Mucochloric Acid: A Useful Synthon for the Selective Synthesis of 4-Aryl-3-chloro-2(5*H*)-furanones, (*Z*)-4-Aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones and 3,4-Diaryl-2(5*H*)-furanones

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3,4-Dichloro-2(5*H*)-furanone, which has been prepared efficiently from mucochloric acid, has been transformed selectively into 4-aryl-3-chloro-2(5*H*)-furanones either by Suzuki- or Stille-type reactions. These monochloro derivatives have been used as precursors either to (Z)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones, including naturally occurring rubrolide M, or to unsymmetrical 3,4-diaryl-2(5*H*)-furanones. Some 2(5*H*)-furanone derivatives so prepared have been found to exhibit significant cytotoxic activity in vitro against the NCI three-cell-line panel, but limited cytotoxicity against the NCI human tumor 60 cell-line panel.

Introduction

The 2(5*H*)-furanone moiety occurs in many natural products that exhibit biological activities ranging from antibiotic,[1,2] cytotoxic,[3−5] and antitumor properties[6] to inhibition of cholesterol biosynthesis.[7] In addition, 2(5*H*)-furanone derivatives find a variety of applications in organic synthesis.[8−10] The long-standing interest in these heterocyclic compounds is testified by the wide variety of methods reported in the literature for their preparation.[11−13] A good many of the recently reported efforts on the synthesis of 2(5*H*)-furanone derivatives have focused, however, on transition metal-catalysed processes.[14−16] Recently, our interest in the design and use of simple and efficient procedures for the synthesis of natural and non-natural oxygen-containing heterocycles[17−22] has led us to explore the utility of 3,4-dibromo-2(5*H*)-furanone (**2**) (Figure 1) for the preparation of compounds containing the 2(5*H*)-furanone moiety by transition-metal-catalysed reactions.[23−26] In particular, we found that **2** could be converted selectively into 4-aryl-3-bromo-2(5*H*)-furanones **3** either by Suzuki-type reaction with arylboronic acids or by Stille-type reactions with trialkyl(aryl)tin reagents[23,24] (Figure 1). Bromides **3** were then converted by Pd-catalysed reaction with trialkyl(aryl)tin reagents into 3,4-diaryl-2(5*H*)-furanones **4**,[23] including **4a**, which is a precursor to Vioxx® (Rofecoxib) (**4b**),[10,23] a cyclooxygenase-2 (COX-2) inhibitor. Bromides **3** were also converted into 4-aryl-3-methyl-2(5*H*)-furanones **5**,[23] which are substances that exhibit antifungal properties,[27] 4-aryl-2(5*H*)-furanones **6**,[23] including **6a**, which is a precursor to rubrolides C and E,[28] and (*Z*)-4-

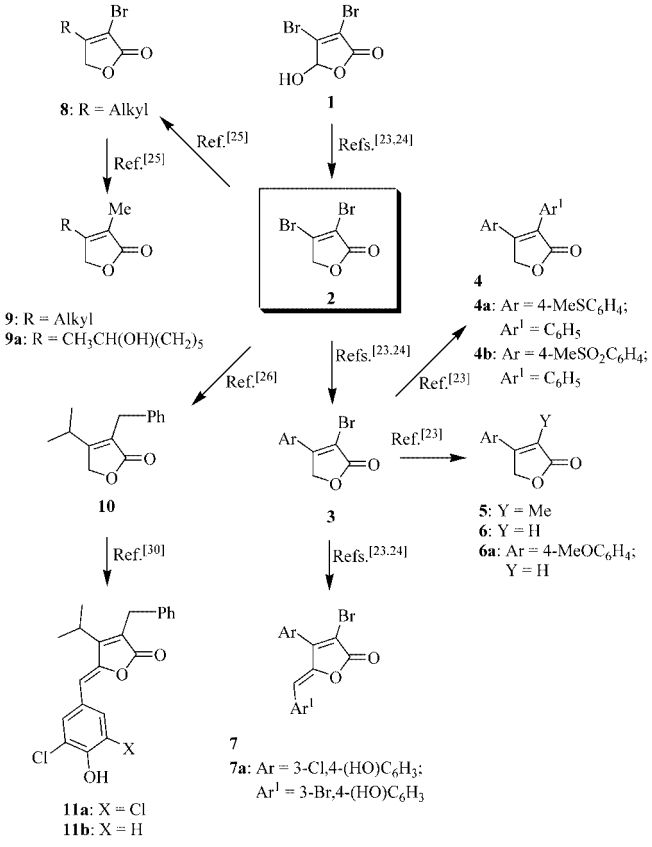

Figure 1. Chemical structures of compounds **2**, **3**, **4**, **4a**, **5**, **6**, **6a**, **7**, **7a**, **8**, **9**, **9a**, **10**, **11a** and **11b** prepared from mucobromic acid (**1**)

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aryl-5-[1-(aryl)methylidene]-3-bromo-2(5*H*)-furanones **7**,[24] including the compound with the structure corresponding to that reported in the literature for naturally occurring rubrolide N (**7a**)[3] (Figure 1). We also showed that **2** is a useful precursor to 4-alkyl-3-bromo-2(5*H*)-furanones **8**,[25] unsymmetrical 3,4-dialkyl-2(5*H*)-furanones **9**,[25] including the racemic form of phytopathogenic seiridin (**9a**),[29] and 3-benzyl-4-isopropyl-2(5*H*)-furanone (**10**),[26] which is a precursor to nostoclide I (**11a**) and II (**11b**),[30] a pair of cytotoxic 2(5*H*)-furanones[31] (Figure 1).

More recently, we decided to investigate the use of 3,4-dichloro-2(5*H*)-furanone (**12**) for the synthesis of 4-aryl-3-chloro-2(5*H*)-furanones **13**, symmetrical and unsymmetrical 3,4-diaryl-2(5*H*)-furanones **4**, and (*Z*)-4-aryl-5-[1-(aryl)-methylidene]-3-chloro-2(5*H*)-furanones **14**, including rubrolide M (**14a**), which is a natural product that proved to be significantly cytotoxic against four cancer cell lines[3] (Figure 2). Our attention towards **14a** and some of its congeners was due to the fact that this rubrolide is the most active among the four (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones isolated from *Synoicum blochmanni*.[3] On the other hand, we were interested in developing a convenient and efficient procedure for the synthesis of 3,4-diaryl-2(5*H*)-furanones **4**, since these compounds can be considered as (*Z*)-restricted analogues of combretastatin A-4 (**15**) (Figure 2), the potent antimitotic and cytotoxic compound isolated from *Combretum caffrum*,[32,33] and some of them have been demonstrated to be potent and selective COX-2 inhibitors.[34,35] In particular, we examined the possibility of accessing compounds **13**, **14** and **4** starting from **12** through chemistry similar to that we have used successfully for the preparation of compounds **3**−**10** starting from **2**. On the other hand, **12** (98% chemically pure) was prepared in 92% yield by treatment of mucochloric acid (**16**), which is a commercially available compound that is much less expensive than mucobromic acid (**1**), with $NaBH_4$ in methanol.[36] In this paper we provide a full account on the results of these studies[37] and describe the results of tests to evaluate the cytotoxic activity exhibited by several compounds of general formula **13**, **14** and **4** against human cancer cell lines.

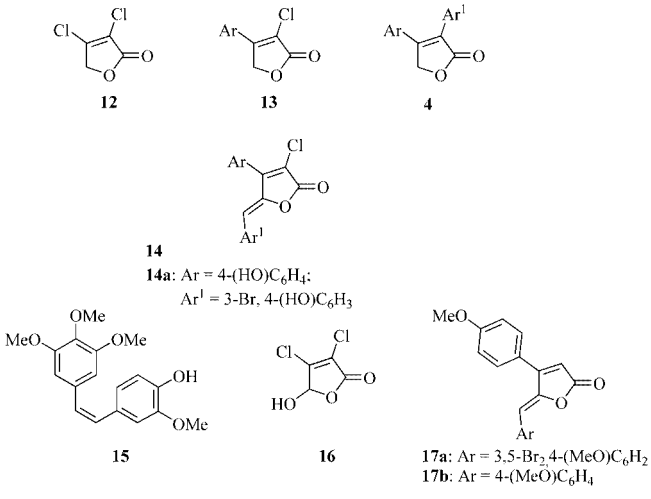
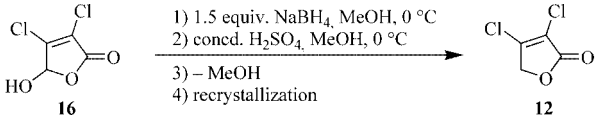


Figure 2. Chemical structures of compounds **4**, **12**, **13**, **14**, **14a**, **15**, **16**, **17a** and **17b**

Results and Discussion

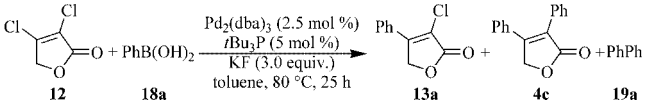
Synthesis of 3,4-Dichloro-2(5H)-furanone and 4-Aryl-3-chloro-2(5H)-furanones

Chemically pure **12**, which was used as a starting material for the synthesis of compounds **13**, **14** and **4**, was prepared by reaction of mucochloric acid (**16**) with $NaBH_4$ in methanol according to a modification of a literature procedure[36] (Scheme 1). This modification, which involved removal of methanol under reduced pressure before the crude reaction mixture underwent the usual workup, allowed us to obtain **12** in 89% yield.



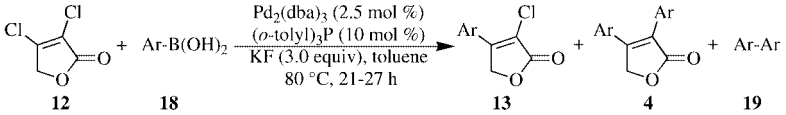
Scheme 1. Synthesis of 3,4-dichloro-2(5*H*)-furanone (**12**)

It is interesting to note that applying a similar modification to the protocol previously employed to prepare 3,4-dibromo-2(5*H*)-furanone (**2**) from **1**,[24] allowed us to increase the yield of chemically pure **2** from 75 to 88% yield. Having secured a good route to **12**, next we turned our attention to the preparation of 4-aryl-3-chloro-2(5*H*)-furanones **13** starting from this dichloride. Determination of reaction conditions that allow the selective production of compounds **13**, however, required considerable experimentation. In fact, in a preliminary attempt to prepare 3-chloro-4-phenyl-2(5*H*)-furanone (**13a**) by reaction of **12** with 1.1 equiv. of phenylboronic acid (**18a**) under the conditions commonly used for monoarylation of **2**,[23,24] i.e., by heating under reflux in THF for 22 h in the presence of $[PdCl_2(MeCN)_2]$ (5 mol %), $AsPh_3$ (20 mol %) and Ag_2O (3.0 equiv.), we found that the conversion of the reaction was very low (ca. 10%) and that the major reaction product was biphenyl (**19a**) derived from the Pd-catalysed self-coupling of **18a**.[38] We observed also that **19a** was the major product when **12** was treated with of **18a** (1.1 equiv.) in methanol at 40 °C for 23 h in the presence of sodium acetate (1.5 equiv.) and $[PdCl_2(PPh_3)_2]$ (3 mol %) or in toluene at 80 °C for 6 h in the presence of Ag_2O (3.0 equiv.), $[Pd_2(dba)_3]$ (2.5 mol %) and tBu$_3$P (5 mol %). We found, however, that the formation of **18a** could be minimized effectively when the Suzuki-type reaction was performed by treating **12** with of **18a** (1.3 equiv.) in toluene at 80 °C in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu$_3$P (Scheme 2).



Scheme 2. Synthesis of compounds **13a** and **4c**

Table 1. Synthesis of 4-aryl-3-chloro-2(5*H*)-furanones **13** by Suzuki-type reactions

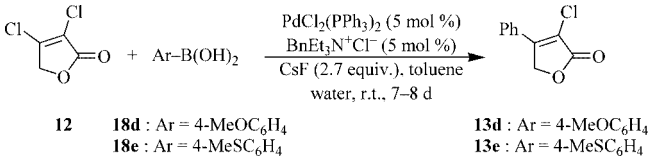


Entry[a]	18	Boronic acid Ar[1]	Reaction time [h]	13	Product 13/4 molar ratio[b]	Isolated yield of **13** (%)
1	18a	C_6H_5	24	**13a**	13	63
2	18b	3-Cl,4-$MeOC_6H_3$	21	**13b**	> 99	57
3	18c	4-ClC_6H_4	27	**13c**	> 99	42
4	18d	4-$MeOC_6H_4$	24	**13d**	> 99	61
5	18e	4-$MeSC_6H_4$	24	**13e**	> 99	33

[a] All these reactions were performed under argon using 1.05 equiv. of **18**. [b] Determined by GLC analysis of the crude reaction mixtures.

Under these conditions, the conversion of the reaction was almost quantitative and the amount of **19a** in the crude reaction mixture was ca. 4%, but the desired product **13a** was obtained along with a comparable amount of 3,4-diphenyl-2(5*H*)-furanone (**4c**). This result indicates that, although it might be expected that the C−Cl bond at the activated 4-position of **12** is more reactive than that at the 3-position and, therefore, that the Pd-catalysed reaction might occur selectively at C-4, the selectivity of the cross-coupling reaction was negligible, probably because of the very high activity of the catalyst system used. Therefore, we examined the use of other electron-rich phosphane ligands, such as Cy_3P (Cy = cyclohexyl) and (*o*-biphenyl)P(*t*Bu)$_2$, in place of tBu_3P. However, this modification, as well as the use of a base such as CsF or Cs_2CO_3 in place of KF, did not increase either the regioselectivity of the reaction or the yield of **13a**. Moreover, the cross-couplings performed using CsF or Cs_2CO_3 in THF at room temperature resulted in side reactions, which produced extensive decomposition of **12**. Finally, we found that the reaction of **12** with 1.05 equiv. of **18a** in the presence of KF and catalytic amounts of [$Pd_2(dba)_3$] and (*o*-tolyl)$_3$P (Method A) produced a reaction mixture containing **13a** contaminated by less than 6 and 12% of **4c** and **19a**, respectively, and that chromatographic purification of this mixture allowed the isolation of pure **13a** in 63% yield (Table 1, Entry 1). These reaction conditions were then used to prepare compounds **13b**, **13c**, **13d**, and **13e**.[39]

As shown in Table 1, which summarizes the results of the preparation of these compounds, the selectivity of the reactions involving arylboronic acids **18b−e** was found unexpectedly to be much higher than that observed for the reaction between **18a** and **12**. On the other hand, similar to the situation that was observed in the preparation of **13a**, the crude reaction mixtures corresponding to the preparation of compounds **13b**, **13c**, **13d** and **13e** were contaminated by less than 12% of the biaryls **19b−e** derived from self-coupling of arylboronic acids **18b−e**. Remarkably, all reaction mixtures derived from the cross-couplings of **12** with **18a−e** (Entries 1−5, Table 1) were free of traces of the regioisomers of the desired monoarylated products **13a−e**. It is also interesting to note that the yields of the reactions between **12** and **18** were increased using the procedure described by Zhang and co-workers for the synthesis of a precursor to Vioxx®.[40] Thus, reaction of **12** with 2.0 equiv. of **18d** in a 1:1 mixture of toluene and water in the presence of CsF and catalytic amounts of [$PdCl_2(PPh_3)_2$] and $BnEt_3N^+Cl^-$ (Method B) furnished **13d** in 80% yield (Scheme 3). Moreover, a very similar reaction of **12** with 2.0 equiv. of **18e** gave **13e** in 80% yield (Scheme 3).

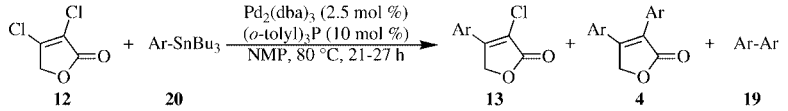


Scheme 3. Pd-catalysed syntheses of compounds **13d** and **13e** by Suzuki-type reactions under phase-transfer conditions

It should be noted, however, that, unlike our method, this literature procedure[40] involves the use of a very large molar excess of the requisite arylboronic acid and that, at least in our hands, it required reaction times significantly longer than those of our protocol. Moreover, this literature procedure furnished reaction mixtures contaminated by large amounts of the biaryl compounds derived from self-coupling of the arylboronic acids.

Even though the results obtained for the synthesis of compounds **13** by Suzuki-type reaction were quite satisfactory, we found it desirable to search for a new and efficient route to these monochloro derivatives from **12**. Thus, we investigated the Pd-catalysed Stille-type reaction of **12** with aryl(tributyl)tin reagents **20**[41] and, after some screening experiments, found that the reaction of **12** with aryltin reagents **20a**, **20b**, **20c**, **20d**, **20e**, **20f** and **20g** in *N*-methylpyrrolidinone (NMP) at 85 °C in the presence of catalytic amounts of [$Pd_2(dba)_3$] and (*o*-tolyl)$_3$P furnished compounds **13a**, **13c**, **13d**, **13e**, **13f**, **13g** and **13h** in 53, 61, 78, 73, 55, 75 and 67% yield, respectively. As shown in Table 2, which summarizes the results of these reactions, the selectivity of the reactions of **12** with aryltin reagents **20**, except for the reaction between **12** and **20g** (Entry 7), was lower

Table 2. Synthesis of 4-aryl-3-chloro-2(5*H*)-furanones **13** by Stille-type reactions



12 20 13 4 19

Entry[a]	Aryltributylstannane 20	Ar[1]	Reaction time [h]	Product 13	13/4 molar ratio[b]	Isolated yield of 13 (%)
1	**20a**	C_6H_5	20	**13a**	36	53
2	**20b**	4-ClC_6H_4	21	**13c**	8	61
3	**20d**	4-$MeOC_6H_4$	21	**13d**	25	78
4	**20e**	4-$MeSC_6H_4$	24	**13e**	23	73
5	**20c**	2-thienyl	21	**13f**	n.d.	55
6	**20f**	3,4-$(MeO)_2C_6H_3$	23	**13g**	> 71	75
7[c]	**20g**	2-naphthyl	44	**13h**	> 99	67

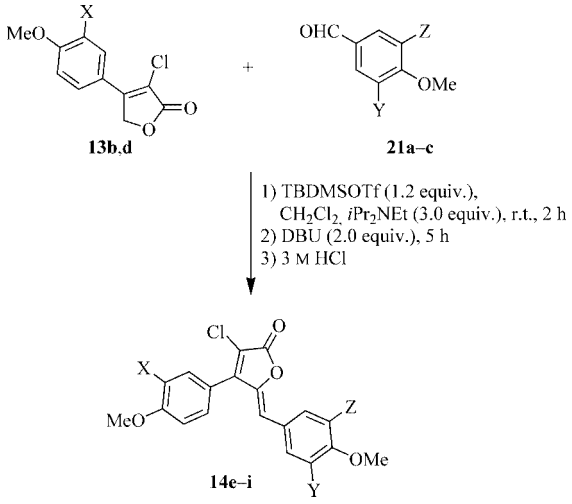
[a] Unless otherwise reported, all these reactions were performed under argon using 1.10 equiv. of **20**. [b] Determined by GLC analysis of the crude reaction mixtures. [c] This reaction was performed using 1.05 equiv. of **20g**.

than that of the reaction of **12** with arylboronic acids **18b−e**, but the yields of compounds **13** prepared by the Stille-type reaction were generally higher than those obtained by reaction of **12** with arylboronic acids in toluene at 85 °C in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and (*o*-tolyl)$_3$P.

Synthesis of (*Z*)-4-Aryl-5-[1-(aryl)methylidene]-3-chloro-2(5H)-furanones, Including Rubrolide M

Having found a good route to compounds **13**, next we turned our attention to their use in the preparation of rubrolide M (**14a**) and some of its non-natural congeners characterized by methoxyaryl moieties. To this end, we examined the possibility of using a procedure similar to that recently employed to prepare compounds **17a** and **17b** starting from 4-(4-methoxyphenyl)-2(5*H*)-furanone.[28] It should be noted that we successfully employed this procedure recently for the preparation of several (*Z*)-4-aryl-5-[1-(aryl)-methylidene]-3-bromo-2(5*H*)-furanones **7**,[10] including a compound whose structure corresponds to that reported in the literature for rubrolide N (**7a**).[3] Thus, compound **13** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), *N*,*N*-diisopropylethylamine and an aryl aldehyde **21**, and the mixture was treated with DBU and then with 3 M HCl to give the required compound **14** stereoselectively (Scheme 4). Compounds **14e** and **14h** were prepared by this procedure in 46 and 43% yield, respectively, from reaction of **21a** with **13d** and **13b**, respectively (Table 3, Entries 1 and 4).

On the other hand, compounds **14f** and **14g** were similarly prepared in 65 and 51% yield, respectively, by reaction of **21b** with **13b** and **13d**, respectively (Table 3, Entries 2 and 3). An attempt to prepare **14i** from **13b** and **21c** according to this procedure was fruitless, however, with the desired compound being obtained in a negligible GLC yield (Table 3, Entry 5). Moreover, another attempt to synthesize **14i** by a protocol very similar to that previously employed to prepare cardenolide **23** from **22** (Figure 3)[42] was also unsuccessful. In fact, no desired compound **14i** was obtained and only the loss of **13b** was observed.



Scheme 4. Synthesis of compounds **14e−i** from **13b,d** and aryl aldehydes **21a−c**

Table 3. Synthesis of (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones **14e−i** by introduction of a 1-(aryl)methylidene unit at the C-5 position of compounds **13b** and **13d**

Entry[a]	Reagents Compound 13	X	Aldehyde 21	Y	Z	Product 14	Isolated yield (%)
1	**13d**	H	**21a**	Br	H	**14e**	46
2	**13b**	Cl	**21b**	H	H	**14f**	65
3	**13d**	H	**21b**	H	H	**14g**	51
4	**13b**	Cl	**21a**	Br	H	**14h**	43
5	**13b**	Cl	**21c**	Br	Br	**14i**	n.d.

[a] These syntheses were performed using the experimental conditions indicated in Scheme 4.

The first total synthesis of rubrolide M (**14a**) was then completed by treatment of **14e** with 9.0 equiv. of BBr_3 in

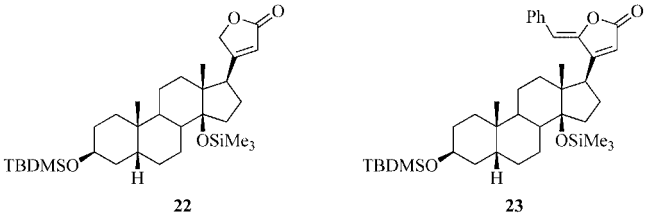
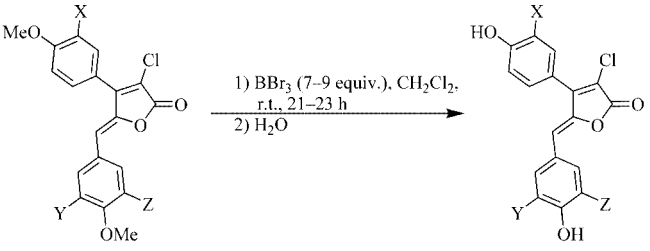


Figure 3. Chemical structures of compounds **22** and **23**



14e : X = Z = H; Y = Br
14f : X = Cl; Y = Z = H

14a : X = Z = H; Y = Br
14j : X = Cl; Y = Z = H

Scheme 5. Demethylation reaction of compounds **14e** and **14f**

CH_2Cl_2 followed by hydrolysis (Scheme 5). This demethylation reaction furnished **14a**, in 97% yield, having spectral properties in good agreement with those reported for the natural product.[3] Compound **14f** gave compound **14j** in 98% yield under similar reaction conditions (Scheme 5).

Synthesis of 3,4-Diaryl-2(5H)-furanones

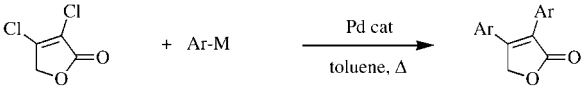
Although several methods have been reported in the literature for the preparation of 3,4-diaryl-2(5*H*)-furanones,[10,23,27,43–48] we decided to study the synthesis of these biologically interesting compounds by Pd-catalysed reactions between **12** or compounds **13** and arylboronic acids **18** or aryl(tributyl)tins **20**. Since the procedures to be used involved C–C bond-forming reactions at the unactivated 3-position of the 2(5*H*)-furanone derivatives, which were intermediates of these coupling reactions or were used as starting materials, we examined the use of some catalyst systems and experimental conditions previously employed successfully for Suzuki-[49] and Stille-type reactions[50] involving unactivated or deactivated aryl or vinyl chlorides. Thus, we investigated the synthesis of symmetrical 3,4-diaryl-2(5*H*)-furanones **4c** and **4d** by reaction of **12** with 3.0 equiv. of **18a** and **18d**, respectively, in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu_3P[49a][49l] and we found that these reactions, when performed in toluene at 85 °C, furnished **4c** and **4d** in 63 and 67% yield, respectively (Table 4, Entries 1 and 2).[51]

Toluene was found to be the solvent of choice since the reactions performed in THF or dioxane furnished large amounts of biaryl **19** derived from self-coupling of arylboronic acids **18**. On the other hand, as shown in Entry 3 of Table 4, **4c** was prepared in 60% yield by reaction of **12** with **20a** in toluene at 95 °C in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu_3P.[49b]

Next we investigated the synthesis of unsymmetrical 3,4-diaryl-2(5*H*)-furanones by Suzuki- and Stille-type reactions involving compounds **13**. As shown in Table 5 – which summarizes the reagents, the experimental conditions used and the results obtained in the synthesis of compounds **4a** and **4e–j** – four of these compounds, i.e., **4e**, **4f**, **4g**, and **4h**, are characterised by a 3,4,5-trimethoxyphenyl group at C-3 of their 2(5*H*)-furanone ring. In fact, this group seems to be essential for the cytotoxicity of 2(5*H*)-furanone derivatives against murine and human tumor cell lines.[52] Moreover, the 3,4,5-trimethoxy substituent in a phenyl ring of combretastatin A-4 (**15**) has been demonstrated to be essential for the bioactivity of this substance,[53] of which compounds **4** can be considered (*Z*)-restricted analogues. The other two unsymmetrical 3,4-diaryl-2(5*H*)-furanones that we synthesized were **4a** and **4i**, which are structurally related to **4f** and **4g**. As shown in Table 5, the catalyst system consisting of $[Pd_2(dba)_3]$ and tBu_3P was suitable for the reaction of **18f** with **13a**, **13d**, **13g** and **13h** in toluene in the presence of KF and furnished **4e**, **4f**, **4g** and **4h** in 42, 58, 58 and 39% yield, respectively (Table 5, Entries 1, 2, 4 and 5).

We also made an attempt to prepare **4h** in a higher yield by using the air-stable palladacycle, [chloro{bis(2-norbornyl)phosphanyl}(2′-dimethylamino-1,1′-biphenyl-2-

Table 4. Synthesis of symmetrical 3,4-diaryl-2(5*H*)-furanones **4**

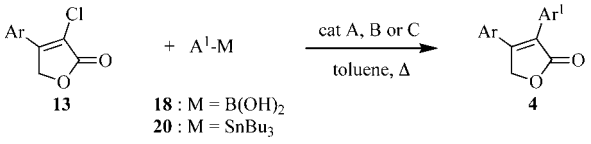


18 : M = $B(OH)_2$
20 : M = $SnBu_3$

Entry[a]	Organometallic compounds			Catalyst system[b]	Reaction conditions [h; °C]	Product	
	18 or **20**	Ar	M			**4**	Yield (%)
1	**18a**	C_6H_5	$B(OH)_2$	A	42; 85	**4c**	63
2	**18d**	4-$MeOC_6H_4$	$B(OH)_2$	A	46; 85	**4d**	67
3	**20a**	C_6H_5	$SnBu_3$	B	114; 95	**4c**	60

[a] All these reactions were carried out in toluene using 3.0 equiv. of **18** or **20**. The reactions involving **18** were performed in the presence of 3.0 equiv. of KF, and the reactions involving **20** were performed in the presence of 2.0 equiv. of KF. [b] Catalyst system A: $Pd_2(dba)_3$ (2.5 mol %), tBu_3P (5 mol %). Catalyst system B: $Pd(OAc)_2$ (5 mol %), Cy_3P (10 mol %).

Table 5. Synthesis of unsymmetrical 3,4-diaryl-2(5*H*)-furanones **4**

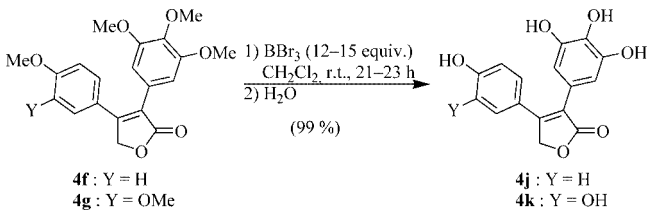


Entry[a]	Organic electrophile 13	Ar	Organometallic compounds 18 or 20	Ar^1	M	Catalyst system[b]	Reaction conditions [h; °C]	Product 4	Yield (%)
1	**13a**	C_6H_5	**18f**	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	A	22; 85	**4e**	42
2	**13d**	4-$MeOC_6H_4$	**18f**	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	A	45; 85	**4f**	58
3	**13d**	4-$MeOC_6H_4$	**18f**	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	C	28; 85	**4f**	14
4	**13g**	3,4-$(MeO)_2C_6H_3$	**18f**	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	A	47; 85	**4g**	58
5	**13h**	2-naphthyl	**18f**	3,4,5-$(MeO)_3C_6H_2$	$B(OH)_2$	A	45; 85	**4h**	39
6	**13d**	4-$MeOC_6H_4$	**20f**	3,4-$(MeO)_2C_6H_3$	$SnBu_3$	B	50; 95	**4i**	46
7	**13e**	4-$MeSC_6H_4$	**20a**	C_6H_5	$SnBu_3$	B	55; 95	**4a**	26
	13e	4-$MeSC_6H_4$	**18a**	C_6H_5	$B(OH)_2$	C	23; 95	**4a**	25

[a] All these reactions were carried out in toluene using 1.5 equiv. of **18** or **20**. The reactions involving **18** were performed in the presence of 3.0 equiv. of KF and those involving **20** were performed in the presence of 2.0 equiv. of KF. [b] Catalyst system A: $[Pd_2(dba)_3]$ (2.5 mol %), tBu$_3$P (5 mol %). Catalyst system B: $[Pd(OAc)_2]$ (5 mol %), Cy_3P (10 mol %). Catalyst system C: [chloro{bis(2-norbornyl)phosphanyl}(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II)] (1 mol %).

yl)palladium(II)], as the catalyst precursor. In fact, this complex has been reported to catalyse efficiently the reaction of 4-chloroanisole with **18a**.[49e] The reaction between **13d** and **18f** in toluene at 85 °C in the presence of KF and 1 mol % of this palladacycle, however, gave **4f** in only 14% yield (Table 5, Entry 3). On the other hand, the use of the catalyst system consisting of $[Pd(OAc)_2]$ and Cy_3P allowed the preparation of compounds **4i** and **4a** in 46 and 26% yield, respectively, by treatment of **13d** and **13e** with **20f** and **20a**, respectively (Table 5, Entries 6 and 7). Compound **4a** was also synthesized in 25% yield by reaction of **13e** with **18f** in the presence of KF and 1 mol % of [chloro{bis(2-norbornyl)phosphanyl}(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II)] (Table 5, Entry 8).

Finally, compounds **4f** and **4g** were treated with a large molar excess of BBr_3 in CH_2Cl_2, followed by hydrolysis (Scheme 6), to evaluate the cytotoxic activities of unsymmetrical 3,4-diaryl-2(5*H*)-furanones characterised by hydroxy groups in their aromatic rings. These reactions provided compounds **4j** and **4k** in almost quantitative yield and having chemical purity greater than 96%.



Scheme 6. Demethylation reaction of compounds **4f** and **4g**

Biological Results

The cytotoxic activities of compounds **13a**, **14a**, **14e**, **14f**, **14g**, **14h**, **14j**, **4e**, **4g**, **4j**, and **4k** were evaluated in vitro against the National Cancer Institute (NCI) three-cell-line panel consisting of MCF-7 (breast), SF-268 (CNS) and NCI-H460 (lung). The protocol used involved inoculation and pre-incubation of each cell line on a microtiter plate. Test agents were then added at a single concentration (1.00×10^{-4} M) and the culture incubated for 48 h. End-point determinations were made with sulforhodamine B, a protein-binding dye. Results for each test (Table 6) are reported as the percentage of growth of the treated cells when compared to the untreated control cells. Compounds that reduced the growth of any one of the cell lines to 32% or less were considered to be active and some of them were passed

Table 6. Primary anticancer assay of some compounds of general formula **13**, **14** and **4**

Entry	Compound	Percentage of growth inhibition NCI-H460 (lung)	MCF-7 (breast)	SF-268 (CNS)	Activity
1	**13a**	91	88	31	active
2	**14a**	0	1	1	active
3	**14e**	88	67	97	inactive
4	**14f**	20	10	20	active
5	**14g**	89	15	32	active
6	**14h**	62	65	3	active
7	**14j**	0	0	1	active
8	**4e**	8	29	32	active
9	**4g**	4	8	14	active
10	**4j**	0	0	32	active
11	**4k**	0	1	62	active

on for evaluation in the full panel of 60 cell lines over a 5-log dose range.[54]

Results from Table 6 indicate that all tested compounds, except **14e**, passed the three-cell-line primary screening, but that only **14a**, **14f**, **14j**, **4e**, **4g** and **4j** were significantly cytotoxic against all three cell lines (Entries 2, 4, 7−10). On the other hand, **4k** showed strong cytotoxic activity against NCI-H-460 and MCF-7, but not against the SF-268 cell line (Entry 11), and compounds **13a**, **14g** and **14h** exhibited limited cytotoxicity. In fact, **13a** and **14h** reduced the growth of the SF-268 cell line only to less than 32% (Entries 1 and 6 and **14g** reduced, to a limited extent, either the MCF-7 or the SF-268 cell line (Entry 5). With regard to the cytotoxicity of the (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones **14**, the data of Table 6 seem also to suggest that, as previously observed for (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-bromo-2(5*H*)-furanones **7**,[24] the presence of phenol subunits is necessary for compounds **14** to exhibit high cytotoxic activities. Moreover, these data also show that: (i) compounds **14** containing methoxyaryl subunits are less potent than the corresponding substances characterised by phenol subunits (compare Entries 3 and 2 or Entries 4 and 7); (ii) the highly cytotoxic compounds reported in Table 6 include some unsymmetrical 3,4-diaryl-2(5*H*)-furanones **4**; i.e., some substances that belong to a class of compounds well known previously as selective COX-2 inhibitors.

Compounds **13a**, **14a**, **14f**, **14g**, **14h** and **14j** were then tested in the USNCI's human tumor cell-line screen.[54] The recorded data showed, however, that all the tested compounds exhibited limited cytotoxic activitites, displaying MGM values of log GI_{50} between −4.05 (for **14g**) and −4.60 (for **13a**).

Conclusion

We have shown for the first time that 3,4-dichloro-2(5*H*)-furanone, which can be prepared efficiently from inexpensive, commercially available mucochloric acid, can undergo regioselective Suzuki- or Stille-type reactions to provide 4-aryl-3-chloro-2(5*H*)-furanones in satisfactory yields. We have also demonstrated that these highly functionalised compounds are useful precursors either to a variety of (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones, including naturally occurring rubrolide M, or to unsymmetrical 3,4-diaryl-2(5*H*)-furanones. Moreover, we have shown that some typical symmetrical 3,4-diaryl-2(5*H*)-furanones can be prepared in satisfactory yields by Pd-catalysed reactions of 3,4-dichloro-2(5*H*)-furanone with a large molar excess of arylboronic acids and aryl(tributyl)tin reagents. Interestingly, some 2(5*H*)-furanone derivatives, including unsymmetrical 3,4-diaryl-2(5*H*)-furanones and (*Z*)-4-aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones, are active in the NCI three-cell-line, one-dose, primary anticancer assay. (*Z*)-4-Aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones were found, however, to exhibit limited cytotoxicity against the NCI 60-cell-line panel.

Experimental Section

General Remarks: Melting and boiling points are uncorrected. Precoated Merck 60 F_{254} aluminium silica gel sheets were used for TLC analyses. GLC analyses were performed with a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani DDS 1000 data station. Two types of capillary columns were used: Alltech AT-35 bonded FSOT column (30 m × 0.25 mm i.d.) and Alltech AT-1 bonded FSOT column (30 m × 0.25 mm i.d). Purifications by MPLC on silica gel (Merck 60 silica gel, particle size 0.015−0.040 mm) were performed with a Büchi B-680 system and a Knauer K-2400 differential refractometer as detector. GLC/EI-MS analyses were performed with a Q-mass 910 spectrometer interfaced with a Perkin−Elmer 8500 gas chromatograph. The HPLC-MS measurements involving **4g** were performed using a Perkin−Elmer 200 liquid chromatograph interfaced with a Perkin−Elmer Sciex API III plus triple-quadrupole mass spectrometer. In these measurements, the HPLC analyses were performed using a Supelco Discovery C 18 column (15 cm × 4.6 mm × 4 μm) and two solvents, A and B, respectively, as mobile phase. Solvent A was a 5 mM aqueous solution of ammonium acetate and solvent B was acetonitrile saturated with ammonium acetate. The operative conditions were: 100% A for 5 min; a linear gradient for 30 min until 100% B; 100% B for 5 min. The APCI-mass spectrum was recorded using the following operative parameters: discharge current: 3 μA; temperature of the nebulizer: 500 °C; orifice voltage: 60 V; scan range: 100−400 amu; step 0.2 amu; dwell time: 1 ms; scan time: 1.58 s; interscan delay: 0.052 ms; resolution > 1 amu. IR spectra were recorded with a Perkin−Elmer 1725 FT-IR spectrophotometer. NMR spectra were recorded with a Varian Gemini 200 MHz spectrometer with TMS as the internal standard. All reactions of air- and water-sensitive materials were performed in flame-dried glassware under argon by standard syringe, cannula and septa techniques. The following compounds were prepared by published procedures: 3-chloro-4-methoxyphenylboronic acid (**18b**),[55] tributyl(4-methoxyphenyl)tin (**20d**),[56] tributyl(4-methylthiophenyl)tin (**20e**),[57] tributyl(3,4-dimethoxyphenyl)tin (**20f**),[58] tributyl(4-chlorophenyl)tin (**20b**),[59] tributyl(2-naphthyl)tin (**20g**).[60]

3,4-Dichloro-2(5*H*)-furanone (12): Sodium borohydride (6.24 g, 165.0 mmol) was added in a portionwise manner to a stirred solution of mucochloric acid (**16**) (18.47 g, 110.0 mmol) in methanol (165 mL), which was cooled to 0 °C, and the mixture was stirred for an additional 30 min. A solution of concentrated sulfuric acid (10.78 g, 110.0 mmol) in methanol (55 mL), which was cooled to 0 °C, was added and the resulting mixture, which was kept cold for an additional 10 min, was then concentrated at room temperature under reduced pressure. The residue was treated with brine (800 mL) and extracted with diethyl ether (5 × 300 mL). The organic extract was dried and concentrated under reduced pressure and the solid residue was recrystallised from a mixture of pentane and diethyl ether (1:1) to give chemically pure **12** (14.97 g, 89%) as a colourless solid; m.p. 49−50 °C (m.p.[36] 49.5−50 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.88 (s, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.9, 121.0, 148.9, 165.7 ppm. The spectral properties of this compound are in satisfactory agreement with those reported.[36]

Synthesis of 4-Aryl-3-chloro-2(5*H*)-furanones 13 by Pd-Catalysed Cross-Coupling Reactions between 12 and Arylboronic Acids 18. Method A: A flame-dried reaction vessel, flushed with argon, was charged with **12** (0.40 g, 2.61 mmol), an arylboronic acid **18** (2.74 mmol), [$Pd_2(dba)_3$] (59 mg, 0.065 mmol), (*o*-tolyl)$_3$P (79 mg,

0.26 mmol) and KF (0.45 g, 7.83 mmol) in de-aerated dry toluene (10 mL), and then the mixture, which was periodically monitored by GLC and TLC, was stirred at 85 °C for the period of time indicated in Table 1. After completion of the reaction (21−27 h), the mixture was cooled to room temperature, diluted with EtOAc (150 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel or by recrystallisation. Compounds **13a−e** were prepared by this procedure (Table 1, Entries 1−5). **Method B:** A de-aerated mixture of compound **12** (0.46 g, 3.00 mmol), an arylboronic acid **18** (6.00 mmol), CsF (1.23 g, 8.10 mmol), $[PdCl_2(PPh_3)_2]$ (0.105 g, 0.15 mmol) and $BnEt_3N^+Cl^-$ (34 mg, 0.15 mmol), toluene (13 mL) and water (13 mL) was stirred at room temperature until compound **12** was completely consumed (7−8 d). The mixture was then partitioned between 2 M HCl (12 mL) and toluene (100 mL) and the toluene extract was concentrated under reduced pressure. The solid residue was purified by recrystallisation or by MPLC on silica gel. Compounds **13d** and **13e** were prepared by this procedure (Scheme 3).

3-Chloro-4-phenyl-2(5*H*)-furanone (13a): The crude product obtained from the Pd-catalysed reaction between **12** and phenylboronic acid (**18a**) according to Method A (Table 1, Entry 1) was purified by MPLC on silica gel with toluene as eluent to give **13a** (0.32 g, 63%) as a pale-yellow solid; m.p. 108−109 °C. EI-MS: *m*/*z* (%) = 196 (22) [M^+], 194 (70) [M^+], 165 (100), 137 (61), 105 (27), 101 (30), 75 (21). IR (KBr disk): $\tilde{\nu}$ = 1736, 1625, 1495, 1327, 1194, 1036, 767 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.22 (s, 2 H), 7.52 (m, 3 H), 7.80 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.1, 117.1, 127.1 (2 C), 128.6, 129.1 (2 C), 131.7, 151.7, 169.0 ppm. $C_{10}H_7ClO_2$ (194.62): calcd. C 61.71, H 3.62; found C 61.92, H 3.67.

3-Chloro-4-(3-chloro-4-methoxyphenyl)-2(5*H*)-furanone (13b): The crude product obtained from the Pd-catalysed reaction between **12** and 3-chloro-4-methoxyphenylboronic acid (**18b**) according to Method A (Entry 2, Table 1) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and hexane (70:30, + 1% EtOAc) as eluent to give **13b** (0.38 g, 57%) as a colourless solid; m.p. 153−154 °C. EI-MS: *m*/*z* (%) = 260 (65) [M^+], 258 (100) [M^+], 231 (38), 229 (59), 185 (23), 166 (25), 157 (18). IR (KBr disk): $\tilde{\nu}$ = 1765, 1615, 1510, 1330, 1265, 1039, 832 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.98 (s, 3 H), 5.18 (s, 2 H), 7.05 (d, *J* = 8.8 Hz, 1 H), 7.75 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.84 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.4, 69.8, 116.1, 121.9, 123.5, 127.3, 129.0, 149.9, 157.4, 168.9 ppm. $C_{11}H_8Cl_2O_3$ (259.09): calcd. C 50.99, H 3.11; found C 50.81, H 3.04.

3-Chloro-4-(4-chlorophenyl)-2(5*H*)-furanone (13c): The crude product obtained from the Pd-catalysed reaction between **12** and 4-chlorophenylboronic acid (**18c**) according to Method A (Table 1, Entry 3) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and hexane (80:20, + 1% EtOAc) as eluent to give **13c** (0.25 g, 42%) as a pale-yellow solid; m.p. 168−170 °C. EI-MS: *m*/*z* (%) = 230 (49) [M^+], 228 (76) [M^+], 199 (100), 139 (24), 136 (51), 99 (22), 74 (19). IR (KBr disk): $\tilde{\nu}$ = 1746, 1619, 1493, 1320, 1198, 1041, 825 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.21 (s, 2 H), 7.50 (m, 2 H), 7.56 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 69.9, 117.7, 127.0, 128.4 (2 C), 129.5 (2 C), 137.9, 150.4, 168.7 ppm. $C_{10}H_6Cl_2O_2$ (229.06): calcd. C 52.43, H 2.64; found C 52.28, H 2.49.

3-Chloro-4-(4-methoxyphenyl)-2(5*H*)-furanone (13d): The crude product obtained from the Pd-catalysed reaction between **12** and 4-methoxyphenylboronic acid (**18d**) according to Method A (Table 1, Entry 4) was purified by recrystallisation from a mixture of CH_2Cl_2 and petroleum ether to give **13d** (0.36 g, 61%) as a colourless solid; m.p. 174−175 °C. EI-MS: *m*/*z* (%) = 226 (34) [M^+], 224 (100) [M^+], 195 (74), 167 (32), 151 (15), 132 (30), 102 (10). IR (KBr disk): $\tilde{\nu}$ = 1758, 1605, 1512, 1334, 1186, 1033, 829 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 5.19 (s, 2 H), 7.01 (m, 2 H), 7.01 (m, 2 H), 7.47 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.5, 70.0, 114.6 (2 C), 121.1, 129.0 (2 C), 130.5, 151.2, 162.1, 169.3 ppm. $C_{11}H_9ClO_3$ (224.64): calcd. C 58.81, H 4.04; found C 59.02, H 4.03. This compound was also prepared in 80% yield using Method B.

3-Chloro-4-(4-methylthiophenyl)-2(5*H*)-furanone (13e): The crude product obtained from the Pd-catalysed reaction between **12** and 4-methylthiophenylboronic acid (**18e**) according to Method A (Table 1, Entry 5) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and petroleum ether (90:10, + 1% EtOAc) as eluent to give **13e** (0.21 g, 33%) as a pale-yellow solid: m.p. 161−163 °C. EI-MS: *m*/*z* (%) = 242 (41) [M^+], 240 (100) [M^+], 213 (13), 211 (36), 167 (12), 148 (22), 74 (9). IR (KBr disk): $\tilde{\nu}$ = 1759, 1622 1493, 1069, 1031, 1011, 817 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 5.20 (s, 2 H), 7.32 (m, 2 H), 7.73 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 69.9, 116.0, 124.6, 125.6 (2 C), 127.3 (2 C), 144.5, 151.0, 169.1 ppm. $C_{11}H_9ClO_2S$ (240.71): calcd. C 54.89, H 3.77; found C 54.74; H 3.65. This compound was also prepared in 83% yield using Method B.

Synthesis of 4-Aryl-3-chloro-2(5*H*)-furanones 13 by Pd-Catalysed Cross-Coupling Reaction between 12 and Aryl(tributyl)tin Reagents 20: A flame-dried reaction vessel, flushed with argon, was charged with **12** (2.40 g, 2.61 mmol), $[Pd_2(dba)_3]$ (60 mg, 0.065 mmol), $(o\text{-tolyl})_3P$ (73 mg, 0.261 mmol) and de-aerated NMP (10 mL). A de-aerated solution of an aryl(tributyl)tin reagent **20** (2.74 mmol) in NMP (5 mL) was added and the resulting mixture, which was periodically monitored by GLC, was stirred under argon at 85 °C for the period of time indicated in Table 2. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (150 mL), stirred at room temperature for 4.5 h in the presence of KF (1.52 g, 26.1 mmol) and filtered through Celite. The filtrate was washed with water (50 mL), dried and concentrated under reduced pressure. The residue, which was analysed by GLC and GLC/MS, was purified by MPLC on silica gel or by recrystallisation. This general procedure was used to prepare compounds **13a**, **13c**, **13d**, **13e**, **13f** and **13g**. Table 2 summarizes the reaction times, the molar ratios between compounds **13** and the symmetrical 3,4-diaryl-2(5*H*)-furanones **4** obtained as by-products of the cross-coupling reactions, as well as the isolated yields of compounds **13**. It should be noted that the physical and spectral properties of compounds **13a**, **13c**, **13d** and **13e** (Table 2, Entries 1, 2, 3 and 4, respectively) are in agreement with those of the same compounds obtained by Pd-catalysed reaction of **12** with arylboronic acids **18a**, **18c**, **18d** and **18e**, respectively. As shown in Table 2, the Pd-catalysed reactions of **12** with **20a**, **20b**, **20d** and **20e** furnished compounds **13a**, **13c**, **13d** and **13e**, respectively, in 53, 61, 78 and 73% yield, respectively.

3-Chloro-4-(2-thienyl)-2(5*H*)-furanone (13f): The crude product obtained from the Pd-catalysed reaction between **12** and tributyl(2-thienyl)tin (**20c**) (Entry 5, Table 2) was purified by MPLC on silica gel with a mixture of toluene and EtOAc (97:3) as eluent to give **13f** (0.29 g, 55%) as a colourless solid; m.p. 126−127 °C. EI-MS: *m*/*z* (%) = 202 (38) [M^+], 200 (100) [M^+], 173 (35), 171 (93), 143 (46), 108 (28), 63 (10). IR (KBr disk): $\tilde{\nu}$ = 1777, 1760, 1621, 1346, 1184, 1035, 747 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.22 (s, 2 H), 7.23 (dd, *J* = 5.1, 3.7 Hz, 1 H), 7.53 (dd, *J* = 3.7, 1.1 Hz, 1 H), 7.73 (dd, *J* = 5.1, 1.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz,

$CDCl_3$): δ = 69.5, 114.25, 127.8, 129.3, 130.7, 131.8, 146.9, 168.5 ppm. $C_8H_5ClO_2S$ (200.64): calcd. C 47.89, H 2.51; found C 48.02, H 2.58.

3-Chloro-4-(3,4-dimethoxyphenyl)-2(5*H*)-furanone (13g): The crude product obtained from the Pd-catalysed reaction between **12** and tributyl(3,4-dimethoxyphenyl)tin (**20f**) (Table 2, Entry 6) was purified by recrystallisation from a mixture of CH_2Cl_2 and hexane to give **13g** (0.50 g, 75%) as a light-brown solid; m.p. 179−180 °C. EI-MS: *m*/*z* (%) = 256 (32) [M^+], 254 (100) [M^+], 239 (12), 220 (15), 147 (20), 131 (11), 89 (12). IR (KBr disk): ṽ = 1771, 1615, 1519, 1291, 1162, 1036, 747 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 3.96 (s, 3 H), 5.22 (s, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.31 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.51 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.1 (2 C), 70.1, 110.0, 111.1, 114.9, 121.0, 121.4, 149.3, 151.5, 152.1, 169.5 ppm. $C_{12}H_{11}ClO_4$ (254.67): calcd. C 56.60, H 4.35; found C 56.54, H 4.27.

3-Chloro-4-(2-naphthyl)-2(5*H*)-furanone (13h): The crude product obtained from the Pd-catalysed reaction between **12** and tributyl(2-naphthyl)tin (**20g**) (Table 2, Entry 7) was purified by recrystallisation from a mixture of CH_2Cl_2 and hexane to give **13h** (0.43 g, 67%) as a pale-brown solid; m.p. 193−194 °C. EI-MS: *m*/*z* (%) = 246 (33) [M^+], 244 (100) [M^+], 217 (23), 215 (69), 187 (12), 152 (66), 75 (17). IR (KBr disk): ṽ = 1758, 1611, 1504, 1248, 1039, 820, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.31 (s, 2 H), 7.60 (m, 2 H), 7.92 (m, 4 H), 8.25 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.2, 123.1, 126.0, 127.2, 127.7, 127.9, 128.3, 128.8, 128.9, 132.6, 133.8, 134.3, 151.6, 169.1 ppm. $C_{14}H_9ClO_2$ (248.68): calcd. C 67.62, H 3.65; found C 67.49, H 3.59.

General Procedure for the Synthesis of (*Z*)-4-Aryl-5-[1-(aryl)methylidene]-3-chloro-2(5*H*)-furanones 14 Starting from Compounds 13 and Aryl Aldehydes 21: A solution of a compound **13** (1.66 mmol) in CH_2Cl_2 (5 mL) was sequentially treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.53 g, 1.99 mmol), *N*,*N*-diisopropylethylamine (0.87 mL, 4.98 mmol) and an arylaldehyde **21** (1.99 mmol), and the resulting mixture was stirred under argon at room temperature for 2 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.50 mL, 3.32 mmol) was then added, and the mixture, which was periodically monitored by TLC analysis, was stirred at room temperature for 5 h. The mixture was then diluted with CH_2Cl_2 (60 mL) and washed with 3 M HCl (2 × 15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the organic extract was washed with brine (3 × 20 mL) until neutrality, dried and concentrated under reduced pressure. The solid residue was purified by recrystallisation and/or by MPLC on silica gel. This procedure was employed to prepare compounds **14e**, **14f**, **14g** and **14h** (Entries 1−4, Table 3).

(*Z*)-5-[1-(3-Bromo-4-methoxyphenyl)methylidene]-3-chloro-4-(4-methoxyphenyl)-2(5*H*)-furanone (14e): The crude product obtained from the reaction between **13d** and 3-bromo-4-methoxybenzaldehyde (**21a**) (Table 3, Entry 1) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and hexane (70:30, + 1% EtOAc) as eluent. The chromatographic fractions containing **14e** were collected and concentrated under reduced pressure and the solid residue was recrystallised from a mixture of $CHCl_3$ and hexane to give **14e** (0.32 g, 46%) as a pale-yellow solid; m.p. 195−196 °C. EI-MS: *m*/*z* (%) = 424 (27) [M^+], 423 (21) [M^+], 422 (100) [M^+], 421 (17) [M^+], 228 (13), 211 (34), 119 (22). IR (KBr disk): ṽ = 1769, 1607, 1498, 1253, 1179, 1009, 839 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 3.94 (s, 3 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 7.07 (m, 2 H), 7.49 (m, 2 H), 7.77 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.91 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4, 56.3, 111.8, 112.0, 112.8, 114.4 (2 C), 117.2, 120.0, 126.7, 130.6 (2 C), 131.3, 135.4, 145.6, 149.4, 156.5, 161.2, 164.5 ppm. $C_{19}H_{14}BrClO_4$ (421.75): calcd. C 54.11, H 3.35; found C 53.95, H 3.06.

(*Z*)-3-Chloro-4-(3-chloro-4-methoxyphenyl)-5-[1-(4-methoxyphenyl)-methylidene]-2(5*H*)-furanone (14f): The crude product obtained from the reaction between **13b** and 4-methoxybenzaldehyde (**21b**) (Table 3, Entry 2) was recrystallised from a mixture of CH_2Cl_2 and petroleum ether to give **14f** (0.41 g, 65%) as a pale-yellow solid; m.p. 148−150 °C. EI-MS: *m*/*z* (%) = 380 (12) [M^+], 379 (14) [M^+], 378 (67) [M^+], 377 (22) [M^+], 376 (100) [M^+], 148 (28), 91 (16). IR (KBr disk): ṽ = 1764, 1605, 1498, 1265, 1178, 1019, 824 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 4.00 (s, 3 H), 6.08 (s, 1 H), 6.91 (m, 2 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 7.43 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 7.73 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4, 56.3, 112.1, 114.4 (2 C), 114.6, 117.3, 121.0, 123.2, 125.2, 128.9, 130.1, 132.6 (2 C), 144.5, 148.3, 156.5, 160.7, 164.4 ppm. $C_{19}H_{14}Cl_2O_2$ (377.22): calcd. C 60.50, H 3.74; found C 60.59, H 3.95.

(*Z*)-3-Chloro-4-(4-methoxyphenyl)-5-[1-(4-methoxyphenyl)methylidene]-2(5*H*)-furanone (14g): The crude product obtained from the reaction between **13d** and 4-methoxybenzaldehyde (**21b**) (Table 3, Entry 3) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and hexane (50:50, + 1% EtOAc) as eluent. The chromatographic fractions containing **14g** were collected and concentrated and the solid residue was recrystallised from a mixture of CH_2Cl_2 and hexane to give pure **14g** (0.29 g, 51%) as a pale-yellow solid; m.p. 169−170 °C. EI-MS: *m*/*z* (%) = 345 (22) [M^+], 343 (100) [M^+], 299 (3), 252 (8), 167 (2), 51 (4), 39 (12). IR (KBr disk): ṽ = 1772, 1605, 1504, 1259, 1181, 1018, 826 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.90 (s, 3 H), 6.12 (s, 1 H), 6.90 (m, 2 H), 7.07 (m, 2 H), 7.49 (m, 2 H), 7.73 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.3, 55.4, 114.3 (4 C), 114.5, 116.5, 120.3, 125.4, 130.6 (2 C), 132.5 (2 C), 144.8, 149.6 160.5, 161.1, 164.8 ppm. $C_{19}H_{15}ClO_4$ (342.78): calcd. C 66.58, H 4.41; found C 66.49, H 4.35.

(*Z*)-5-[1-(3-Bromo-4-methoxyphenyl)methylidene]-3-chloro-4-(3-chloro-4-methoxyphenyl)-2(5*H*)-furanone (14h): The crude product obtained from the reaction between **13b** and **21a** (Table 3, Entry 4) was purified by MPLC on silica gel with a mixture of $CHCl_3$ and hexane (50:50, + 1% EtOAc) as eluent. The chromatographic fractions containing **14h** were collected and concentrated under reduced pressure and the residue was recrystallised from a mixture of CH_2Cl_2 and hexane (ca. 1.5:1) to give pure **14h** (0.33 g, 43%) as a pale-yellow solid; m.p. 215−217 °C. EI-MS: *m*/*z* (%) = 458 (42) [M^+], 457 (100) [M^+], 456 (47) [M^+], 455 (42) [M^+], 210 (19). IR (KBr disk): ṽ = 1784, 1606, 1499, 1288, 1271, 1009, 818 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 4.00 (s, 3 H), 6.01 (s, 1 H), 6.91 (d, *J* = 8.7 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 1 H), 7.42 (dd, *J* = 8.7, 2.2 Hz, 1 H), 7.56 (d, *J* = 2.2 Hz, 1 H), 7.77 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.92 (d, *J* = 1.8 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.3 (2 C), 111.8, 112.1 (2 C), 112.8, 118.1, 120.7, 123.3, 126.5, 128.9, 130.7, 131.4, 135.5, 145.2, 148.1, 156.6, 156.7, 164.1 ppm. $C_{19}H_{13}BrCl_2O_4$ (456.12): calcd. C 50.03, H 2.87; found C 49.95, H 2.79.

Demethylation of 14e. Synthesis of (*Z*)-5-[1-(3-Bromo-4-hydroxyphenyl)methylidene]-3-chloro-4-(4-hydroxyphenyl)-2(5*H*)-furanone (Rubrolide M) (14a): A 1 M solution of BBr_3 in CH_2Cl_2 (2.13 mL, 2.13 mmol) was added to a solution of **14e** (0.10 g, 0.24 mmol) in dry CH_2Cl_2 (8 mL) stirred at −78 °C. The mixture was warmed to room temperature and stirred for 23 h. Water (10 mL) was then added and the mixture was extracted with EtOAc (4 × 25 mL).

The organic extract was washed with brine (15 mL), dried and concentrated under reduced pressure, and then the solid residue was purified by MPLC on silica gel with a mixture of $CHCl_3$ and methanol (96:4) as eluent. The chromatographic fractions containing **14a** were collected and concentrated under reduced pressure and the solid residue was recrystallised from a mixture of ethanol and water (ca. 5:1) to give pure **14a** (92 mg, 97%) as a yellow solid; m.p. 227−230 °C. IR (KBr disk): $\tilde{\nu}$ = 3473, 1750, 1611, 1509, 1246, 1163, 837 cm^{-1}. ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 6.29 (s, 1 H), 7.06 (m, 3 H), 7.53 (m, 2 H), 7.74 (dd, *J* = 8.8, 2.2 Hz, 1 H), 8.06 (d, *J* = 2.2 Hz, 1 H), 9.29 (br. s, 2 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.7, 113.4, 116.7 (2 C), 116.9, 117.5, 119.8, 127.3, 131.8 (2 C), 132.4, 136.2, 146.3, 150.8, 155.9, 160.3, 164.6 ppm. $C_{17}H_{10}BrClO_4$ (393.61): calcd. C 51.87, H 2.56; found C 51.79, H 2.44.

Demethylation of 14f. Synthesis of (*Z*)-3-Chloro-4-(3-chloro-4-hydroxyphenyl)-5-[1-(4-hydroxyphenyl)methylidene]-2(5*H*)-furanone (14j): A 1 M solution of BBr_3 in CH_2Cl_2 (3.71 mL, 3.71 mmol) was added to a solution of **14f** (0.20 g, 0.53 mmol) in dry CH_2Cl_2 (15 mL) that was stirred at −78 °C. The mixture was warmed to room temperature, stirred for 20 h and then worked up according to the same procedure used for the preparation of **14a**. The crude reaction product was purified by MPLC on silica gel, with a mixture of $CHCl_3$ and methanol (96:4) as eluent, to give **14j** (0.18 g, 98%) as a yellow solid; m.p. 266−270 °C. IR (KBr disk): $\tilde{\nu}$ = 3418, 1728, 1603, 1444, 1282, 1163, 829 cm^{-1}. ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 6.24 (s, 1 H), 6.89 (m, 2 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 7.39 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 10.15 (br. s, 1 H), 10.98 (br. s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 114.7, 115.1, 115.8 (2 C), 116.8, 119.0, 120.1, 123.5, 129.2, 130.4, 132.7 (2 C), 143.4, 148.6, 154.9, 158.9, 163.8 ppm. $C_{17}H_{10}Cl_2O_4$ (349.16): calcd. C 58.48, H 2.89; found C 58.32, H 2.77.

Synthesis of Symmetrical 3,4-Diaryl-2(5*H*)-furanones 4 by Pd-Catalysed Reaction of 12 with Arylboronic Acids 18 or Aryl(tributyl)tin Reagents 20: A flame-dried reaction vessel, flushed with argon, was charged with **12** (2.40 g, 2.61 mmol), an arylboronic acid **18** (7.83 mmol), KF (0.45 g, 7.83 mmol), [Pd$_2$(dba)$_3$] (59 mg, 0.065 mmol), a 1 M toluene solution of *t*Bu$_3$P (0.13 mL, 0.13 mmol) and de-aerated toluene (10 mL), and then the mixture, which was periodically monitored by GLC and TLC, was stirred at 85 °C for the period of time indicated in Table 4. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (150 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel. This procedure was used to prepare compounds **4c** and **4d** (Table 4, Entries 1 and 2). Compound **4c** was also prepared by reaction of **12** (0.19 g, 1.27 mmol) with tributyl(phenyl)tin (**20a**, 1.40 g, 3.81 mmol), KF (0.29 g, 5.08 mmol), [Pd$_2$(dba)$_3$] (29 mg, 0.032 mmol), a 1 M toluene solution of *t*Bu$_3$P (0.063 mL, 0.063 mmol) and de-aerated toluene (6.5 mL) at 95 °C for 114 h, followed by purification by MPLC on silica gel (Table 4, Entry 3).

3,4-Diphenyl-2(5*H*)-furanone (4c): The crude product obtained from the Pd-catalysed reaction between **12** and phenylboronic acid (**18a**) according to the above reported procedure (Table 4, Entry 1) was purified by MPLC on silica gel, with benzene as eluent, to give **4c** (0.39 g, 63%) as a yellow solid; m.p. 98−99 °C (m.p.[61] 104−105). EI-MS: *m*/*z* (%) = 236 (65) [M$^+$], 179 (100), 178 (67), 165 (8), 131 (13), 105 (28), 76 (9). IR (KBr disk): $\tilde{\nu}$ = 1752, 1638, 1159, 1062, 1029, 957, 789 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.16 (s, 2 H), 7.28−7.49 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.3, 125.7, 127.0 (2 C), 128.2 (2 C), 128.3, 128.5 (2 C), 128.8 (2 C), 129.7, 130.0, 130.3, 155.6, 172.8 ppm. $C_{16}H_{12}O_2$ (236.27): calcd. C 81.34, H 5.12; found C 81.27, H 5.06. Compound **4c** was also synthesized in 60% yield by Pd-catalysed reaction between **12** and tributyl(phenyl)tin (**20a**) according the above reported procedure (Table 4, Entry 3).

3,4-Bis(4-methoxyphenyl)-2(5*H*)-furanone (4d): The crude product obtained from the Pd-catalysed reaction between **12** and 4-methoxyphenylboronic acid (**18d**) according to the above reported procedure (Table 4, Entry 2) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (90:10, + 1% EtOAc) as eluent, to give **4d** (0.52 g, 67%) as a pale-yellow solid; m.p. 151−152 °C (m.p.[61] 144−146 °C). EI-MS: *m*/*z* (%) = 297 (22) [M$^+$ +1], 296 (100) [M$^+$], 239 (68), 224 (18), 219 (71), 135 (90), 121 (11). IR (KBr disk): $\tilde{\nu}$ = 1731, 1604, 1507, 1255, 1017, 962, 843 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 3.83 (s, 3 H), 5.13 (s, 2 H), 6.80−6.95 (m, 4 H), 7.38 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.2, 55.3, 70.3, 114.1 (2 C), 114.3 (2 C), 122.7, 123.2, 123.7, 128.9 (2 C), 130.5 (2 C), 154.4, 159.7, 161.1, 173.9 ppm. $C_{18}H_{16}O_4$ (296.32): calcd. 72.96, H 5.44; found C 72.90, H 5.41.

Synthesis of Unsymmetrical 3,4-Diaryl-2(5*H*)-furanones 4 by Pd-Catalysed Reaction of 4-Aryl-3-chloro-2(5*H*)-furanones 13 with Arylboronic Acids 18 or Aryl(tributyl)tin Reagents 20: A flame-dried reaction vessel, flushed with argon, was charged with a compound **13** (1.3 mmol), an arylboronic acid **18** (1.95 mmol), KF (0.11 g, 3.90 mmol), [Pd$_2$(dba)$_3$] (29 mg, 0.032 mmol), a 1 M toluene solution of *t*Bu$_3$P (0.065 mL, 0.065 mmol) and de-aerated toluene (8 mL), and the mixture, which was periodically monitored by GLC and TLC, was stirred at 85 °C until compound **13** was completely consumed. The mixture was then cooled to room temperature, diluted with EtOAc (150 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure and the solid residue was purified by recrystallisation or by MPLC on silica gel. This procedure was used to prepare compounds **4e**, **4f**, **4g** and **4h** (Entries 1, 2, 4 and 5, respectively, Table 5). On the other hand, compounds **4f** and **4a** were synthesized by cross-coupling reactions of **13d** and **13e** with 1.5 equiv. of **18f** and **18a**, respectively, in toluene at 85 °C in the presence of 1 mol % [chloro(di-2-norbornylphosphanyl)(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II)] and 3.0 equiv. of KF (Table 5, Entries 3 and 8). Moreover, as shown in Entries 6 and 7 of Table 5, compounds **4i** and **4a** were synthesized by Pd-catalysed reactions of **13d** and **13e**, respectively, with aryltin reagents **20f** and **20a**, respectively. The following procedure was used: A flame-dried reaction vessel, flushed with argon, was charged with a compound **13** (3.54 mmol), an aryl(tributyl)tin reagent **20** (5.32 mmol), [Pd(OAc)$_2$] (29.8 mg, 0.18 mmol), Cy$_3$P (99.3 mg, 0.35 mmol), KF (0.41 g, 7.10 mmol) and de-aerated toluene (18 mL). The resulting mixture was maintained at 95 °C for the period of time indicated in Table 5 and then it was cooled to room temperature, diluted with EtOAc (100 mL) and stirred at room temperature for 4.5 h in the presence of KF (3.08 g, 53.1 mmol). The mixture was then diluted with EtOAc (100 mL) and filtered through Celite. The filtrate was washed with water (50 mL), dried and concentrated under reduced pressure and the residue was purified by MPLC on silica gel.

4-Phenyl-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (4e): The crude product obtained from the reaction between **13a** and **18f** in the presence of catalytic amounts of [Pd$_2$(dba)$_3$] and *t*Bu$_3$P (Table 5, Entry 1) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and hexane (95:5, + 1% EtOAc) as eluent, to give **4e** (0.18 g, 42%) as a pale-orange solid; m.p. 155−156 °C. EI-MS: *m*/*z* (%) = 327 (21) [M$^+$ + 1], 326 (100) [M$^+$], 311 (25), 269 (14),

193 (25), 152 (21), 105 (71). IR (KBr disk): $\tilde{\nu}$ = 1738, 1639, 1510, 1249, 1130, 1007, 769 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.73 (s, 6 H), 3.87 (s, 3 H), 5.17 (s, 2 H), 6.67 (s, 2 H), 5.38 (br. s, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.0, (2 C), 60.9, 70.5, 106.2 (2 C), 125.2, 125.8, 127.5 (2 C), 128.9 (2 C), 130.5 (2 C), 130.8, 138.4, 153.2, 155.8, 173.2 ppm. $C_{19}H_{18}O_5$ (326.35): calcd. C 69.93, H 5.56; found C 69.87, H 5.48.

4-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (4f): The crude product obtained from the reaction between **13d** and **18f** in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu_3P (Table 5, Entry 2) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and EtOAc (95:5) as eluent, to give **4f** (0.27 g, 58%) as a yellow solid; m.p. 139−141 °C. EI-MS: *m*/*z* (%) = 357 (2) [M^+ + 1], 356 (85) [M^+], 254 (1), 135 (100). IR (KBr disk): $\tilde{\nu}$ = 1727, 1602, 1508, 1256, 1123, 1026, 838 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.77 (s, 6 H), 3.83 (s, 3 H), 3.88 (s, 3 H), 5.16 (s, 2 H), 6.67 (s, 2 H), 6.87 (m, 2 H), 7.33 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.4, 56.0 (2 C), 60.8, 70.3, 106.2, (2 C), 114.2 (2 C), 122.8, 123.8, 125.9, 129.2 (2 C), 138.2, 153.4 (2 C), 155.4, 161.4, 173.7 ppm. $C_{20}H_{20}O_6$ (356.37): calcd. C 67.41, H 5.66; found C 67.40, H 5.59. This compound was also synthesized in 14% yield by reaction of **13d** with **18f** in toluene at 85 °C for 28 h in the presence of KF, [chloro(di-2-norbornylphosphanyl)(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II)] (1 mol %) and KF (3.0 equiv.) (Table 5, Entry 3).

4-(3,4-Dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (4g): The crude product obtained from the reaction between **13g** and **18f** in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu_3P (Table 5, Entry 4) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and EtOAc (85:15) as eluent, to give **4g** (0.29 g, 58%) as a light-brown solid; m.p. 118−120 °C. APCI-MS: *m*/*z* (%) = 387 [M^+]. IR (KBr disk): $\tilde{\nu}$ = 1731, 1646, 1519, 1240, 1131, 1025, 825 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.60 (s, 3 H), 3.79 (s, 6 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 5.20 (s, 2 H), 6.68 (s, 2 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 6.88 (d, *J* = 2.2 Hz, 1 H), 6.98 (dd, *J* = 8.8, 2.2 Hz, 1.H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.6, 55.9, 56.1 (2 C), 60.8, 70.3, 106.4 (2 C), 110.5, 110.9, 120.6, 122.9, 124.1, 126.0, 138.2, 148.8, 151.1, 153.4 (2 C), 155.4, 173.6 ppm. $C_{21}H_{22}O_7$ (387.40): calcd. C 65.28, H 5.74; found C 65.19, H 5.68.

4-(2-Naphthyl)-3-(3,4,5-trimethoxyphenyl)-2(5*H*)-furanone (4h): The crude product obtained from the reaction between **13h** and **18f** in the presence of KF and catalytic amounts of $[Pd_2(dba)_3]$ and tBu_3P (Table 5, Entry 5) was purified by recrystallisation from a mixture of CH_2Cl_2 and hexane (ca. 1.5:1) to give **4h** (0.19 g, 39%) as a light-brown solid; m.p. 199−202 °C. EI-MS: *m*/*z* (%) = 377 (13) [M^+ + 1], 376 (55) [M^+], 319 (11), 221 (17), 202 (19), 155 (100), 101 (18). IR (KBr disk): $\tilde{\nu}$ = 1733, 1640, 1581, 1243, 1130, 1030, 997 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.70 (s, 3 H), 3.89 (s, 3 H), 5.30 (s, 2 H), 6.72 (s, 2 H), 7.40 (dd, *J* = 8.8, 1.8 Hz, 1 H), 7.55 (m, 2 H), 7.82 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.0 (2 C), 60.9, 70.5, 106.4 (2 C), 124.6, 125.4, 125.9, 126.9, 127.3, 127.7, 128.3, 128.5, 132.8, 133.1, 133.8, 133.9, 148.8, 153.3 (2 C), 155.5, 173.3 ppm. $C_{23}H_{20}O_5$ (376.41): calcd. C 73.39, H 5.36; found C 73.45, H 5.31.

3-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-2(5*H*)-furanone (4i): The crude product obtained from the reaction between **13d** and **20f** in the presence of KF and catalytic amounts of $[Pd(OAc)_2]$ and Cy_3P (Table 5, Entry 6) was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and EtOAc (97:3) as eluent, to give **4i** (0.53 g, 46%) as a beige solid; m.p. 103−105 °C. EI-MS: *m*/*z* (%) = 327 (7) [M^+ + 1], 326 (66) [M^+], 269 (28), 191 (19), 163 (10), 135 (100), 121 (7). IR (KBr disk): $\tilde{\nu}$ = 1732, 1639, 1519, 1241, 1140, 1015, 829 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.82 (s, 3 H), 3.91 (s, 3 H), 5.14 (s, 2 H), 6.89 (m, 4 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 7.30 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.3, 55.8 (2 C), 70.3, 111.3, 112.1, 114.2 (2 C), 122.0, 122.9, 123.2, 123.8, 129.0 (2 C), 148.8, 149.2, 154.6, 161.2, 173.8 ppm. $C_{19}H_{18}O_5$ (326.35): calcd. C 69.93, H 5.56; found C 69.83, H 5.50.

4-(4-Methylthiophenyl)-3-phenyl-2(5*H*)-furanone (4a): The crude product obtained from the reaction between **13e** and **20a** in the presence of catalytic amounts of $[Pd(OAc)_2]$ and Cy_3P (Table 5, Entry 7) was purified by MPLC on silica gel, with a mixture of toluene and EtOAc (95:5) as eluent, to give **4a** (0.26 g, 26%) as a yellow solid; m.p. 138−139 °C. EI-MS: *m*/*z* (%) = 282 (57) [M^+], 225 (50), 178 (84), 177 (54), 165 (20), 149 (51), 105 (100). IR (KBr disk): $\tilde{\nu}$ = 1749, 1339, 1158, 1083, 1033, 956, 7732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 5.14 (s, 2 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.34−7.45 (m, 7 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.9, 70.3, 125.2, 125.6 (2 C), 126.7, 127.6 (2 C), 128.5, 128.7 (2 C), 129.2 (2 C), 130.3, 142.7, 155.3, 173.4 ppm. $C_{17}H_{14}O_2S$ (282.36): calcd. C 72.31, H 5.00; found C 72.18, H 4.89. This compound was also prepared in 25% yield by reaction of **13e** with **18a** in the presence of KF and a catalytic amount of [chloro(di-2-norbornylphosphanyl)(2′-dimethylamino-1,1′-biphenyl-2-yl)palladium(II)] (Entry 8, Table 5).

4-(4-Hydroxyphenyl)-3-(3,4,5-trihydroxyphenyl)-2(5*H*)-furanone (4j): A 1 M CH_2Cl_2 solution of BBr_3 (7.68 mL, 7.68 mmol) was added over 15 min to a stirred solution of **4f** (0.23 g, 0.64 mmol) in dry CH_2Cl_2 (25 mL), which was cooled to −78 °C. The mixture was warmed to room temperature and stirred for 24 h. Water (30 mL) and CH_2Cl_2 (70 mL) were added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the collected organic extracts were washed with water (3 × 15 mL), dried and concentrated under reduced pressure to give **4j** (0.19 g, 99%) as a yellow solid. ^1H NMR analysis showed that this crude compound had chemical purity higher than 96%. M.p. 255 °C (decomp.). IR (KBr disk): $\tilde{\nu}$ = 3400, 1701, 1608, 1446, 1251, 1182, 836 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.23 (s, 2 H), 6.26 (s, 2 H), 6.76 (m, 2 H), 7.29 (m, 2 H), 8.25 (br. s, 1 H), 8.96 (br. s, 2 H), 10.06 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.1, 107.9 (2 C), 115.5 (2 C), 120.9, 121.5, 122.2, 129.3 (2 C), 133.4, 146.1 (2 C), 155.3, 159.4, 173.5 ppm. $C_{16}H_{12}O_6$ (300.27): calcd. C 64.00, H 4.03; found C 63.87, H 3.91.

4-(3,4-Dihydroxyphenyl)-3-(3,4,5-trihydroxyphenyl)-2(5*H*)-furanone (4k): A solution of compound **4g** (0.18 g, 0.46 mmol) in dry CH_2Cl_2 was treated with a 1 M CH_2Cl_2 solution of BBr_3 (6.97 mL, 6.97 mmol) at room temperature for 24 h according to the same procedure used to prepare **4j** from **4f**. Usual workup provided **4k** (0.14 g, 99%) as a yellow solid. M.p. 260 °C (decomp.). IR (KBr disk): $\tilde{\nu}$ = 3395, 1702, 1604, 1444, 1262, 1047, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.18 (s, 2 H), 6.26 (s, 2 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.78 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.84 (d, *J* = 1.8 Hz, 1 H), 8.29 (s, 1 H), 8.94 (s, 2 H), 9.15 (s, 1 H), 9.56 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.1, 107.9(2 C), 114.9, 115.5, 119.6, 120.8, 121.9, 122.0, 133.3, 145.2, 146.0 (2 C), 147.9, 155.5, 173.6 ppm. $C_{16}H_{12}O_7$ (316.27): calcd. C 60.76, H 3.82; found C 60.65, H 3.75.

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