2Cl_2 as solvent (entry 2, Table 1). On the other hand, purification by MPLC on silica gel of the crude reaction mixture which derived from iodolactonization of **15c** in C_6H_6 or MeCN according to this method (entries 14 and 12, Table 1) allowed isolation of **17c**. It should also be noted that purification by MPLC of the crude reaction mixture, which derived from iodolactonization of **15c** in MeCN (entry 12, Table 1), also allowed isolation of compounds (*E*)- and (*Z*)-**27c**. Finally, iodides **17b** and **d** were isolated by purification of the crude reaction mixture, which derived from iodolactonization of **15b** and **d**, respectively, in CH_2Cl_2 according to this method (entries 7 and 17, respectively, Table 1).

4.2.1. 5-Iodo-6-pentyl-2(2*H*)-pyranone (17a) and 5-[(*E*)-1-iodohexylidene]-2(5*H*)-furanone [(*E*)-27a]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **15a** in CH_2Cl_2 according to Method C (entry 2, Table 1), showed the presence of three compounds in a 86:6:8 molar ratio. This mixture was purified by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed isolation of (*E*)-**27a** as a red liquid in 5% yield. MS, *m/z* (%): 292 (4), 147 (10), 109 (100), 97 (6), 81 (28), 55 (10). IR (film): ν 1779, 1751, 1632, 1553, 1379, 1196, 728 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (1H, d, J=5.5 Hz), 6.28 (1H, d, J=5.5 Hz), 2.81 (2H, t, J=7.5 Hz), 1.61–1.54 (2H, m), 1.35–1.27 (4H, m), 0.90 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.5, 149.5, 144.9, 122.3, 95.7, 37.9, 30.5, 28.8, 22.3, 13.9 ppm. The spectral properties of this compound were in agreement with those previously reported.[6] Concentration of the intermediate chromatographic fractions allowed to obtain in ca. 6%

yield a compound, which presumably corresponded to (*Z*)-**27a**, but which was not fully characterized owing to its low isomeric purity. This compound had the following MS spectrum. MS, *m/z* (%): 292 (26), 180 (10), 109 (100), 81 (18), 55 (69). Finally, concentration of the last eluted chromatographic fractions allowed isolation of compound **17a** as a yellow liquid in 80% yield. MS, *m/z* (%): 292 (18), 221 (36), 165 (60), 119 (24), 109 (30), 95 (56), 81 (100). IR (film): ν 1735, 1600, 1541, 1189, 1062, 1011, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (1H, d, J=10.0 Hz), 5.99 (1H, d, J=10.0 Hz), 2.71 (2H, t, J=7.5 Hz), 1.72–1.65 (2H, m), 1.38–1.31 (4H, m), 0.91 ppm (3H, t, J=5.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.6, 161.2, 151.7, 114.5, 67.6, 36.5, 31.0, 26.6, 22.2, 13.8 ppm. The spectral properties of this compound were in agreement with those previously reported.[6] It should be noted that iodolactonization of **15a** according to Method B furnished a crude reaction mixture in which **17a** was found to be free from (*Z*)- and (*E*)-**27a** (entry 4, Table 1). Purification of this crude mixture by MPLC on silica gel,using toluene as eluant, furnished pure **17a** in 72% yield.

4.2.2. 3-Bromo-6-[(*Z*)-2-butenyl]-5-iodo-2(2*H*)-pyranone (17b). A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **15b** in CH_2Cl_2 according to Method C (entry 7, Table 1), showed the presence of two compounds in a 99:1 molar ratio. The major product was subsequently identified as **17b**. On the other hand the structure of 5-[(5*E*,7*Z*)-1-iodo-2-methylbutylidene]-2(5*H*)-furanone [(*E*)-**27b**] was tentatively assigned to the minor product. The mixture was purified by MPLC on silica gel using toluene as eluant. Concentration of the last eluted chromatographic fractions allowed isolation of **17b** in 64% yield as a colourless solid. Mp 102–104°C. MS, *m/z* (%): 356 (97), 354 (100), 201 (20), 199 (21), 173 (33), 171 (34), 91 (74). IR (KBr): ν 1718, 1594, 1530, 1196, 1009, 950, 909 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.88 (1H, s), 5.70 (1H, qq, J=7.0 and 1.5 Hz), 1.93 (3H, pseudo-quint, J=1.5 Hz), 1.64 ppm (3H, dq, J=7.0 and 1.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.4, 158.0, 151.8, 130.5, 129.7, 110.6, 67.3, 20.8, 15.7 ppm. The spectral properties of this compound were in agreement with those previously reported.[8] The MS spectrum of (*E*)-**27b** was as follows. MS, *m/z* (%): 356 (100), 354 (100), 201 (26), 199 (29), 173 (53), 171 (49), 92 (84). It should be noted that whereas iodolactonization of carboxylic acid **16b** furnished a mixture of **17b** and (*E*)-**27b** in a ca. 97:3 molar ratio, respectively (entry 10, Table 1), iodolactonization of **15b** according to Method B (entry 9, Table 1) provided **17b** free from isomers. Purification by MPLC on silica gel of the crude products of these reactions allowed isolation of **17b** in 75 and 62% yield, respectively.

4.2.3. 3-Bromo-5-iodo-6-pentyl-2(2*H*)-pyranone (17c) and 3-bromo-5-[(*E*)-1-iodohexylidene]- and 3-bromo-5-[(*Z*)-1-iodohexylidene]-2(5*H*)-furanone, [(*E*)]- and [(*Z*)]-27c, respectively. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **15c** in MeCN according to Method C (entry 12, Table 1), showed the presence of three compounds in a 58:20:22 molar ratio, which were subsequently identified as **17c**, (*E*)-**27c** and (*Z*)-**27c**, respectively. This mixture was purified by MPLC on silica gel using a mixture of petroleum ether and benzene (60:40) as eluant. Concentration of the first eluted chromatographic fractions allowed isolation of (*E*)-**27c** in 17% yield as an orange liquid. MS, *m/z* (%): 372 (12), 370 (12), 187 (100), 161 (8), 153 (8), 81 (10), 53 (11). IR (film): ν 1783, 1733, 1285, 1216, 1115, 976, 749 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (1H, s), 2.77 (2H, t, J=7.0 Hz), 1.57 (2H, pseudo-quint, J=7.0 Hz), 1.39–1.25 (4H, m), 0.89 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.0, 148.0, 142.7, 115.5, 96.4, 37.6, 30.4, 28.7, 22.2, 13.9 ppm. Anal. Calcd for $C_{10}H_{12}BrIO_2$: C, 32.37; H, 3.26. Found: C, 32.45; H, 3.44. Concentration of the intermediate chromatographic fractions allowed isolation of (*Z*)-**27c** in 19% yield as an orange liquid. MS, *m/z* (%): 372 (21), 370 (21), 189 (96), 187 (100), 153 (9), 81 (9), 53 (11). IR (film): ν 1781, 1629, 1553, 1248, 1126, 973, 749 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (1H, s), 2.68 (2H, t, J=7.5 Hz), 1.61 (2H, pseudo-quint, J=7.5 Hz), 1.39–1.20 (4H, m), 0.90 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.3, 149.8, 135.4, 114.1, 95.2, 38.0, 30.4, 29.5, 22.3, 13.9 ppm. Anal. Calcd for $C_{10}H_{12}BrIO_2$: C, 32.37; H, 3.26. Found: C, 32.40; H, 3.22. On the other hand, concentration of the last eluted chromatographic fractions allowed isolation of compound **17c** as a pale yellow liquid in 46% yield. MS, *m/z* (%): 372 (97), 370 (100), 287 (42), 285 (43), 189 (41), 187 (35), 117 (20). IR (film): ν 1735, 1598, 1528, 1465, 1263, 1015, 746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.82 (1H, s), 2.70 (2H, t, J=8.0 Hz), 1.72–1.61 (2H, m), 1.39–1.25 (4H, m), 0.91 ppm (3H, t, J=7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.0, 157.9, 151.8, 109.2, 66.4, 36.1, 31.0, 26.6, 22.2, 13.8 ppm. Anal. Calcd for $C_{10}H_{12}BrIO_2$: C, 32.37; H, 3.26. Found: C, 32.31; H, 3.44. It should be noted that iodolactonization of **15c** according to Method B (entry 15, Table 1) furnished a mixture of **17c**, (*E*)-**27c** and (*Z*)-**27c** in a 94:4:2 molar ratio, respectively. This mixture also contained ca. 11 and 5% of two compounds, which presumably corresponded to the two stereoisomers of 3-bromo-5-(1-chlorohexylidene)-2(5*H*)-furanone (**28**). The MS spectrum of the major stereoisomer of this compound was as follows. MS, *m/z* (%): 280 (16), 278 (12), 224 (40), 222 (28), 202 (37), 200 (35), 53 (100). The MS spectrum of the minor stereoisomer was as follows. MS, *m/z* (%): 280 (26), 278 (20), 224 (56), 222 (42), 202 (58), 200 (47), 53 (100). Purification of this crude mixture by MPLC on silica gel allowed isolation of pure **17c** in 51% yield. The spectral properties of this compound were in agreement with those of **17c** prepared from **15c** by *Method C*.

4.2.4. 4,6-Dipentyl-5-iodo-2(2*H*)-pyranone (17d) and 5-[(*E*)-1-iodohexylidene]-4-pentyl- and 5-[(*Z*)-1-iodohexylidene]-4-pentyl-2(5*H*)-furanone, [(*E*)-27d] and [(*Z*)-27d], respectively. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **15d** in CH_2Cl_2 according to Method C (entry 17, Table 1), showed the presence of three compounds in a 87:10:3 molar ratio, which were subsequently identified as **17d**, (*E*)- and (*Z*)-**27d**, respectively. This mixture was purified by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed isolation of (*E*)-**27d** as an orange liquid in 9% yield. MS, *m/z* (%): 362 (36), 179 (100), 123 (28), 121 (12), 109 (15), 55 (98), 53 (77). IR (film): ν 1772, 1589, 1465, 1170, 996, 937, 730 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.10 (1H, t,

J=1.5 Hz), 2.92 (2H, t, J=7.5 Hz), 2.79 (2H, dt, J=7.5 and 1.5 Hz), 1.64–1.25 (12H, m), 0.92 (3H, t, J=6.5 Hz), 0.89 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.1, 159.5, 148.2, 118.5, 91.2, 41.2, 31.3, 30.7, 30.5, 28.6, 27.8, 22.3 (2C), 13.9 ppm (2C). Anal. Calcd for $C_{15}H_{23}IO_2$: C, 49.73; H, 6.39. Found: C, 49.80; H, 6.51. Concentration of the intermediate chromatographic fractions allowed isolation of (*Z*)-**27d** (85% pure) in 2% yield as an orange liquid. MS, *m/z* (%): 362 (26), 235 (23), 179 (100), 123 (28), 78 (12), 55 (53), 53 (76), 51 (21). IR (film): ν 1768, 1591, 1465, 1169, 1118, 1097, 912 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.09 (1H, br s), 2.82 (2H, t, J=7.5 Hz), 2.59 (2H, t, J=7.5 Hz), 1.75–1.15 (12H, m), 0.95–0.89 ppm (6H, m). On the other hand, concentration of the last eluted chromatographic fractions allowed isolation of **17d** in 76% yield as a pale yellow solid. Mp 35°C. MS, *m/z* (%): 362 (27), 306 (48), 278 (53), 94 (26), 78 (28), 64 (32), 54 (100). IR (KBr): ν 1713, 1597, 1530, 1465, 1016, 859, 732 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.03 (1H, s), 2.80 (2H, t, J=7.5 Hz), 2.48 (2H, t, J=7.5 Hz), 1.73–1.31 (12H, m), 0.92 (3H, t, J=6.6 Hz), 0.91 ppm (3H, t, J=7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.8, 161.7, 160.9, 110.1, 77.3, 40.3, 37.4, 31.2 (2C), 27.9, 26.7, 22.3 (2C), 13.9 ppm (2C). Anal. Calcd for $C_{15}H_{23}IO_2$: C, 49.73; H, 6.39. Found: C, 49.83; H, 6.47. It should be noted that iodolactonization of **15d** according to Method B (entry 19, Table 1) furnished a crude reaction mixture in which **17d** was free from isomers but was contaminated by ca. 6 and 1% of two compounds which had similar mass spectra and likely corresponded to the two stereoisomers of 5-(1-chlorohexylidene)-4-pentyl-2(5*H*)-furanone (**29**). The major isomer of this compound had the following MS spectrum. MS, *m/z* (%): 270 (19), 235 (100), 214 (22), 179 (38), 157 (24), 123 (29), 55 (50). The minor isomer had the following MS spectrum. MS, *m/z* (%): 270 (11), 235 (100), 214 (11), 179 (24), 157 (15), 123 (13). Purification by MPLC on silica gel of this crude reaction mixture allowed isolation of **17d** in 63% yield.

4.2.5. Methyl 6-methoxysalicylate (31b). A CH_2Cl_2 solution of BCl_3 (1.0 M, 168 ml, 168 mmol) was added dropwise to a solution of methyl 2,6-dimethoxybenzoate (**30**) (11.0 g, 56.1 mmol) in CH_2Cl_2 (330 ml) which was maintained under stirring at 0°C. After stirring for additional 21.5 h at 0°C the reaction mixture was poured into ice water (200 ml) and extracted with CH_2Cl_2 (3×300 ml). The organic extract was washed with 2N HCl (150 ml) and brine (150 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by MPLC on silica gel, using benzene as eluant, to give **31b** (9.17 g, 90% yield) as a colourless solid. Mp 50–52°C (lit.[29] mp 43–45°C). MS, *m/z* (%): 182 (39), 151 (29), 150 (100), 122 (43), 107 (27), 79 (14), 51 (8). IR (KBr): ν 1656, 1610, 1583, 1457, 1232, 1087, 811 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.49 (1H, s), 7.33 (1H, t, J=8.5 Hz), 6.60 (1H, d, J=8.5 Hz), 6.42 (1H, d, J=8.5 Hz), 3.96 (3H, s), 3.86 ppm (3H, s). The spectral properties of this compound were in agreement with those previously reported.[29]

4.3. General procedure for the synthesis of methyl 2-(perfluoro-1-butanesulfonyloxy)benzoates (32)

A 60% dispersion of NaH in mineral oil (1.92 g, 48.0 mmol), which was maintained under an atmosphere of nitrogen, was washed with pentane (3×30 ml). Dry DMF (64 ml was added to the residue and the mixture was stirred at 0°C. A solution of methyl 2-hydroxybenzoate **31** (32.0 mmol) in dry DMF (19 ml) was then added dropwise and the mixture was stirred at 0°C for 40 min and at rt for 1 h. Perfluoro-1-butanesulfonyl fluoride (6.61 ml, 36.8 mmol) was added and the resulting mixture was stirred at rt for 2 h. It was then poured into a saturated aqueous NH_4Cl solution (300 ml) and extracted with Et_2O (4×200 ml). The organic extract was washed with water (4×50 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give crude compounds **32** in 94–96% yield.

4.3.1. Methyl 4-methoxy-2-(perfluoro-1-butanesulfonyloxy)benzoate (32a). This crude compound was obtained in 96% yield as a pale yellow solid starting from **31a** according to the above-mentioned procedure. Compound **32a** had the following properties. MS, *m/z* (%): 464 (65), 433 (45), 369 (46), 153 (100), 125 (43), 107 (31), 69 (48). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (1H, d, J=9.0 Hz), 6.95 (1H, dd, J=9.0 and 2.5 Hz), 6.79 (1H, d, J=2.5 Hz), 3.93 (3H, s), 3.88 ppm (3H, s). This compound was used in the next step without any further purification and characterization.

4.3.2. Methyl 6-methoxy-2-(perfluoro-1-butanesulfonyloxy)benzoate (32b). This crude compound was prepared in 96% yield starting from **31b** according to the same procedure employed for the synthesis of **32a**. Compound **32b** had the following properties. MS, *m/z* (%): 464 (24), 433 (58), 153 (86), 151 (24), 150 (100), 149 (73), 107 (75). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (1H, t, J=8.5 Hz), 6.97 (1H, d, J=8.5 Hz), 6.95 (1H, d, J=8.5 Hz), 3.94 (3H, s), 3.89 ppm (3H, s). This compound was used in the next step without any further purification and characterization.

4.3.3. Methyl 2-(perfluoro-1-butanesulfonyloxy)-benzoate (32c). This crude product, which was prepared in 94% yield starting from methyl 2-hydroxybenzoate (**31c**) according to the above-mentioned procedure, had the following properties. Mp 42–45°C. Ms, *m/z* (%): 434 (6), 339 (33), 151 (16), 135 (33), 123 (65), 95 (90), 69 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (1H, dd, J=7.5 and 1.5 Hz), 7.64 (1H, dt, J=8.0 and 1.0 Hz), 7.48 (1H, pseudo-t, J=7.0 Hz), 7.30 (1H, t, J=8.0 Hz), 3.97 ppm (3H, s). The spectral properties of this compound were in agreement with those previously reported.[16] This crude product was used in the next step without any further purification and characterization.

4.4. General procedure for the Pd-catalyzed cross-coupling reactions between 2-arylethynylzinc chlorides and aryl nonaflates 32

A slurry of a 2-arylethynylzinc chloride in THF was prepared by addition of a THF solution of the corresponding Grignard reagent (0.504 M, 73 ml, 36.8 mmol) to a slurry of dry $ZnCl_2$ (6.52 g, 47.8 mmol) in THF (50 ml), which was stirred at 0°C. After stirring for additional 20 min, a solution of $Pd_2(dba)_3$ (0.28 g, 0.31 mmol), dppf (0.34 g, 0.61 mmol) and aryl nonaflate **32** (30.7 mmol) in THF (125 ml) was added. The resulting mixture was allowed to warm up to

rt and then heated to 60°C until completion of the reaction (2–21 h). After usual workup the crude reaction product was diluted with the solvent (100 ml) which was subsequently used for its purification by MPLC on silica gel and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel. Compounds **18a**,–**d** were prepared according to this procedure.

4.4.1. Methyl 4-methoxy-2-(4-methoxphenyl)ethynylbenzoate (18a). The crude reaction product, which was obtained from the Pd-catalyzed reaction between (4-methoxyphenyl)ethynylzinc chloride (**33**) and **32a** according to the above-mentioned procedure, was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (50:50) as eluant, to give in 87% yield **18a** as a pale yellow solid. Mp 84–87°C. MS, *m/z* (%): 297 (14), 296 (70), 281 (100), 265 (17), 253 (26), 225 (13), 151 (10). IR (KBr): ν 2211, 1719, 1597, 1510, 1258, 1120, 839 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (1H, d, J=9.0 Hz), 7.53 (2H, d, J=9.0 Hz), 7.10 (1H, d, J=2.5 Hz), 6.96–6.80 (3H, m), 3.93 (3H, s), 3.87 (3H, s), 3.83 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.2, 161.9, 159.8, 133.2 (2C), 132.5, 126.0, 123.7, 118.0, 115.3, 114.0, 113.9 (2C), 94.4, 87.2, 55.5, 55.3, 51.9 ppm. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.04; H, 5.61. GLC analysis showed that **18a** had chemical purity higher than 97%.

4.4.2. Methyl 2-(3,4-dimethoxyphenyl)ethynyl-6-methoxybenzoate (18b). The crude reaction product, which was obtained from the Pd-catalyzed reaction between (3,4-dimethoxyphenyl)ethynylzinc chloride (**34**) and **32b** according to the above mentioned procedure, was purified by MPLC on silica gel, using a mixture of CH_2Cl_2, hexane and Et_2O (70:27:3) as eluant, to give compound **18b** in 86% yield as a pale yellow solid. Mp 92–94°C. MS, *m/z* (%): 327 (21), 326 (100), 312 (15), 311 (74), 296 (12), 295 (23), 253 (14). IR (KBr): ν 2209, 1728, 1513, 1275, 1250, 1066, 802 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.32 (1H, t, J=8.5 Hz), 7.13 (1H, d, J=7.5 Hz), 7.09 (1H, dd, J=7.5 and 1.5 Hz), 6.98 (1H, d, J=1.5 Hz), 6.89 (1H, d, J=8.5 Hz), 6.82 (1H, d, J=8.5 Hz), 3.96 (3H, s), 3.89 (6H, s), 3.85 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.4, 156.1, 149.6, 148.5, 130.4, 125.7, 125.0, 124.0, 122.4, 114.9, 114.1, 111.0 (2C), 93.0, 84.9, 56.0, 55.9 (2C), 52.4 ppm. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.75; H, 5.46. GLC analysis showed that compound **18b** had chemical purity higher than 99%.

4.4.3. Methyl 6-methoxy-2-phenylethynylbenzoate (18c). The crude reaction product, which was obtained from the Pd-catalyzed reaction between phenylethynylzinc chloride (**35**) and **32b** according to the above mentioned procedure, was purified by MPLC on silica gel, using a mixture of hexane and benzene (10:90) as eluant, to give **18c** in 90% yield as a pale yellow solid. Mp 47–48°C. MS, *m/z* (%): 266 (81), 251 (100), 235 (78), 233 (41), 191 (48), 162 (50), 87 (67). IR (KBr): ν 2214, 1728, 1573, 1262, 1068, 796, 759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.60–7.43 (2H, m), 7.45–7.13 (4H, m), 7.18 (1H, d, J=8.5 Hz), 6.93 (1H, d, J=8.5 Hz), 3.99 (3H, s), 3.87 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.3, 156.1, 131.6 (2C), 130.4, 128.6, 128.3 (2C), 125.9, 124.1, 122.7, 122.1, 111.2, 92.8, 86.2, 56.0, 52.5 ppm. The spectral properties of this compound were in agreement with those previously reported.[29]

4.4.4. Methyl 2-(phenylethynyl)benzoate (18d). The crude reaction product, which was obtained from the Pd-catalyzed reaction between **35** and **32c** according to the above mentioned procedure, was purified by MPLC on silica gel, using a mixture of toluene and hexane (80:20) as eluant, to give **18d** in 85% yield as a pale yellow liquid. MS, *m/z* (%): 236 (100), 221 (76), 205 (24), 176 (46), 165 (41), 88 (18), 75 (6). IR (film): ν 2218, 1730, 1598, 1294, 1129, 1080, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.94 (1H, dd, J=7.5 and 1.5 Hz), 7.64–7.53 (3H, m), 7.42 (1H, dt, J=7.5 and 1.6 Hz), 7.36–7.26 (4H, m), 3.92 ppm (3H, s). The spectral properties of this compound were in agreement with those previously reported.[1f]

4.4.5. 4-Methoxy-2-(4-methoxyphenyl)ethynylbenzoic acid (19a). Compound **18a** (3.50 g, 11.8 mmol) was added to a solution of KOH (7.16 g, 127 mmol) in water (26 ml) and 96% EtOH (96 ml) and the resulting mixture was stirred at rt for 18 h. It was then cooled to 0°C and neutralized with Amberlite IRC-76. The resin was then removed by filtration. Evaporation of the solvent from the filtrate at rt under reduced pressure furnished **19a** (3.29 g, 99% yield) as a colourless solid. Mp 86–89°C. IR (KBr): ν 2198, 1603, 1510, 1379, 1248, 1090, 831 cm^{-1}. ^1H NMR (200 MHz, DMSO-d^6): δ 7.80 (1H, d, J=9.0 Hz), 7.48 (2H, d, J=8.5 Hz), 7.01 (1H, d, J=2.5 Hz), 7.02–6.86 (3H, m), 3.81 (3H, s), 3.77 ppm (3H, s). This compound was used in the next step without any further purification and characterization.

4.4.6. 2-(Phenylethynyl)benzoic acid (19c). Compound **18d** (1.00 g, 4.23 mmol) was added to a solution of KOH (2.57 g, 45.8 mmol) in water (9.40 ml) and 96% EtOH (34.4 ml) and the resulting mixture was stirred at rt for 18 h. It was then concentrated at rt under reduced pressure and the residue was diluted with water (90 ml) and extracted with Et_2O (2×30 ml). The aqueous phase was then cooled to 0°C, acidified with cold 5% H_2SO_4 and extracted with Et_2O (4×40 ml). The organic extract was dried over Na_2SO_4 and concentrated under reduced presure to give **18d** (0.877 g, 93% yield) as a colourless solid. Mp 126–128°C (lit.[1f] mp 127–128°C). IR (KBr): ν 2211, 1689, 1493, 1299, 1261, 755, 686 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 10.59 (1H, br s), 8.15 (1H, dd, J=8.0 and 1.5 Hz), 7.71–7.25 ppm (8H, m). This compound was used in the next step without any further purification and characterization.

4.5. General procedure for iodolactonization of methyl 2-[(aryl)ethynyl]benzoates 18 and 2-[(aryl)ethynyl]-benzoic acids 19. Synthesis of 3-aryl-4-iodoisocoumarins 20 and (*E*)-3-[(1-aryl-1-iodo)methylidene]phthalides 39

Two methods were used for iodolactonization of methyl esters **18** (Methods B and C). Method B was used for iodolactonization of **18c** and **d** (entries 5 and 9, Table 2). In particular, to a deaerated solution of **18c** or **d** (3.01 mmol) in CH_2Cl_2 (27 ml) was added a solution of ICl in CH_2Cl_2 (1.00 M, 3.01 ml, 3.01 mmol) and the resulting mixture was

stirred under nitrogen at rt in the dark for 3.5 h. It was then poured into a 10% aqueous $Na_2S_2O_3$ solution (50 ml) and extracted with $CHCl_3$ (5×40 ml). The organic extract was washed with water (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue, which was analyzed by GLC, was purified by MPLC on silica gel.

Method C was used for iodolactonization of **18a–d** in MeCN at rt (entries 1–4, Table 2). In particular, to a solution of an ester **18** (8.77 mmol) in MeCN (48 ml) was added iodine (6.68 g, 26.3 mmol) and the mixture was stirred at rt under nitrogen in the dark for 3 h. After usual workup the crude reaction product was purified by MPLC on silica gel. It should be noted that Method C was also used for iodolactonization of **18a** and **b** in MeCN at 52–57°C for 1.5 h (entries 6 and 7, Table 2).

On the other hand, Method A was employed for iodolactonization of **19a** and **c** (entries 8 and 10, Table 2). In particular, to a suspension of $NaHCO_3$ (3.31 g, 39.4 mmol) in MeCN (20 ml) were added sequentially a solution of **19a** or **c** (13.1 mmol) in MeCN (68 ml) and iodine (10.0 g, 39.4 mmol) and the mixture was stirred vigorously under nitrogen in the dark at rt for 1.5 h at which time the reaction was complete as shown by TLC analysis. The reaction mixture was then poured into a 10% aqueous $Na_2S_2O_3$ solution (70 ml) and extracted with AcOEt (5×100 ml). The organic extract was washed with water (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue, which was analyzed by GLC, was purified by MPLC on silica gel.

4.5.1. 4-Iodo-6-methoxy-3-(4-methoxyphenyl)iso-coumarin (20a). The crude reaction product, which was obtained by iodolactonization of **18a** according to Method C (entry 1, Table 2), was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and petroleum ether (70:30) as eluant, to give **20a** in 98% yield as a colourless solid. Mp 187–188°C. MS, *m/z* (%): 408 (94), 380 (54), 253 (100), 225 (36), 210 (26), 135 (26), 77 (21). IR (KBr): ν 1729, 1610, 1483, 1305, 1076, 1028, 829 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.22 (1H, d, J=8.5 Hz), 7.66 (2H, d, J=9.0 Hz), 7.29 (1H, d, J=2.5 Hz), 7.06 (1H, dd, J=8.5 and 2.5 Hz), 6.97 (2H, d, J=9.0 Hz), 3.98 (3H, s), 3.88 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.4, 161.3, 160.7, 155.3, 140.7, 132.1, 131.5 (2C), 127.6, 116.6, 114.6, 113.2 (2C), 113.1, 75.9, 55.8, 55.3 ppm. Anal. Calcd for $C_{17}H_{13}IO_4$: C, 50.02; H, 3.21. Found: C, 49.85; H, 3.25. It should be noted that iodolactonization of **18a** at 52–57°C according to this same method provided **20a** in 80% yield (entry 6, Table 2). On the other hand, this same compound having 90% chemical purity was obtained in 18% yield by iodolactonization of **19a** according to Method A (entry 8, Table 2).

4.5.2. 4-Iodo-3-(3,4-dimethoxyphenyl)-8-methoxyiso-coumarin (20b). The crude reaction product, which was obtained by iodolactonization of **18b** according to Method C (entry 2, Table 2), was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and petroleum ether (70:30) as eluant, to give **20b** in 89% yield as a colourless solid. Mp 220–224°C. IR (KBr): ν 1736, 1510, 1473, 1257, 1171, 1001, 806 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (1H, t, J=8.5 Hz), 7.51 (1H, dd, J=8.5 and 1.0 Hz), 7.32 (1H, dd, J=8.5 and 2.0 Hz), 7.21 (1H, d, J=2.0 Hz), 7.07 (1H, dd, J=8.5 and 1.0 Hz), 6.93 (1H, d, J=8.5 Hz), 4.04 (3H, s), 3.94 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.4, 158.1, 155.5, 150.3, 148.1, 140.7, 136.0, 127.6, 123.7, 123.5, 112.9, 110.8, 110.1, 108.6, 75.4, 56.6, 56.0, 55.9 ppm. Anal. Calcd for $C_{18}H_{15}IO_5$: C, 49.34; H, 3.45. Found: C, 49.14; H, 3.27. It should be noted that iodolactonization of **18b** at 52–57°C according to this same method furnished **20b** in 24% yield (entry 7, Table 2). It is is also worth mentioning that purification by MPLC on silica gel of the crude reaction mixture derived from this last reaction allowed isolation of 3-(3,4-dimethoxyphenyl)-8-methoxy-isocoumarin (**40**) solid in 4% yield as a pale yellow. Mp 148–150°C. MS, *m/z* (%): 312 (100), 284 (46), 269 (22), 165 (12), 142 (10), 119 (15), 76 (10). IR (KBr): ν 1729, 1698, 1566, 1515, 1254, 991, 805 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.59 (1H, t, J=8.0 Hz), 7.46 (1H, dd, J=8.5 and 2.0 Hz), 7.35 (1H, d, J=2.0 Hz), 6.99 (1H, dd, J=8.0 and 1.0 Hz), 6.92 (1H, d, J=8.5 Hz), 6.90 (1H, br d, J=8.0 Hz), 6.74 (1H, s), 4.01 (3H, s), 3.98 (3H, s), 3.93 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.5, 159.0, 153.8, 150.6, 149.0, 140.6, 135.6, 124.6, 118.5, 117.7, 111.0, 109.4, 108.8, 108.2, 100.5, 56.3, 56.1, 56.0 ppm. The spectral properties of this compound were in agreement with those previously reported.[17]

4.5.3. 4-Iodo-8-methoxy-3-phenylisocoumarin (20c) and (*E*)-3-[(1-iodo-1-phenyl)methylidene]-7-methoxy-phthalide (39c). The crude reaction mixture, which was obtained by iodolactonization of **18c** according to Method B (entry 9, Table 2), was purified by MPLC on silica gel using a mixture of benzene and AcOEt (90:10) as eluant. Concentration of the first eluted chromatographic fractions allowed isolation of **39c** in 38% yield as a pale yellow solid. Mp 155–158°C. MS, *m/z* (%): 378 (5), 252 (17), 236 (18), 195 (23), 165 (11), 152 (10). IR (KBr): ν 1778, 1489, 1288, 1047, 1014, 997, 688 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.52, (1H, d, J=8.0 Hz), 7.76 (1H, dd, J=8.5 and 8.0 Hz), 7.54 (2H, m), 7.40 (2H, m), 7.29 (1H, m), 7.09 (1H, d, J=8.5 Hz), 4.04 ppm (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.4, 158.7, 144.1, 140.7, 140.4, 136.1, 130.1 (2C), 128.9, 128.1 (2C), 116.9, 113.2, 112.6, 80.0, 56.3 ppm. Anal. Calcd for $C_{16}H_{11}IO_3$: C, 50.82; H, 2.93. Found: C, 50.93; H, 3.15. Concentration of the last eluted chromatographic fractions allowed isolation of compound **20c** in 47% yield as a pale yellow solid. Mp 150–152°C. MS, *m/z* (%): 378 (30), 233 (46), 223 (23), 195 (33), 152 (20), 105 (100), 77 (61). IR (KBr): ν 1741, 1721, 1567, 1474, 1257, 1211, 692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (1H, t, J=8.0 Hz), 7.71–7.63 (2H, m), 7.51 (1H, dd, J=8.0 and 1.0 Hz), 7.48–7.41 (3H, m), 7.07 (1H, d, J=8.0 Hz), 4.04 ppm (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.5, 157.9, 155.7, 140.4, 136.0, 135.3, 130.0, 129.9 (2C), 127.9 (2C), 123.7, 110.9, 108.7, 75.8, 56.6 ppm. Anal. Calcd for $C_{16}H_{11}IO_3$: C, 50.82; H, 2.93. Found: C, 50.90; H, 2.99. It should be noted that iodolactonization of **18c** according to Method C (entry 3, Table 2) furnished compounds **39c** and **20c** in 66 and 26% yield, respectively.

4.5.4. 4-Iodo-3-phenylisocoumarin (20d). The crude reaction product, which was obtained by iodolactonization of

19c according to Method A (entry 10, Table 2), was purified by MPLC on silica gel using a mixture of benzene and hexane (90:10) to give **20d** in 88% yield as a colourless solid. Mp 136–138°C (lit.[1d] mp 135°C). MS, *m/z* (%): 348 (91), 320 (48), 193 (65), 165 (100), 105 (92), 88 (48), 77 (87). IR (KBr): ν 1738, 1624, 1073, 1054, 1017, 767, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.29 (1H, dd, J=8.0 and 1.5 Hz), 7.88 (1H, dd, J=8.0 and 1.5 Hz), 7.81 (1H, dt, J=8.0 and 1.5 Hz), 7.73–7.63 (2H, m), 7.56 (1H, dt, J=8.0 and 1.5 Hz), 7.51–7.42 ppm (3H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.3, 154.6, 138.0, 135.6, 135.1, 131.4, 130.0, 129.9 (2C), 129.6, 129.1, 128.0 (2C), 120.1, 76.4 ppm. Anal. Calcd for $C_{15}H_9IO_2$: C, 51.75; H, 2.60. Found: C, 51.66; H, 2.45. Interestingly, iodolactonization of **18d** according to Methods B and C furnished **20d** in 81 and 83% yield, respectively (entries 5 and 4, Table 2).

4.6. Synthesis of 3-(3,4-dimethoxyphenyl)-8-methoxyisocoumarin (40) by Pd-catalyzed triethyl-ammonium formate reduction of 4-iodo-3-(3,4-dimethoxyphenyl)-8-methoxyisocoumarin (20b)

Formic acid, 99%, (226 mg, 4.92 mmol) was added to a deaerated mixture of **20b** (1.08 g, 2.46 mmol), Et_3N (1.03 ml, 7.38 mmol), $Pd(OAc)_2$ (11.0 mg, 0.0492 mmol) and PPh_3 (25.8 mg, 0.984 mmol) in dry DMF (60 ml) and the mixture was stirred at 60°C for 5 h under argon. It was then cooled to rt, poured into a saturated aqueous NH_4Cl solution (100 ml) and extracted with AcOEt (5×100 ml). The organic extract was washed with brine (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using a mixture of benzene and AcOEt (65:35) as eluant, to give compound **40** (0.716 g, 93% yield) as a pale yellow solid. Mp 148–150°C. The spectral properties of this compound were in agreement either with those of **40** obtained from iodolactonization of **18b** by Method C at 52–57°C or with those previously reported.[17]

4.7. General procedure for the synthesis of 2(2*H*)-pyranone derivatives of general formula 21 by a one-pot sequence of iodolactonization–Stille-type reactions

To a deaerated solution of an ester **15** (3.0 mmol) in CH_2Cl_2 or 1,2-dichloroethane (20 ml) was added a deaerated solution of ICl (487 mg, 3.0 mmol) in CH_2Cl_2 or 1,2-dichloroethane (10 ml) and the mixture was stirred in the dark under argon at rt until a GLC analysis showed that the reaction was complete. A deaerated solution of an organotributyltin (3.3–3.7 mmol) in CH_2Cl_2 or 1,2-dichloroethane (20 ml) and a Pd catalyst were sequentially added and the mixture was stirred at the temperature and for the period of time reported in Table 3. This table also indicates the solvent used for the reaction. The reaction mixture was then cooled to rt, treated with solid KF (2.61 g, 45.0 mmol) and the resulting mixture was stirred for 5 h at rt. It was then filtered through Celite and the filtrate was extracted with CH_2Cl_2 or 1,2-dichloroethane (3×25 ml). The organic extract was washed with water (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. This procedure was used to prepare compounds **21a–e** (Table 3). It should be noted that two types of Pd catalysts were used for the synthesis of compounds **21**. The reactions involving 1-alkynyltributyltin derivatives (entries 1 and 2, Table 3) were performed using 3 mol% $PdCl_2(PPh_3)_2$ (catalyst A), whereas those involving aryltributyltin derivatives (entries 3–5, Table 3) were carried out in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$ (catalyst B).

4.7.1. 3-Bromo-5-(1-hexynyl)-6-pentyl-2(2*H*)-pyranone (21a). The crude reaction product, which was obtained by iodolactonization of **15c** in CH_2Cl_2 followed by treatment with 1-hexynyltributyltin (**41a**) in the presence of catalyst A (entry 1, Table 3), was purified by MPLC on silica gel using toluene as eluant to give compound **21a** in 38% yield as an orange liquid. MS, *m/z:* (%): 326 (86), 324 (83), 269 (94), 267 (100), 227 (47), 115 (44), 99 (41). IR (film): ν 2234, 1747, 1621, 1533, 1465, 938, 748 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.62 (1H, s), 2.66 (2H, t, J=7.5 Hz), 2.38 (2H, t, J=6.5 Hz), 1.73–1.17 (10H, m), 0.97–0.86 ppm (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.6, 157.9, 147.3, 107.8, 102.4, 95.7, 72.5, 32.4, 31.1, 30.5, 26.7, 22.2, 21.9, 19.0, 13.9, 13.6 ppm. Anal. Calcd for $C_{16}H_{21}BrO_2$: C, 59.08; H, 6.50. Found: C, 58.90; H, 6.61.

4.7.2. 3-Bromo-6-pentyl-5-phenylethynyl-2(2*H*)-pyranone (21b). The crude reaction product, which was obtained by iodolactonization of **15c** in 1,2-dichloroethane followed by treatment with phenylethynyltributyltin (**41b**) in the presence of catalyst A (entry 2, Table 3), was purified by MPLC on silica gel, using a mixture of toluene and hexane (88:12) as eluant, to give compound **21b** in 52% yield as an orange solid. Mp 49–52°C. MS, *m/z* (%): 346 (27), 344 (30), 289 (97), 287 (100), 152 (48), 138 (30), 105 (54). IR (KBr): ν 2208, 1745, 1620, 1533, 1490, 934, 755 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.73 (1H, s), 7.74–7.34 (5H, m), 2.76 (2H, t, J=7.5 Hz), 1.75 (2H, pseudo-quint, J=7.5 Hz), 1.41–1.31 (4H, m), 0.90 ppm (3H, t, J=7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.2, 157.5, 146.6, 131.2 (2C), 128.8, 128.4 (2C), 122.0, 108.0, 102.0, 94.3, 81.1, 32.6, 31.1, 26.7, 22.2, 13.9 ppm. Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.88; H, 4.91.

4.7.3. 3-Bromo-6-pentyl-5-phenyl-2(2*H*)-pyranone (21c). The crude reaction product, which was obtained by iodolactonization of **15c** in 1,2-dichloroethane followed by treatment with phenyltributyltin (**41c**) in the presence of catalyst B (entry 3, Table 3), was purified by MPLC on silica gel, using a mixture of petroleum ether and AcOEt (95:5) as eluant, to give compound **21c** in 43% yield as a pale yellow liquid. MS, *m/z* (%): 322 (99), 320 (100), 265 (22), 263 (16), 251 (45), 237 (57), 235 (53). IR (film): ν 1737, 1629, 1532, 1495, 943, 768, 749 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.66 (1H, s), 7.46–7.20 (5H, m), 2.48 (2H, t, J=7.5 Hz), 1.67 (2H, pseudo-quint, J=7.5 Hz), 1.32–1.17 (4H, m), 0.83 ppm (3H, t, J=6.5 Hz).). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.5, 158.7, 147.7; 134.6, 128.8 (2C), 128.7 (2C), 128.2, 118.6, 108.3, 31.1 (2C), 27.2, 22.1, 13.8 ppm. Anal. Calcd for $C_{16}H_{17}BrO_2$: C, 59.83; H, 5.33. Found: C, 60.01; H, 5.42.

4.7.4. 3-Bromo-5-(4-chlorophenyl)-6-pentyl-2(2*H*)-pyranone (21d). The crude reaction product, which was obtained by iodolactonization of **15c** in 1,2-dichloroethane followed by treatment with 4-chlorophenyltributyltin (**41d**) in the

presence of catalyst B (entry 4, Table 3), was purified by MPLC on silica gel, using toluene as eluant, to give in 30% yield compound **21d** as a pale yellow liquid. MS, *m/z*: 356 (82), 354 (71), 285 (100), 283 (70), 229 (63), 162 (42), 113 (58). IR (film): ν 1737, 1628, 1533, 1493, 1088, 999, 833 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.66 (1H, s), 7.43 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 2.48 (2H, t, J=7.5 Hz), 1.69 (2H, pseudo-quint, J=7.0 Hz), 1.40–1.15 (4H, m), 0.87 ppm (3H, t, J=6.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.6, 158.3, 147.1, 134.3, 133.0, 130.1 (2C), 129.0 (2C), 117.5, 108.4, 31.2, 31.1, 27.2, 22.1, 13.8 ppm. Anal. Calcd for $C_{16}H_{16}BrClO_2$: C, 54.03; H, 4.53. Found: C, 53.89; H, 4.42.

4.7.5. 4,6-Dipentyl-5-phenyl-2(2*H*)pyranone (21e). The crude reaction product, which was obtained by iodolactonization of **15d** in 1,2-dichloroethane followed by treatment with phenyltributyltin (**41c**) in the presence of catalyst B (entry 5, Table 3), was purified by MPLC on silica gel, using a mixture of petroleum ether and AcOEt (95:5) as eluant, to give compound **21e** in 38% yield as a pale yellow liquid. MS, *m/z* (%): 312 (22), 256 (37), 228 (100), 227 (23), 185 (18), 171 (15), 55 (18). IR (film): ν 1731, 1631, 1544, 1444, 1006, 769, 705 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.45–7.35 (3H, m), 7.16–7.10 (2H, m), 6.07 (1H, s), 2.23 (2H, t, J=7.7 Hz), 2.10 (2H, t, J=7.5 Hz), 1.57 (2H, pseudo-quint, J=7.5 Hz), 1.34 (2H, pseudo-quint, J=7.5 Hz), 1.25–1.05 (8H, m), 0.83–0.75 ppm (6H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8, 162.1, 160.6, 134.3, 130.0 (2C), 128.5 (2C), 127.9, 119.1, 109.8, 33.4, 31.6, 31.1 (2C), 27.6, 27.2, 22.1 (2C), 13.8, 13.7 ppm. Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.86; H, 9.12.

4.7.6. Methyl-6-pentyl-5-phenylethynyl-2(2*H*)-pyranone (22a) and 6-pentyl-5-phenylethynyl-2(2*H*)pyranone (42). To a deaerated solution of **15c** (1.02 g, 3.9 mmol) in 1,2-dichloroethane (20 ml) was added a deaerated solution of ICl (633 mg, 3.9 mmol) in 1,2-dichloroethane (10 ml) and the mixture was stirrred in the dark under argon until the reaction was complete (6 h). A deaerated solution of phenylethynyltributyltin (**41b**) (1.90 g, 4.9 mmol) in 1,2-dichloroethane (20 ml) and $PdCl_2(PPh_3)_2$ (137 mg, 0.19 mmol) were sequentially added and the resulting mixture was stirred at 70°C under argon for 16 h. After this period a GLC analysis of a sample of the reaction mixture showed that **17b**, which was an intermediate of this sequence, and compound **41b** had been completely consumed. The mixture was then cooled to rt, treated with a deaerated solution of tetramethyltin (2.09 g, 11.7 mmol) in 1,2-dichloroethane (10 ml) and the resulting mixture was heated to 90°C for 48 h under argon. It was then cooled to rt and worked up using a procedure very similar to that employed in the preparation of compounds **21**. The crude reaction product was purified by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed isolation of **22a** (87 mg, 8% yield) as a pale yellow liquid. MS, *m/z* (%): 280 (23), 224 (15), 223 (100), 153 (22), 152 (28), 105 (39), 77 (11). IR (film): ν 2213, 1728, 1566, 1382, 1032, 997, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.57–7.40 (5H, m), 7.20 (1H, q, J=1.5 Hz), 2.79 (2H, t, J=7.5 Hz), 2.12 (3H, br s), 1.77 (2H, pseudo-quint, J=7.5 Hz), 1.45–1.30 (4H, m), 0.92 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.2, 162.8, 141.7, 131.2 (2C), 128.5, 128.3 (2C), 122.6, 122.3, 101.0, 93.4, 82.8, 32.5, 31.2, 26.9, 22.3, 16.4, 13.9 ppm. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.47; H, 7.25. Concentration of the last eluted chromatographic fractions allowed isolation of **42** (52 mg, 5% yield) as a pale yellow liquid. MS, *m/z* (%): 266 (34), 210 (16), 209 (100), 153 (8), 152 (10), 139 (32), 105 (9). IR (film): ν 2216, 1743, 1542, 1490, 1080, 823, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.60–7.20 (6H, m), 6.21 (1H, d, J=9.5 Hz), 2.81 (2H, t, J=7.5 Hz), 1.79 2H, pseudo-quint, J=7.5 Hz), 1.45–1.20 (4H, m), 0.93 ppm (3H, t, J=6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.1, 161.0, 145.8, 131.2 (2C), 128.6, 128.4 (2C), 122.4, 112.9, 101.0, 93.9, 82.4, 32.9, 31.2, 26.8, 22.3, 13.9 ppm. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.31; H, 6.97.

Acknowledgements

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) and the University of Pisa. We thank Dr Stéphane Viel for obtaining the ^1H NMR spectra at 600 MHz and the ^{13}C NMR spectra at 150 MHz and Professor Annalaura Segre for the use of NMR facilities of the Servizio NMR dell'Area della Ricerca di Roma (CNR). We are also grateful to Mr Piergiorgio Vergamini for recording IR spectra.

References

1. (a) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459–5466. (b) Daniels, S. B.; Cooney, E.; Sofia, M.-J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1983**, *258*, 15046–15053. (c) Spencer, R. W.; Tam, T.-F.; Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589–5597. (d) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem. Sect. B* **1988**, *27*, 380. (e) Doi, J. T.; Luehr, G. W.; del Carmen, D.; Lippsmeyer, B. C. *J. Org. Chem.* **1989**, *54*, 2764–2767. (f) Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561–568.
2. For leading references on this subject, see: (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171–197. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408. (c) Harding, K. E.; Tiner, T. H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp. 363–421. (d) Brown, R. T.; Duckworth, D. M.; Santos, C. A. M. *Tetrahedron Lett.* **1991**, *32*, 1987–1990. (e) Bedford, S. B.; Fenton, G.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1505–1509. (f) Roux, M.-C.; Paugam, R.; Rousseau, G. *J. Org. Chem.* **2001**, *66*, 4304–4310. (g) Chavan, S. P.; Sharma, A. K. *Tetrahedron Lett.* **2001**, *42*, 4923–4924 and references therein. (h) Rousset, S.; Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **2000**, 260–262. (i) Delle Monache, G.; Misiti, D.; Salvatore, P.; Zappia, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1137–1149.
3. (a) Jäger, V.; Günther, H. J. *Tetrahedron Lett.* **1977**, *29*, 2543–2546. (b) Garratt, D. G.; Ryan, M. D.; Beaulieu, P. L. *J. Org. Chem.* **1980**, *45*, 839–845. (c) Macritchie, J. A.; Peakman, T. M.; Silcock, A.; Willis, C. L. *Tetrahedron Lett.* **1998**, *39*, 7415–7418.

4. Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318–3325.
5. (a) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023–2027. (b) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 3851–3854. (c) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479–487. (d) Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281–5286. (e) Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749–1752. (f) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1163–1172. (g) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799–7802. (h) Rossi, R.; Bellina, F.; Biagetti, M. *Synth. Commun.* **1999**, *29*, 3415–3420. (i) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599–7602. (j) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017–3020. (k) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L. *Tetrahedron* **1998**, *54*, 135–156.
6. Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857–2870.
7. Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859–2863.
8. Biagetti, M.; Bellina, F.; Carpita, A.; Viel, S.; Mannina, L.; Rossi, R. *Eur. J. Org. Chem.* **2002**, 1063–1076.
9. Very recently, a related process has been described involving the synthesis of isoquinolines by electrophilic ring closure of iminoalkynes:Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973–2976.
10. For reviews on the Stille reaction, see: (a) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73–78. (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524. (c) Mitchell, T. N. *Synthesis* **1992**, 803–815. (d) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 167–202.
11. Rossi, R.; Bellina, F.; Carpita, A.; Gori, R. *Gazz. Chim. Ital.* **1995**, *125*, 381–392.
12. Myers, A. G.; Alauddin, M. M.; Fury, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6977–6980.
13. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470. (b) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp. 521–549. (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced.* **1995**, 129–160.
14. Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron* **1997**, *53*, 1025–1044.
15. Biagetti, M. PhD Thesis, Pisa, 2002.
16. Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533–2545.
17. Morikawa, T.; Kumadaki, I.; Shiro, M. *Chem. Pharm. Bull.* **1985**, *33*, 5144–5146.
18. For a three step synthesis of 3-aryl-4-iodoisocoumarins from methyl 2-(arylethynyl)benzoates, see: Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem. Sect. B* **1987**, *26*, 917–919.
19. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541–5544.
20. For another recent method for the synthesis of trisubstituted 2(2*H*)-pyranones, see: Hua, R.; Tanaka, M. *New J. Chem.* **2001**, *25*, 179–184.
21. Kang, S.-K.; Namkoong, E.-Y.; Yamaguchi, T. *Synth. Commun.* **1997**, *27*, 641–646.
22. For a sequential synthesis of 3,5,6-trisubstituted 2(2*H*)-pyranones from methyl (*E*)-2-bromo-2-en-4-ynoates, see: Ref. 8.
23. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121–124.
24. Doyle, J. R.; Slade, P. E.; Jonassen, M. B. *Inorg. Synth.* **1960**, *6*, 216–219.
25. Itatani, H.; Bailar, J. C. *J. Am. Chem. Oil Soc.* **1967**, *44*, 127–151.
26. Crisp, G. T.; O'Donoghue, A. I. *Synth. Commun.* **1989**, *19*, 1745–1758.
27. Owton, W. M.; Brunavas, M. *Synth. Commun.* **1991**, *21*, 981–987.
28. Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775–2790.
29. Azzena, U.; Melloni, G.; Pisano, L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 261–266.