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Studies on the Transition Metal-Catalyzed Synthesis of Variously Substituted (*E*)-3-[1-(Aryl)methylidene]- and (*E*)-3-(1-Alkylidene)-3*H*-furan-2-ones

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Abstract : 5-Aryl and 5-alkyl substituted (*E*)-3-[1-(aryl)methylidene]- and (*E*)-3-(1-alkylidene)-3H-furan-2-ones, (*E*)-**9**, have been selectively synthesized by cyclization of the corresponding (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids, (*E*)-**11**, in the presence of $AgNO_3$ or Pd-catalysts such as *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II) or that constituted of a mixture of Et_3N and $PdCl_2(PhCN)_2$ or $PdCl_2(CH_3CN)_2$, in a 3 : 1 molar ratio, respectively. A representative (*E*)-5-aryl-3-[1-(aryl)methylidene]-3H-furan-2-one, *i.e.* (*E*)-**9i**, has been also prepared by a tandem process involving a Pd(0)- and Cu(I)-catalyzed cross-coupling reaction between an 1-alkyne and a (*Z*)-3-aryl-2-bromopropenoic acid followed by a catalytic intramolecular oxypalladation of the resulting cross-coupled product. However, when this same approach was used to prepare an (*E*)-5-alkyl-3-[1-(aryl)methylidene]-3*H*-furan-2-one, *i.e.* (*E*)-**9j**, a mixture of (*E*)-**9j** and the corresponding (*E*)/(*Z*)-5-(1-alkylidene)-3-(aryl)methyl-5*H*-furan-2-one, *i.e.* (*E*)/(*Z*)-**20**, was obtained. Finally, in an attempt to prepare an (*E*)-4-alkyl-5-aryl-3-[1-(aryl)methylidene]-3*H*-furan-2-one, *i.e.* (*E*)-**14a**, by a tandem process involving the intramolecular oxypalladation of an (*E*)-enynoic acid, (*E*)-**11**, followed by a cross-coupling reaction of the resulting compound with an aryl iodide, a (*Z*)-5-(1-alkynyl)-4-aryl-3-arylmethyl-5*H*-furan-2-one, *i.e.* (**Z**)-**22**, has been stereoselectively obtained. © 1997 Elsevier Science Ltd. All rights reserved.

In recent years considerable attention has been devoted to the synthesis of five-membered lactone derivatives by Ag-, Hg-, Rh- or Pd-catalyzed intramolecular additions of carboxylic acids to alkynes.[1-4] Lactone derivatives, which have been prepared according to these procedures include 5-substituted 3*H*-furan-2-ones, **1**,[4c] 5-ylidene-tetrahydrofuran-2-ones, **2**,[1c,d,2b-e,3a,b,4c] (Z)-5-ylidene-5H-furan-2-ones, **3**,[1b,1e,4b] and (Z)-3-ylidenephthalides, **4**.[1a,1e] On the other hand, modifications of these procedures, in which an alkynoate, **5**, is reacted with an allyl halide,[5] a 1-bromo-1-alkyne[6] or an aryl halide or triflate, **6**,[7] in the presence of a Pd-catalyst, have been employed to synthesize 5-ylidene-tetrahydrofuran-2-ones of general formula **7**.

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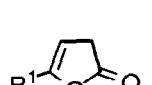
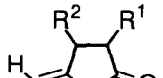


1



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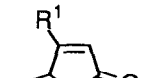
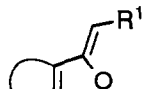
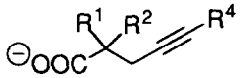


(Z)-3



(Z)-4

More recently, analogous carbopalladation-heterocyclization sequences involving the potassium salts of pentynoic acids 3- or 5-substituted with an iodoaryl moiety have been used to prepare in satisfactory yields a variety of benzo-annulated 5-ylidene-tetrahydrofuran-2-ones of general formula **8**.[8]



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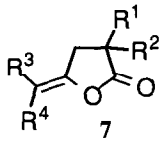

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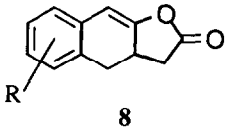
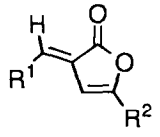


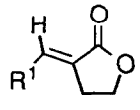
8

Interestingly, compounds **3** e **4** have been also recently synthesized by tandem processes involving intermolecular Pd-catalyzed cross-coupling reactions between 1-alkynes and *o*-iodobenzoic acid or 3-halo-2-alkenoic acids, respectively, followed by Pd-catalyzed cyclization of the resulting cross-coupled products.[9-11]

Nevertheless, strategies similar to those used for the synthesis of compounds **1-4**, **7** and **8** have not been employed so far for the stereocontrolled synthesis of 5-substituted (*E*)-3-ylidene-3*H*-furan-2-ones of general formula (*E*)-**9**. In fact, the only method reported in the literature for the synthesis of some compounds of this class, *i.e.* (*E*)-3-[1-(aryl)methylidene]-5-aryl-3*H*-furan-2-ones, involves a Pd-catalyzed cyclocarbonylation of 3-aryl-1-propynes and iodoarenes or carboxylic acid chlorides.[12] On the other hand, previous methods, which consist of reactions between γ-ketoacids and aromatic aldehydes under Perkin-Erlenmeyer conditions, afford 5-substituted 3-[1-(aryl)methylidene]-3*H*-furan-2-ones of unknown configuration[13] and are unsuitable for the preparation of the corresponding 3-(1-alkylidene) derivatives.



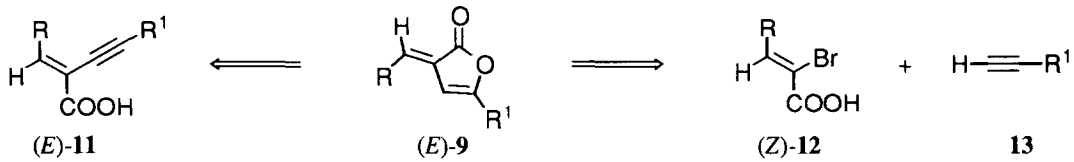
(*E*)-**9** : R^1 = alkyl, aryl
R^2 = alkyl, aryl



(*E*)-**10**

Since we are currently interested in developing efficient and selective methods for the synthesis of compounds with potential toxic activity against fungi which are noxious to agricultural crops or to wooden or papery materials,[14] we decided to explore new methods for the selective and stereocontrolled synthesis of compounds (*E*)-**9**. In fact, these substances have structural features common either to compounds **1** or(*E*)-3-ylidene-tetrahydrofuran-2-ones, (*E*)-**10**, some of which have proven to be characterized by antifungal activity.[15,16] Thus, with the findings gained in the studies on the synthesis of compounds **1-4** in mind,[1-4,9-11] we investigated the synthesis of compounds (*E*)-**9** either by a transition metal-catalyzed cyclization of the corresponding (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids, (*E*)-**11**, or by a tandem process involving a Pd-catalyzed cross-coupling between (*Z*)-3-aryl-2-bromopropenoic acids, (*Z*)-**12**, and 1-alkynes, **13**, under the Sonogashira conditions[17] and a subsequent Pd-catalyzed cyclization of the (*E*)-2-(1-alkynyl)-3-arylpropenoic

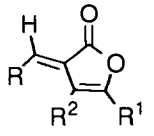
acids, (*E*)-**11**, so obtained (Scheme 1).



(*E*)-**11** (*E*)-**9** (*Z*)-**12** **13**

Scheme 1

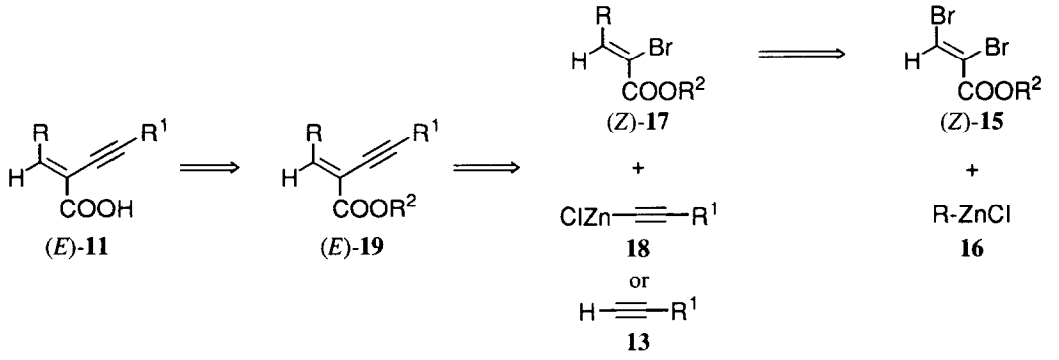
In this paper we wish to report the results obtained in the study of these synthetic strategies as well as that of an attempt to prepare an (*E*)-5-alkyl-4-aryl-3-[1-(aryl)methylidene]-3*H*-furan-2-one, (*E*)-**14** by a tandem process involving the oxypalladation of an (*E*)-2-(1-alkynyl)-3-arylpropenoic acid, (*E*)-**11**, followed by a cross-coupling reaction of the resulting product with an aryl iodide.



(*E*)-**14** : R = aryl; R^1 = alkyl; R^2 = aryl

RESULTS AND DISCUSSION

Stereoisomerically pure compounds (*E*)-**11**, which in our first synthetic strategy were used as precursors to 5-substituted (*E*)-3-ylidene-3*H*-furan-2-ones, (*E*)-**9**, were synthesized from alkyl (*Z*)-2,3-dibromopropenoates, (*Z*)-**15**, according to the retrosynthetic analysis shown in Scheme 2.

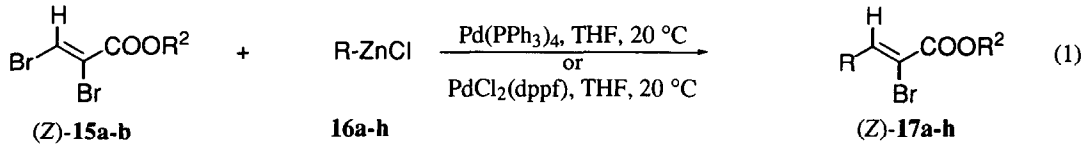


(*E*)-**11** (*E*)-**19** (*Z*)-**17** **18** **13** (*Z*)-**15** **16**

Scheme 2

Thus, 3-aryl and 3-alkyl substituted alkyl (*Z*)-2-bromopropenoates, (*Z*)-**17**, were prepared according to a procedure developed in our laboratory for the selective and stereospecific monoarylation and monoalkynylation of alkyl (*Z*)-2,3-dibromopropenoates.[18,19] In particular, easily available (*Z*)-**15a** or (*Z*)-**15b**[18] were reacted with 1.2 equiv of an arylzinc chloride, **16a**, **16d**, **16e**, **16f**, **16g** or **16h**, in THF at 20 °C, in the presence of 5 mol %

$Pd(PPh_3)_4$, to give the corresponding stereoisomerically pure compounds (*Z*)-**17a,** (*Z*)-**17d,** (*Z*)-**17e,** (*Z*)-**17f,** (*Z*)-**17g** and (*Z*)-**17h** in 84, 65, 77, 84, 85 and 88 % yield respectively. [Eq. (1)].



(*Z*)-**15a-b** **16a-h** (*Z*)-**17a-h** (1)

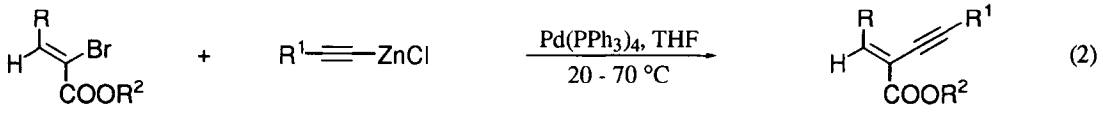
	R^2
a	CH_3
b	C_2H_5

	R
a	3,4- 
b	*n*-C_4H_9
c	*i*-C_4H_9
d	3,5-$Cl_2C_6H_3$
e	C_6H_5
f	4-F-C_6H_4
g	2-thienyl
h	4-Cl-C_6H_4

	R	R^2	yield (%)
a	3,4-	C_2H_5	84[18c]
b	*n*-C_4H_9	CH_3	63
c	*i*-C_4H_9	CH_3	79
d	3,5-$Cl_2C_6H_3$	CH_3	65
e	C_6H_5	C_2H_5	77[18a]
f	4-F-C_6H_4	CH_3	84[18a]
g	2-thienyl	CH_3	85[18a]
h	4-Cl-C_6H_4	CH_3	88

A similar procedure, in which the catalyst precursor was $PdCl_2$(dppf) and the organometallic reagents were butyl and isobutylzinc chloride, **16b** and **16c**, was used to synthesize the stereoisomerically pure alkyl (*Z*)-3-alkyl-2-bromopropenoates (*Z*)-**17b** and (*Z*)-**17c** in 63 and 79 % yield, respectively [Eq. (1)].

Two different methods were then employed to convert stereospecifically compounds (*Z*)-**17a-h** so prepared into the corresponding methyl (*E*)-2-(1-alkynyl)-2-alkenoates, (*E*)-**19**. The first method, which was used to prepare compounds (*E*)-**19a-e**, involved a cross-coupling reaction between compounds (*E*)-**17b-e** and 1.5 equiv of 1-alkynylzinc chlorides, **18a-d**, in THF under reflux, in the presence of a catalytic amount of $Pd(PPh_3)_4$ [Eq. (2)]. Stereoisomerically pure (*E*)-**19a,** (*E*)-**19b,** (*E*)-**19c,** (*E*)-**19d** and (*E*)-**19e** were so obtained in 62, 71, 84, 74 and 88 % yield, respectively.



(*Z*)-**17a-e** **18** (*E*)-**19a-f** (2)

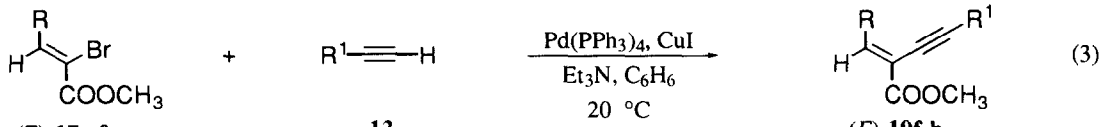
	R	R^2
b	*n*-C_4H_9	CH_3
c	*i*-C_4H_9	CH_3
d	3,5-$Cl_2C_6H_3$	CH_3
e	C_6H_5	C_2H_5

	R^1
a	C_6H_5
b	*n*-C_6H_{13}
c	4-CH_3-C_6H_4
d	*n*-C_3H_7

	R	R^1	R^2	yield (%)
a	*n*-C_4H_9	*n*-C_6H_{13}	CH_3	62
b	*i*-C_4H_9	C_6H_5	CH_3	71
c	3,5-$Cl_2C_6H_3$	4-CH_3-C_6H_4	CH_3	84
d	3,5-$Cl_2C_6H_3$	*n*-C_3H_7	CH_3	74
e	C_6H_5	C_6H_5	C_2H_5	88

The second method, which involved a Pd(0)- and Cu(I)-catalyzed coupling reaction between compounds (*E*)-**17** and 1-alkynes, **13**, under the Sonogashira conditions,[17] allowed to prepare stereoisomerically pure (*E*)-

19f, (*E*)-**19g** and (*E*)-**19h** in 56, 66 and 53 % yield, respectively [Eq. (3)].



(3)

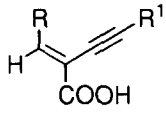
(*Z*)-**17a,f-g** **13** (*E*)-**19f-h**

	R
a	3,4- 
f	4-F-C_6H_4
g	2-thienyl

	R^1
a	C_6H_5
b	*n*-C_6H_{13}
c	*n*-C_4H_9

	R	R^1	yield (%)
f	3,4-	C_6H_5	56
g	4-F-C_6H_4	*n*-C_6H_{13}	66
h	2-thienyl	*n*-C_4H_9	53

Finally, treatment of THF solutions of compounds (*E*)-**19a-h** with a molar excess of aqueous 3N NaOH at room temperature for 24 h followed by acidification with diluted H_2SO_4 provided the corresponding carboxylic acids (*E*)-**11** in 95-100 % yield.



(*E*)-**11a-h**

	a	b	c	d	e	f	g	h
R	*n*-C_4H_9	*i*-C_4H_9	3,5-$Cl_2C_6H_3$	3,5-$Cl_2C_6H_3$	C_6H_5	3,4-	4-F-C_6H_4	2-thienyl
R^1	*n*-C_6H_{13}	C_6H_5	4-CH_3-C_6H_4	*n*-C_3H_7	C_6H_5	C_6H_5	*n*-C_6H_{13}	*n*-C_4H_9

With an efficient route to compounds (*E*)-**11** established, three different procedures (procedures A-C) for the transition metal-catalyzed cyclization of these carboxylic acids to the corresponding 5-substituted (*E*)-3-ylidene-3H-furan-2-ones, (*E*)-**9**, were examined. Procedure A, in which the catalyst system was the same that Utimoto and coworkers[4c] employed for cyclization of 3-, 4- and 5-alkynoic acids, involved the reaction of compounds (*E*)-**11** with 5 mol % $PdCl_2(CH_3CN)_2$ or $PdCl_2(PhCN)_2$ and 15 mol % Et_3N in THF at 65°C or in DMF at 90 °C. In procedure B, unprecedently employed for similar reactions, the cyclization of compounds (*E*)-**11** was carried out in toluene under reflux, in the presence of 5 mol % of a palladacycle, *i.e. trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II)[20] and in the absence of any base. On the other hand, procedure C involved treatment of acetone solutions of compounds (*E*)-**11** with 20 mol % $AgNO_3$ at room temperature. The results obtained using these procedures, which are summarized in the Table, reveal the following features. All cyclizations carried out using procedure A (Entries 1, 4, 7, 8 and 9) required long reaction times and, among these reaction, those which were carried out in THF solution (Entries 1, 7, 8 and 9) gave the desired products, *i.e.* (*E*)-**9f**, (*E*)-**9g**, (*E*)-**9e** and (*E*)-**9h**, respectively, in modest to satisfactory yields. On the contrary, cyclization of (*E*)-**11c** (Entry 4), which was carried out in DMF solution since this carboxylic acid was not soluble in THF, afforded (*E*)-**9c** in very low yield. It must be noted that an attempt was made to increase the yield of this reaction by using $Pd(PPh_3)_4$ as catalyst in the absence of Et_3N. Unfortunately, in contrast to the good results obtained by Kotora and Negishi for lactonization of (Z)-2-en-4-ynoic acids in DMF or CH_3CN solution in the presence of $Pd(PPh_3)_4$,[1b] only traces of compound (*E*)-**9c** were obtained.

Interestingly, procedure B gave results comparable or better than those obtained when procedure A was employed. In fact, the cylization reactions were cleaner than those perfomed using procedure A and proceeded in times comparable or shorter than those which were necessary when this last procedure was employed. Moreover, cyclization of (*E*)-**11e** according to procedure B (Entry 6) afforded (*E*)-**9e** in a yield (87 %) better than that obtained in the preparation of this compound according to procedure A (42 %) (Entry 8).

Table 1. Synthesis of 5-Substituted (*E*)-3-Ylidene-3*H*-furanones, (*E*)-**9**, by Cyclization of the Corresponding 3-Substituted (*E*)-2-(1-Alkynyl)propenoic acids, (*E*)-**11**.

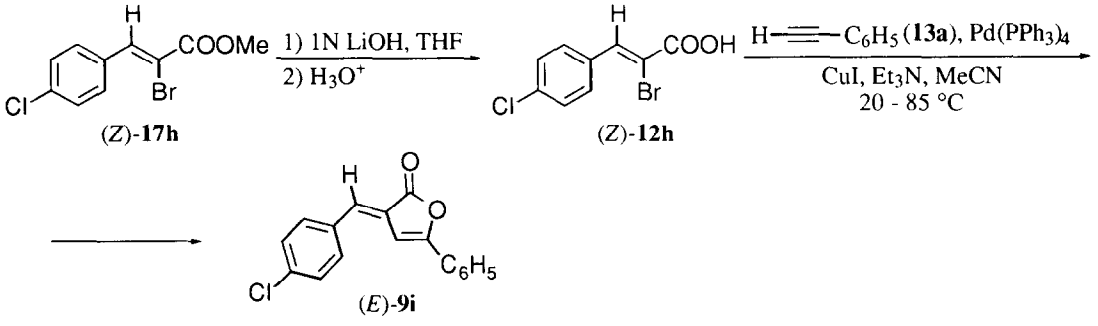
Entry	Carboxylic acid (*E*)-**11**	Catalyst	Solvent	reaction conditions (°C / h)	Product			Yield (%)
					(*E*)-**9**	R	R^1	
1[a]	(*E*)-**11f**	$PdCl_2(PhCN)_2$	THF	65 / 42	(*E*)-**9f**	3,4- 	C_6H_5	64
2[b]	(*E*)-**11a**	$AgNO_3$	Acetone	20 / 20	(*E*)-**9a**	*n*-C_4H_9	*n*-C_6H_{13}	39
3[b]	(*E*)-**11b**	$AgNO_3$	Acetone	20 / 55	(*E*)-**9b**	*i*-C_4H_9	C_6H_5	38
4[c]	(*E*)-**11c**	$PdCl_2(MeCN)_2$	DMF	90 / 90	(*E*)-**9c**	3,5-$Cl_2C_6H_3$	4-CH_3-C_6H_4	9
5[d]	(*E*)-**11d**	Palladacycle	Toluene	110 / 42	(*E*)-**9d**	3,5-$Cl_2C_6H_3$	*n*-C_3H_7	67
6[d]	(*E*)-**11e**	Palladacycle	Toluene	110 / 24	(*E*)-**9e**	C_6H_5	C_6H_5	87
7[c]	(*E*)-**11g**	$PdCl_2(MeCN)_2$	THF	65 / 64	(*E*)-**9g**	4-F-C_6H_4	*n*-C_6H_{13}	79
8[c]	(*E*)-**11e**	$PdCl_2(MeCN)_2$	THF	65 / 42.5	(*E*)-**9e**	C_6H_5	C_6H_5	42
9[c]	(*E*)-**11h**	$PdCl_2(MeCN)_2$	THF	65 / 65	(*E*)-**9h**	2-thienyl	*n*-C_4H_9	39
10[b]	(*E*)-**11h**	$AgNO_3$	Acetone	20 / 21	(*E*)-**9h**	2-thienyl	*n*-C_4H_9	72

a) Entry 1 was performed using 5 mol% $PdCl_2(PhCN)_2$ and 15 mol% Et_3N as catalytic system (Procedure A). b) Entries 2, 3 and 10 were performed using 20 mol% $AgNO_3$ as catalyst (Procedure C). c) Entries 4, 7, 8 and 9 were performed using 5 mol% $PdCl_2(MeCN)_2$ and 15 mol% Et_3N as catalytic system (Procedure A). d) Entries 5 and 6 were performed using 5 mol% *trans*-di(μ-acetate)-bis[(di-*o*-tolylphosphino)benzyl]dipalladium as catalyst (Procedure B).

The results obtained using procedure B also allowed to draw a conclusion about the oxidation state of the palladium compounds which catalyze the cyclization of carboxylic acids (*E*)-**11**. In fact, on the contrary to procedure A in which, at least in principle, Et_3N could reduce the palladium(II) compounds used as catalyst precursors,[21] in procedure B there were not reagents able to perform the reduction of the palladium(II) compound used to perform the desired cyclizations. Therefore, the catalyst for cyclization of compounds (*E*)-**11** should be a palladium(II) complex. On the other hand, the results obtained using procedure A as well as those obtained by Kotora and Negishi in the lactonization of (*Z*)-2-en-4-ynoic acids promoted by $Pd(PPh_3)_4$,[1b] could be explained by supposing that the true catalyst of these reactions derives from an oxidative addition reaction of the carboxylic acids, which were used as substrates, to the palladium(0) complex which was formed in the reaction conditions employed or was used as catalyst precursor.[22] Finally, as regards the cyclization reactions which were carried out using procedure C (Entries 2, 3 and 10) it must be noted that they occurred in very mild experimental conditions, but, except for the synthesis of **9h** in which the yield was 72 % (Entry 10), they provided the desired compounds in modest yields.

Compounds (*E*)-**9a-h**, which were synthesized according to these procedures, were characterized by MS, IR and ^{1}H NMR analyses as well as by elemental analysis. Moreover, the structure and stereochemistry of three representative 5-substituted (*E*)-3-[1-(aryl)methylidene]-3*H*-furan-2-ones, *i.e.* (*E*)-**9f**, (*E*)-**9g** and (*E*)-**9h**, were unambiguously assigned on the basis of their ^{1}H NMR and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of NMR techniques, which included homonuclear shift correlation (COSY), 1D- or 2D-Overhauser experiments (NOESY) and ^{1}H-^{13}C heteronuclear multi-quantum coherence (HMQC) experiments. On the other hand, the (*E*)-stereochemistry was assigned to compounds **9d-f** taking into account that: *i)* as demonstrated for (*E*)-**9f**, (*E*)-**9g** and (*E*)-**9h**, the reactions which were used for their synthesis from (*Z*)-**15** were completely stereospecific; *ii)* in compounds **9c**, **9d** and **9e** the chemical shifts of the olefinic protons (H-α) of their arylidene groups were very similar to those of the corresponding protons in (*E*)-**9f**, (*E*)-**9g** and (*E*)-**9h**.

In spite of the relative effectiveness of the cyclization reactions of compounds (*E*)-**11a-h** to the corresponding 5-substituted (*E*)-3-ylidene-3*H*-furan-2-ones was generally satisfactory, it was right to address our attention to an alternative method for their synthesis. In particular, the synthetic usefulness of a tandem cross coupling-oxypalladation reaction for the preparation of two representative compounds of general formula (*E*)-**9**, *i.e.* (*E*)-3-[1-(4-chlorophenyl)methylidene]-5-phenyl-3*H*-furan-2-one, (*E*)-**9i**, and (*E*)-5-butyl-3-[1-(4-chloro-phenyl)methylidene]-3*H*-furan-2-one, (*E*)-**9j**, was attempted. Thus, compound (*Z*)-**12h**, which was obtained by reaction of a THF solution (*Z*)-**17h** with 1N LiOH at room temperature followed by acidification, was reacted with 1.5 equiv of phenylacetylene, **13a**, in CH_3CN solution for 23.5 h at 20 °C and for 23 h at 85 °C in the presence of 4 equiv of Et_3N, 9 mol % $Pd(PPh_3)_4$ and 9 mol % CuI (Scheme 3). Purification by MPLC on silica gel of the crude reaction mixture allowed chemically and stereoisomerically pure (*E*)-**9i** to be isolated in 23 % yield.

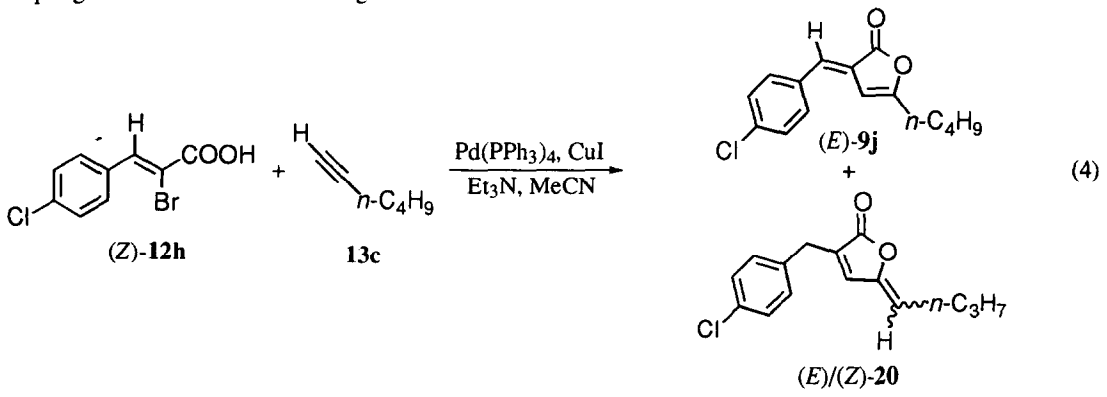


Scheme 3

On the other hand, an analogous reaction between (*Z*)-**12h** and 1-hexyne, **13c** afforded a mixture of (*E*)-**9j** and (*E*)/(*Z*)-3-[1-(4-chlorophenyl)methyl]-5-(1-propylidene)-5*H*-furan-2-one, (*E*)/(*Z*)-**20**, which were isolated in 11 and 34 % yield, respectively [Eq (4)].

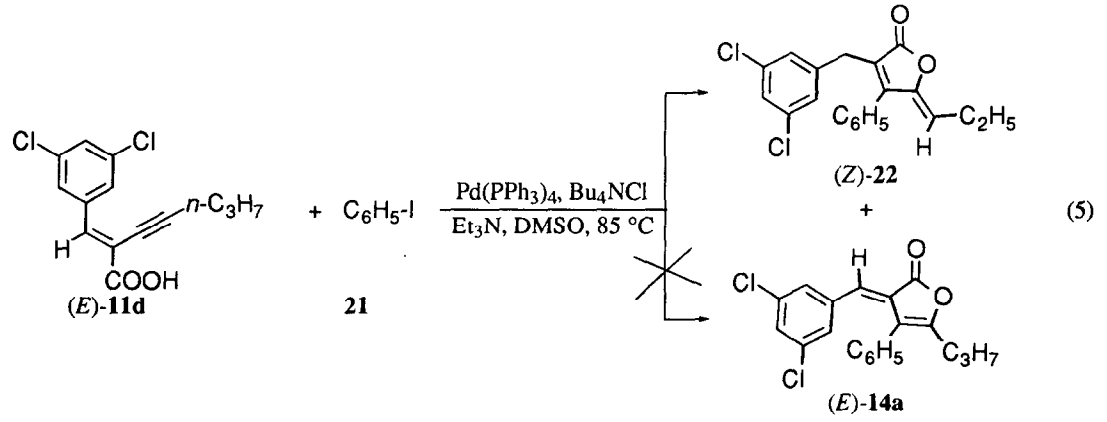
Compounds (*E*)- and (*Z*)-**20** could be separated by MPLC on silica gel and their structure and stereochemistry could be unambiguously established by NMR experiments which included selective NOE experiments. It was also found that treatment of (*E*)-**9j** with 2.5 equiv of Et_3N in CH_3CN at 85 °C gave a mixture of (*E*)- and (*Z*)-**20** in a *ca.* 60 : 40 ratio, respectively. Thus, the stereoisomeric mixture of 5H-furan-2-ones, which was obtained by reacting (*Z*)-**12h** with **13b**, derived from isomerization of so obtained (*E*)-**9j** by

means of Et_3N, which was still present in the reaction mixture after the Pd(0)- and Cu(I)-catalyzed cross-coupling reaction between these reagents.



(4)

Interestingly, a similar but quantitative and stereoselective isomerization was observed in an attempt to synthesize an (*E*)-5-alkyl-4-aryl-3-[1-(aryl)methylidene]-3H-furan-2-one, (*E*)-**14**, by a tandem process involving the oxypalladation of an (*E*)-2-(1-alkynyl)-3-arylpropenoic acid, (*E*)-**11d**, and a subsequent cross-coupling reaction of the resulting product with an aryl iodide. In particular, according to a procedure similar to that previously employed for the synthesis of (*E*)-[1,1-(disubstituted)methylidene]-tetrahydrofuran-2-ones,[7] compound (*E*)-**11d** was reacted with 2 equiv of iodobenzene, **21**, in DMSO at 85 °C for 22 h in the presence of 1 equiv of Bu_4NCl, 0.5 equiv of $Pd(PPh_3)_4$ and a large excess of Et_3N [Eq (5)]. However, this reaction afforded in 23 % yield stereoisomerically pure (*Z*)-3-(3,5-dichlorophenyl)methyl-4-phenyl-5-(1-propylidene)-5*H*-furan-2-one, (*Z*)-**22**, instead of (*E*)-3-[1-(3,5-dichlorophenyl)methylidene]-4-phenyl-5-propyl-3*H*-furan-2-one, (*E*)-**14a**. The structure and stereochemistry of (*Z*)-**22** were unambiguously established by IR, MS and elemental analyses and by NMR experiments.



(5)

In conclusion, several 5-aryl and 5-alkyl substituted (*E*)-3-[1-(aryl)methylidene]- and (*E*)-3-(1-alkylidene)-3*H*-furan-2-ones, (*E*)-**9**, have been synthesized in modest to satisfactory yields by Pd- or Ag-catalyzed cyclization of the corresponding (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids, (*E*)-**11**. Among the cyclization reactions examined, those which were catalyzed by *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium(II), a complex not previously employed for intramolecular additions of

carboxylic acids to alkynes, were particularly clean and efficient. An (*E*)-5-aryl-3-[1-(aryl)methylidene]-3*H*-furan-2-one has also been synthesized, although in modest yield, by a tandem cross coupling-lactonization process. However, when a similar tandem procedure was employed to prepare an (*E*)-5-alkyl-3-[1-(aryl)methylidene]-3*H*-furan-2-one, owing to the experimental conditions employed, a mixture of the desired 3H-furan-2-one and the corresponding (*E*)/(*Z*)-5-(1-alkylidene)-3-(aryl)methyl-5*H*-furan-2-one was obtained. This last compound proved to derive from isomerization of the 3H-furan-2-one by means Et_3N which was present in the reaction mixture. Thus, taking into account that the synthesis of compounds (*E*)-**9** from (*Z*)-**15** by this tandem process involves a number of synthetic steps identical to that based on cyclization of compounds (*E*)-**11**, that compounds (*E*)-**9** synthesized by this tandem process are obtained in modest yields and that, in the case of the synthesis of 5-alkyl susbstituted 3H-furan-2-ones, an undesired isomerization occurs, it is possible to conclude that the preparation of 5-aryl and 5-alkyl substituted (*E*)-3-[1-(aryl)methylidene]-3*H*-furan-2-ones by transition metal-catalyzed cyclization of the corresponding carboxylic acids (*E*)-**11** must be preferred. Finally, it must be mentioned that a quantitative and stereoselective isomerization, which was similar to that observed in the synthesis of an (*E*)-5-alkyl-3-[1-(aryl)methylidene]-3*H*-furan-2-one by the above mentioned tandem process, occurred in an experiment aimed to prepare an (*E*)-5-alkyl-4-aryl-3-[1-(aryl)methylidene]-3*H*-furan-2-one, (*E*)-**14**, which consisted of a tandem process involving the oxypalladation of an (*E*)-2-(1-alkynyl)-3-arylpropenoic acid, (*E*)-**11**, and a subsequent cross-coupling reaction of the resulting product with an aryl iodide.

Studies on the bioactivity of the 3*H*-furan-2-ones (*E*)-**9a-j**, which have been synthesized by the above mentioned procedures, are in progress.

EXPERIMENTAL

All boiling and melting points are uncorrected. Precoated plastic silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m × 0.25 mm i.d.) and a AT-WAX bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. IR spectra were recorded on a Perkin-Elmer 1725-X FT-IR spectrophotometer. All reactions of air- and water-sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive solutions were transferred with hypodermic syringes or double ended needles. Solvents were dried and distilled before use. The following compounds were prepared according to the literature: methyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**15a**,[18a] ethyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**15b**,[18a] $Pd(PPh_3)_4$,[23] $PdCl_2(dppf)$,[24] $PdCl_2(PhCN)_2$,[25] $PdCl_2(CH_3CN)_2$,[26] *trans-di*(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium,[20] ethyl (*Z*)-2-bromo-3-[3,4-(methylenedioxy)-phenyl]propenoate, (*Z*)-**17a**,[18a] ethyl (*Z*)-2-bromo-3-phenylpropenoate, (*Z*)-**17e**,[18a] methyl (*Z*)-2-bromo-3-(2-thienyl)propenoate, (*Z*)-**17g**,[18a] methyl (*Z*)-2-bromo-3-(4-fluorophenyl)propenoate, (*Z*)-**17f**,[18a] and ethyl (*E*)-3-(3,4-methylenedioxy)phenyl-2-(phenylethynyl)-propenoate, (*E*)-**19f**.[18a] Slurries of aryl- and alkylzinc chlorides, **16**, in THF were prepared by addition of 0.5 M

THF solutions of aryl- and alkylmagnesium bromides, respectively, to THF solutions of dry $ZnCl_2$ (1.3 equiv) maintained at 0 °C and by stirring the resulting mixtures for 0.5 h at room temperature. A similar procedure was used for the preparation of slurries of 1-alkynylzinc chlorides, **18**, in THF from 1-alkynylmagnesium bromides and $ZnCl_2$.

*General procedure for the synthesis of alkyl (Z)-3-aryl- and (Z)-3-alkyl-2-bromopropenoates, (Z)-**17**.* According to the literature,[18] $Pd(PPh_3)_4$ (1.44 g, 1.25 mmol) and a solution of an alkyl (Z)-2,3-dibromopropenoate, (Z)-**15**, (25.0 mmol) in THF (10 ml) were sequentially added to a solution of a slurry of an arylzinc chloride, **16**, (30.0 mmol) in THF (80 ml), which was stirred at 0 °C under argon. The resulting mixture was allowed to warm up to 20 °C and stirred at this temperature for 24 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered over Celite, dried and concentrated *in vacuo*. The residue, which was analyzed by GLC/MS, was purified by MPLC on silica gel or by fractional distillation. Compounds (Z)-**17d** and (Z)-**17h** were prepared according to this general procedure. A very similar procedure, in which the Pd-catalyst precursor was $PdCl_2$(dppf), was used to prepare compounds (Z)-**17b** and (Z)-**17c** by reaction between (Z)-**15a** and alkylzinc chlorides **16a** and **16b**, respectively.

*Methyl (Z)-2-bromo-2-heptenoate, (Z)-**17b**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (Z)-**15a** and butylzinc chloride, **16b**, was purified by fractional distillation to give in 63 % yield chemically and stereoisomerically pure (Z)-**17b**. B.p. 55 °C/0.07 Torr. MS, *m/z* (%): 221 (16), 219 (16), 190 (60), 166 (100), 147 (28), 132 (47), 108 (53). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (1H, t, J = 7.2 Hz, H-3), 3.83 (3H, s, OCH_3), 2.35 (2H, q, J = 7.2 Hz, H-4), 1.60-1.20 (4H, m, H-5 and H-6), 0.93 ppm (3H, t, J = 7.0 Hz, H-7). Anal. Calc for $C_8H_{13}BrO_2$: C, 43.46; H, 5.92. Found: C, 43.89; H, 5.93.

*Methyl (Z)-2-bromo-5-methyl-2-hexenoate, (Z)-**17c**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (Z)-**15a** and *iso*-butylzinc chloride, **16c**, was purified by fractional distillation to give in 79 % yield chemically and stereoisomerically pure (Z)-**17c**. B.p. 99-101 °C/12 Torr. MS, *m/z* (%): 222 (4), 220 (4),180 (98), 178 (100), 148 (37), 146 (38), 99 (21), 81 (33), 56 (27). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (1H, t, J = 7.2 Hz, H-3), 3.83 (3H, s, OCH_3), 2.25 (2H, t, J = 7.2 Hz, H-4), 1.86 (1H, sept, J = 6.7 Hz, H-5), 0.97 (6H, d, J = 6.7 Hz, $C(CH_3)_2$). Anal. Calc for $C_8H_{13}BrO_2$: C, 43.46; H, 5.92. Found: C, 43.17; H, 5.68.

*Methyl (Z)-2-bromo-3-(3,5-dichlorophenyl)propenoate, (Z)-**17d**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (Z)-**15a** and 3,5-dichlorophenylzinc chloride, **16d**, was purified by MPLC on silica gel, using a mixture of hexane and benzene (70 : 30) as eluent, to give in 65 % yield chemically and stereoisomerically pure (Z)-**17d** as a colourless crystalline solid. M.p. 114 °C. MS, *m/z* (%): 312 (11), 310 (26), 279 (13), 231 (66), 229 (100), 197 (35), 172 (34), 170 (58). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (1H, s, H-3), 7.69 (2H, br s, H-2' and H-6'), 7.39 (1H, s, H-4'), 3.91 ppm (3H, s, OCH_3). Anal. Calc for $C_{10}H_7BrCl_2O_2$: C, 38.75; H, 2.27. Found: C, 38.50; H, 2.10.

*Methyl (Z)-2-bromo-3-(4-chlorophenyl)propenoate, (Z)-**17h**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (Z)-**15a** and 4-chlorophenylzinc chloride, **16h**, was purified by MPLC

on silica gel, using a mixture of hexane and benzene (60 : 40) as eluent, to give in 88 % yield stereoisomerically pure (*Z*)-**17h** as a colourless crystalline solid. This compound had chemical purity higher than 97.5 %. M.p. 73 °C. MS, *m/z* (%) : 276 (32), 274 (24), 197 (57), 195 (100), 138 (28), 136 (71), 115 (15), 101 (45), 75 (46). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.18 (1H, s, H-3), 7.80 (2H, d, J = 8.4 Hz, H-3' and H-5'), 7.40 (2H, d, J = 8.4 Hz, H-2' and H-6'), 3.91 ppm (3H, s, OCH_3). Anal. Calc for $C_{10}H_8BrClO_2$: C, 43.59; H, 2.92. Found: C, 43.55; H, 3.01.

*Synthesis of alkyl (E)-2-(1-alkynyl)-3-aryl/alkyl-propenoates, (E)-**19**, by Pd-catalyzed cross-coupling reaction between alkyl (Z)-2-bromo-3-aryl/alkyl-propenoates, (Z)-**17**, and 1-alkynylzinc chloride, **18**.* Compounds (*E*)-**19b-f** were prepared according to a procedure very similar to that reported in the literature for the synthesis of (*E*)-**19a**.[18a] In particular, $Pd(PPh_3)_4$ (0.87 g, 0.75 mmol) and a solution of an alkyl (*Z*)-2-bromo-3-aryl/alkylpropenoate, (*Z*)-**17**, (15.0 mmol) in THF (20 ml) were sequentially added to a slurry of a 1-alkynylzinc chloride, **18**, (22.5 mmol) in THF (50 ml), which was stirred at 0 °C under argon. The resulting mixture, which was periodically monitored by GLC and GLC/MS analyses, was stirred for 1.5 h at 20 °C and at 70 °C until the reaction was complete. In particular, the reaction times at 70 °C which were required for the preparation of compounds (*E*)-**19a**, (*E*)-**19b**, (*E*)-**19c**, (*E*)-**19d** and (*E*)-**19e** were 25, 40, 6, 17 and 15 h, respectively. The reaction mixture was then cooled to room temperature, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with CH_2Cl_2. The collected organic extracts were washed with water, dried, filtered over Celite and concentrated *in vacuo*. The residue, which was analyzed by GL/MS and TLC, was diluted with the mixture of solvents, which was used for TLC analysis, and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel.

*Methyl (E)-2-(1-octynyl)-2-heptenoate, (E)-**19a*** . The crude reaction product, which was obtained from the Pd-catalyzed reaction between (*Z*)-**17b** and 1-octynylzinc chloride, **18b**, was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (95 : 5) as eluent, followed by fractional distillation of the chromatographic frctions which contained the desired product. Chemically and stereoisomerically pure (*E*)-**19a** was obtained in 62 % yield as a pale yellow liquid. B.p. 95 °C/0.07 Torr. MS, *m/z* (%): 250 (13), 221 (12), 219 (10), 179 (29), 137 (26), 133 (29), 119 (42), 91 (100), 77 (52). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (1H, t, J = 7.7 Hz, H-3), 3.78 (3H, s, OCH_3), 2.60-2.25 (4H, br m, H-4 and H-3'), 1.70-1.20 (12H, br m, H-5, H-6, H-4', H-5', H-6' and H-7'), 1.05-0.83 ppm (6H, br m, H-7 and H-8'). Anal. Calc for $C_{16}H_{26}O_2$: C, 76.80; H, 10.41. Found: C, 77.01; H, 10.41.

*Methyl (E)-5-methyl-2-phenylethynyl-2-hexenoate, (E)-**19b**.* The crude reaction product, which was obtained from the Pd-catalyzed cross-coupling reaction between (*Z*)-**17c** and phenylethynylzinc chloride, **18a**, was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (95 : 5) as eluent, to give in 71 % yield 98 % chemically pure (*E*)-**19b** as a colourless liquid. MS, *m/z* (%): 242 (40), 227 (64), 199 (19), 171 (21), 141 (53), 129 (33), 115 (51), 105 (100), 91 (24). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58-7.20 (6H, br m, H-3 and C_6H_5), 3.83 (3H, s, OCH_3), 2.43 (2H, t, J = 7.2 Hz, H-4), 1.88 (1H, sept, J = 6.6 Hz, H-5), 0.99 ppm (6H, d, J = 6.6 Hz, $C(CH_3)_2$). Anal. Calc for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.29; H, 7.77.

*Methyl (E)-3-(3,5-dichlorophenyl)-2-[(p-tolyl)ethynyl]propenoate, (E)-**19c**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (*Z*)-**17d** and (*p*-tolyl)ethynylzinc chloride,**18c**, was

purified by MPLC on silica gel, using a mixture of toluene and hexane (80 :20) as eluent, to give in 84 % yield pure (*E*)-**19c** as a colourless crystalline solid. M.p. 120-122 °C. MS, *m/z* (%): 346 (19), 344 (30), 315 (10), 313 (19), 215 (58), 213 (52), 207 (18), 119 (100), 91 (21). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 1.7 Hz, H-2" and H-6"), 7.75 (1H, s, H-3), 7.49 (2H, d, J = 7.8 Hz, H-2' and H-6'), 7.38 (1H, t, J = 1.7 Hz, H-4"), 7.19 (2H, d, J = 7.8 Hz, H-3' and H-5'), 3.91 (3H , s, OCH_3), 2.38 ppm (3H, s, CH_3). Anal. Calc for $C_9H_{14}Cl_2O_2$: C, 66.10; H, 4.09. Found: C, 66.17; H, 3.87.

*Methyl (E)-3-(3,5-dichlorophenyl)-2-(1-pentynyl)propenoate, (E)-**19d**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (*Z*)-**17d** and 1-pentynylzinc chloride, **18d**, was purified by MPLC on silica gel, using a mixture of benzene and hexane (50 : 50) as eluent, to give in 74 % yield pure (*E*)-**19d** as a colourless oil. MS, *m/z* (%): 298 (7), 286 (10), 269 (62), 267 (100), 256 (43), 254 (67), 223 (55),165 (73), 137 (31). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (2H, t, J = 1.7 Hz, H-2" and H-6"), 7.68 (1H, t, J = 1.7 Hz, H-4"), 7.36 (1H, s, H-3), 3.86 (3H, s, OCH_3), 2.52 (2H, t, J = 7.3 Hz, H-3'), 1.72 (2H, sext, J = 7.3 Hz, H -4'), 1.08 ppm (3H, t, J = 7.3 Hz, H-5'). Anal. Calc for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.75. Found: C, 61.00; H, 5.10.

*Ethyl (E)-3-phenyl-2-(phenylethynyl)propenoate, (E)-**19e**.* The crude reaction product, which was obtained from the Pd-catalyzed reaction between (*Z*)-**17e** and phenylethynylzinc chloride, **18a**, was purified by MPLC on silica gel, using a mixture of hexane and benzene (60 : 40) as eluent, to give in 88 % yield chemically and stereoisomericalyy pure (*E*)-**19e** as a pale yellow oil. MS, *m/z* (%): 276 (17), 247 (19), 203 (26), 202 (49), 201 (13), 105 (100) 77 (117. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.15-8.05 (2H, br m, Harom), 7.94 (1H, s, H-3), 7.65-7.27 (8H, br m, Harom), 4.35 (2H, q, J = 7.2 Hz, OCH_2), 1.40 ppm (3H, t, J = 7.2 Hz, O-C-CH_3). The spectral properties of this compound were in agreement with those previously reported.[27]

*Synthesis of methyl (E)-2-(1-alkynyl)-3-(hetero)arylpropenoates, (E)-**19** by Pd(0)- and Cu(I)-mediated reaction of 1-alkynes, **13**, with methyl (Z)-2-bromo-3-(hetero)arylpropenoates, (Z)-**17**.* In this procedure, which was used to prepare compounds (*E*)-**19g** and (*E*)-**19h**, Et_3N (2.50 ml, 18.0 mmol), a deareated solution of a methyl (*Z*)-2-bromo-3-(hetero)arylpropenoate, (*Z*)-**17**, (8.99 mmol) in benzene (10 ml) and a deareated solution of a 1-alkyne, **13**, (10.79 mmol) in benzene (3 ml) were sequentially added to a suspension of $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol) and CuI (0.171 g, 0.899 mmol) in benzene (16 ml). The resulting mixture was stirred at 20-40 °C under argon until a GLC analysis of a sample of the reaction mixture, which was treated with a saturated aqueous NH_4Cl solution and extracted with Et_2O, showed that compound (*Z*)-**17** had been consumed. In particular, the reaction conditions used for the preparation of (*E*)-**19g** and (*E*)-**19h** were 23 h at 20 °C and 24 h at 20 °C and 6 h at 40 °C, respectively. The reaction mixture was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The collected organic extracts were washed with water, dried, filtered over Celite and concentrated *in vacuo*. The residue, which was analyzed by GLC/MS and TLC, was diluted with the mixture of solvents which was used as eluent for TLC analysis and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel.

*Methyl (E)-3-(4-fluorophenyl)-2-(1-octynyl)propenoate, (E)-**19g**.* The crude reaction product, which was obtained by Pd(0)- and Cu(I)-catalyzed reaction between (*Z*)-**17f** and 1-octyne, **13b**, was purified by MPLC on silica gel, using a mixture of benzene and hexane (50 : 50) as eluent, to afford in 66 % yield pure (*E*)-**19g** as a colourless crystalline solid. M.p. 36-38 °C. MS , *m/z* (%): 288 (65), 217 (42), 185 (26), 159 (87), 157 (48), 133

(52), 109 (59), 59 (100), 55 (94). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04 (2H, dd, J = 8.7 and 5.7 Hz, Harom), 7.80 (1H, s, H-3), 7.08 (2H, t, J = 8.7 Hz, Harom), 3.85 (3H, s, OCH_3), 2.52 (2H, t, J = 6.8 Hz, H-3'), 1.70-1.20 (8H, br m, H-4', H-5', H-6' and H-7'), 0.90 ppm (3H, t, J = 6.5 Hz, H-8'). Anal. Calc for $C_{18}H_{21}FO_2$: C, 74.97; H, 7.34. Found: C, 75.15; H, 7.51.

*Methyl (E)-2-(1-hexynyl)-3-(2-thienyl)propenoate, (E)-**19h***. The crude reaction product, which was obtained from the Pd(0)- and Cu(I)-catalyzed reaction between (Z)-**17g** and 1-hexyne, **13c**, was purified by MPLC on silica gel, using a mixture of benzene and hexane (60 : 40) as eluent, to give in 53 % yield 98 % chemically pure (*E*)-**19h** as a colourless oil. MS, m/z (%): 249 (10), 248 (62), 205 (71), 187 (20), 161 (34), 147 (100), 145 (42), 134 (29), 115 (28). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (1H, s, H-3), 7.53-7.47 (2H, br m, H-5' and H-3'), 7.11 (1H, *pseudo* t, J = 4.1 Hz, H-4'), 3.85 (3H, s, OCH_3), 2.59 (2H, t, J = 7.0 Hz, H-3''), 1.67 (2H, quint, J = 7.0 Hz, H-4''), 1.54 (2H, sext, J = 7.1 Hz, H-5''), 0.96 ppm (3H, t, J = 7.1 Hz, H-6''). Anal. Calc for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.77; H, 6.79.

*(E)-3-(3,4-Methylenedioxy)phenyl-2-(phenylethynyl)propenoic acid, (E)-**11f***. A 3N aqueous KOH solution (17.7 ml, 53.2 mmol) was added to a solution of (*E*)-**19f** (1.63 g, 5.32 mmol) in THF (20 ml), which was cooled to 0 °C. The resulting mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The residue was diluted with water and extracted repeatedly with CH_2Cl_2. The resulting aqueous suspension was cooled to 0 °C, acidified with 10 % H_2SO_4 and extracted repeatedly with a mixture of THF and Et_2O (1 : 1). The collected organic extracts were washed with water, dried and concentrated *in vacuo* to afford (*E*)-**11f** (1.50 g, 96 % yield). ^{1}H NMR (200 MHz, DMSO-d^6): δ 7.91 (1H, br s, H-3 or H-2''), 7.88 (1H, s, H-2'' or H-3), 7.64-7.39 (6H, br m, Harom), 7.08 (1H, d, J = 8.2 Hz, H-5'' or H-6''), 6.13 ppm (2H, s, O-CH_2-O). This crude compound, which was a solid, was used in the next step without any further purification and characterization.

*(E)-2-(1-Octynyl)-2-heptenoic acid, (E)-**11a***. This compound was prepared in 99 % yield from (*E*)-**19a** by a procedure similar to that employed to prepare (*E*)-**11f**. Compound (*E*)-**11a**, which was a colourless oil, had ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.9 (1H, br s, COOH), 7.25 (1H, t, J = 7.6 Hz, H-3), 2.42 (4H, br t, J = 6.8 Hz, H-4 and H-3'), 1.70-1.15 (12H, br m, H-5, H-6, H-4', H-5', H-6' and H-7'), 1.05-0.80 ppm (6H, br m, H-7 and H-8'). This crude compound was used in the next step without any further purification and characterization.

*(E)-5-Methyl-2-phenylethynylpropenoic acid, (E)-**11b***. This compound was prepared in quantitative yield from (*E*)-**19b** by a procedure very similar to that employed for the synthesis of (*E*)-**11f**. Compound (*E*)-**11b** had ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.40 (1H, br s, COOH), 7.60-7.05 (6H, br m, H-3 and C_6H_5), 2.45 (2H, t, J = 7.2 Hz, H-4), 1.92 (1H, br m, H-5), 1.00 ppm (6H, d, J = 6.6 Hz, $C(CH_3)_2$). This crude compound, which was a solid, was used in the next step without any further purification and characterization.

*(E)-3-(3,5-Dichlorophenyl)-2-(p-tolylethynyl)propenoic acid, (E)-**11c*** . A 6N aqueous KOH solution (12.1 ml, 77.4 mmol) was added to a solution of (*E*)-**19c** (2.50 g, 7.24 mmol) in THF (25 ml), which was cooled to 0 °C and the resulting mixture was stirred for 18 h at room temperature. It was then concentrated *in vacuo* and the solid residue so obtained was diluted with water, filtered and washed repeatedly with Et_2O. The aqueous filtrate was extracted repeatedly with Et_2O and the resulting aqueous phase was added to the washed solid. The resulting mixture was cooled to 0 °C, acidified with diluted H_2SO_4 and extracted repeatedly with CH_2Cl_2 and

then with benzene. The collected organic extracts were washed with water, dried and concentrated *in vacuo* to afford compound (*E*)-**11c** (2.40 g, 100 % yield) as a colourless solid. ^{1}HNMR (200 MHz, DMSO-d^6): δ 8.18 (2H, br s, H-2" and H-6"), 7.78 (1H, s, H-3), 7.66 (1H, br s, H-4"), 7.43 (2H, br s, H-2' and H-6'), 7.31 (2H, br s, H-3' and H-5'), 2.36 ppm (3H, s, CH_3). This crude compound was used in the next step without any further purification and characterization.

*(E)-3-(3,5-Dichlorophenyl)-2-(1-pentynyl)propenoic acid, (E)-**11d**.* This compound was obtained in quantitative yield from (*E*)-**19d** by a procedure very similar to that employed to prepare (*E*)-**11f**. Compound (*E*)-**11d** had: m.p. 130 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.8 (1H, br s, COOH), 7.96 (2H, br s, H-2" and H-6"), 7.77 (1H, s, H-4"), 7.39 (1H, t, J = 1.8 Hz, H-3), 2.54 (2H, t, J = 7.2 Hz, H-3'), 1.73 (2H, sext, J = 7.2 Hz, H-4'), 1.09 ppm (3H, t, J = 7.2 Hz, H-5'). This crude compound was used in the next step without any further purification and characterization.

*(E)-3-Phenyl-2(phenylethynyl)propenoic acid, (E)-**11e**.* This compound was obtained in 99 % yield from (*E*)-**19e** by a procedure very simlar to that employed to prepare (*E*)-**11f**. Compound (*E*)-**11e** had: m.p. 168-170 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.10 (1H, br s, COOH), 8.18-8.08 (2H, br m, Harom), 8.05 (1H, s, H-3), 7.62-7.52 (2H, br m, Harom), 7.52-7.32 ppm (6H, m, Harom). This crude product was used in the next step with out any further purification and characterization.

*(E)-3-(4-Fluorophenyl)-2-(1-octynyl)propenoic acid, (E)-**11g**.* This compound was obtained in 98 % yield from (*E*)-**19g** by a procedure very similar to that employed to prepare (*E*)-**11f**. Compound (*E*)-**11g** had ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.90 (1H, br s, COOH), 8.09 (2H, dd J = 8.6 e 5.8 Hz, Harom), 7.89 (1H, s, H-3), 7.10 (2H, t, J = 8.6 Hz, Harom), 2.54 (2H, t, J = 6.9 Hz, H3'), 1.74-1.25 (8H, br m, H-4', H-5', H-6' and H-7'), 0.91 ppm (3H, t, J = 6.2 Hz, H-8'). This crude compound was used in the next step without any further purification and characterization.

*(E)-2-(1-Hexynyl)-3-(2-thienyl)propenoic acid, (E)-**11h**.*. This compound was obtained in 95 % yield from (*E*)-**19h** by a procedure very simlar to that employed to prepare (*E*)-**11f**. Compound (*E*)-**11h** had: m.p. 156-158 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.65 (1H, br s, COOH), 8.16 (1H, s, H-3), 7.57-7.45 (2H, br m, H-5" and H-3"), 7.13 (1H, pseudo t, J = 4.1 Hz, H-4'), 2.60 (2H, t, J = 6.9 Hz, H-3'), 1.70 (2H, quint, J = 7.3 Hz, H-4'), 1.54 (2H, sext, J = 7.3 Hz, H-5'), 0.97 ppm (3H, t, J = 7.3 Hz, H-6'). This crude compound was used in the next step without any further purification and characterization.

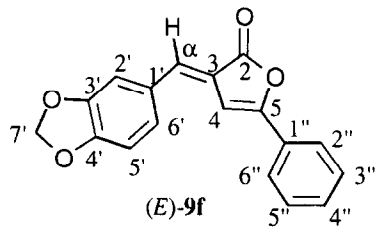
*Synthesis of (E)-3-[1-(aryl)methylidene]-5-aryl/alkyl-3H-furan-2-ones, (E)-**9**, by cyclization of the corresponding (E)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids, (E)-**11**, in the presence of Et_3N and $PdCl_2(CH_3CN)_2$ or $PdCl_2(PhCN)_2$ (Procedure A).* In a typical preparation, Et_3N (0.11 ml, 0.78 mmol) was added to a deareated solution of $PdCl_2(CH_3CN)_2$ (0.067 g, 0.259 mmol) and an (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acid, (*E*)-**11**, (5.18 mmol) in THF (22 ml), which was stirred at room temperature. The resulting mixture was refluxed for the period of time reported in the Table. It was then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with a large excess of CH_2Cl_2 and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel. This procedure was employed for the synthesis of compounds (*E*)-**9e**, (*E*)-**9g** and (*E*)-**9h** starting from crude (*E*)-**11f**,

(*E*)-**11g** and (*E*)-**11h**, respectively (Entries 8, 7 and 9, Table). A very similar procedure, in which the palladium compound employed was $PdCl_2(PhCN)_2$, was used for the preparation of (*E*)-**9f** starting from crude (*E*)-**11f** (Entry 1, Table). Finally, the synthesis of compound (*E*)-**9c** was carried out by cyclization of crude (*E*)-**11c** in DMF solution at 90 °C, in the presence of Et_3N and $PdCl_2(CH_3CN)_2$ (Entry 4, Table). In fact, (*E*)-**11c** was insoluble in THF.

*Synthesis of (E)-3-[1-(aryl)methylidene]-3-aryl/alkyl-3H-furan-2-ones, (E)-**9**, by cyclization of the coresponding (E)-2-(1-alkynyl)-3-aryl-propenoic acids, (E)-**11**, in the presence of trans-di(μ-acetato)bis[(di-o-tolylphosphino)benzyl]dipalladium (Procedure B).* In a typical preparation, *trans*-di(μ-acetato)bis[(di-o-tolylphosphino)benzyl]dipalladium (0.147 g, 0.15 mmol) was added to a deareated solution of an (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acid, (*E*)-**11**, (3.11 mmol) in toluene (30 ml) and the resulting mixture for refluxed under argon for the period of time reported in the Table. The reaction mixture was the concentrated *in vacuo* and the residue was purified by MPLC on silica gel. This procedure was employed to prepare compounds (*E*)-**9d** and (*E*)-**9e** from (*E*)-**11d** and (*E*)-**11e**, respectively (Entries 5 and 6, Table).

*Synthesis of (E)-3-[1-(aryl)methylidene]- and (E)-3-(1-alkylidene)-3-aryl/alkyl-2(3H)-furanones, (E)-**9**, by cyclization of the corresponding (E)-2-(1-alkynyl)-3-aryl/alkylpropenoic acids, (E)-**11**, in the presence of $AgNO_3$ (Procedure C).* In a typical preparation, $AgNO_3$ (0.14 g, 0.81 mmol) was added to a deareated solution of an (*E*)-2-(1-alkynyl)-3-aryl/alkylpropenoic acid, (*E*)-**11**, (4.05 mmol) in acetone and the resulting mixture was stirred at room temperature for the period of time reported in the Table. The reaction mixture was then concentrated *in vacuo* and the residue was purified by MPLC on silica gel. This procedure was employed to prepare compounds (*E*)-**9a**, (*E*)-**9b** and (*E*)-**9h** from the corresponding carboxylic acids (*E*)-**11a**, (*E*)-**11b** and (*E*)-**11h**, respectively (Entries 2, 3 and 10, Table).

*(E)-3-[1-(3,4-Methylenedioxyphenyl)methylidene]-5-phenyl-3H-furan-2-one, (E)-**9f**.* The crude reaction product, which was obtained by cyclization of (*E*)-**11f** in the presence of Et_3N and $PdCl_2(PhCN)_2$ (Entry 1, Table), was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and hexane (60 : 40) as eluent, to give in 64 % yield chemically and stereoisomerically pure (*E*)-**9f** as a yellow crystalline solid. M.p. 159-161 °C. MS, *m/z* (%): 293 (8), 292 (42), 246 (6), 159 (14), 105 (100), 101 (7), 77 (56), 75 (15), 51 (28). IR (KBr): 1754, 1503, 1490, 1451, 1268, 1247, 1046, 1006, 937, 923, 898, 884, 812, 797, 788, 737 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (2H, dd, J = 8.3 and 1.6 Hz, H-6" and H-2"), 7.47-7.39 (3H, m, H-3", H-4" and H-5"), 7.33 (1H, ddd, J = 0.7, 0.6 and 1.0 Hz, H-α), 7.16 (1H, ddd, J = 0.7, 1.8 and 8.5 Hz, H-6'), 7.15 (1H, dd, J = 1.8 and 0.6 Hz, H-2'), 6.90 (1H, d, J = 8.5 Hz, H-5'), 6.89 (1H, d, J = 1.0 Hz, H-4), 6.06 ppm (2H, s, H-7'). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.69 (C-2), 156.33 (C-5), 149.71 (C-4'), 148.55 (C-3'), 135.35 (C-α), 130.34 (C-4"), 129.62 (C-3), 128.89 (C-3" and C-5"), 128.24 (C-1'), 126.75 (C-6'), 125.26 (C-2" and C-6"), 123.44 (C-1"), 109.06 (C-5'), 108.77 (C-2"), 101.83 (C-7'), 99.73 ppm (C-4). Anal. Calc for $C_{18}H_{12}O_4$: C, 73.97; H, 4.14. Found: C, 74.15; H, 4.35. The structure and stereochemistry of compound (*E*)-**9f** were confirmed by a combination of NMR techniques which included ^1H-^1H-COSY, 2D-NOESY and ^1H-^{13}C heteronuclear shift correlation.



(*E*)-**9f**

*(E)-5-Hexyl-3-(1-pentylidene)-3H-furan-2-one, (E)-**9a**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11a** in the presence of $AgNO_3$ (Entry 2; Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (70 : 30) as eluent, to give in 39 % yield chemically and steroisomerically pure (*E*)-**9a** as a colourless liquid. MS, *m/z* (%): 236 (46), 181 (32), 165 (30), 137 (22), 123 (99), 110 (100), 95 (54), 81 (27), 43 (58). IR (film): 1777, 1653, 1632, 1467, 1128, 923, 735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.57 (1H, t, J = 7.8 Hz, H-α), 5.79 (1H, s, H-4), 2.39 (2H, t, J = 7.3 Hz, H-1"), 2.29 (2H, t, J = 7.8 Hz, H-2'), 1.70-1.15 (12H, br m, H-2", H-3", H-4", H-5", H-3' and H-4'), 0.92 ppm (6H, br t, J = 7.0 Hz, H-6" and H-5'). Anal.Calc for $C_{15}H_{24}O_4$: C, 76.23; H, 10.23. Found: C, 76.11; H, 9.93.

*(E)-3-(3-Methyl-1-butylidene)-5-phenyl-3H-furan-2-one, (E)-**9b**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11b** in the presence of $AgNO_3$ (Entry 3, Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (70 : 30) as eluent, to give in 38 % yield chemically and stereoisomerically pure (*E*)-**9b** as a colourless crystalline solid. M.p. 56-58 °C. MS, m/z (%): 228 (26), 185 (44), 172 (94), 157 (27), 129 (20), 105 (100), 77 (78). IR (KBr): 1776, 1762, 1646, 1134, 1043, 988, 904, 879, 824, 761, 738, 687 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.75-7.62 (2H, m, Harom), 7.48-7.35 (3H, m, Harom), 6.78 (1H, t, J = 8.1 Hz, H-α), 6.47 (1H, s, H-4), 2.32 (2H, t, J = 8.1 Hz, H-2'), 1.89 (1H, m, H-3'), 0.99 ppm (6H, d, J = 6.7 Hz, $C(CH_3)_2$). Anal. Calc for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.94; H, 7.11.

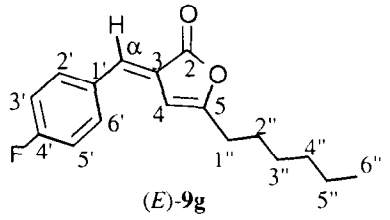
*(E)-3-[1-(3,5-Dichlorophenyl)methylidene]-5-(p-tolyl)-3H-furan-2-one, (E)-**9c**.* The crude reaction product, which was obtained by cyclization of (*E*)-**11c** in DMF solution, in the presence of Et_3N and $PdCl_2(CH_3CN)_2$ (Entry 4, Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (65 : 35) as eluent, to give in 9 % yield pure (*E*)-**9c** as a yellow crystalline solid. M.p. 158 °C. MS, *m/z* (%): 332 (10), 330 (14), 119 (100), 91 (38), 65 (8). IR (KBr): 1790, 1591, 1175, 926, 848, 815, 801, 740, 670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.69 (2H, d, J = 8.1 Hz, H-2' and H-6'), 7.46 (2H, br s, Harom), 7.38 (1H, s, H-α), 7.31-7.20 (3H, m, Harom), 6.79 (1H, s, H-4), 2.42 ppm (3H, s, CH_3). Anal. Calc for $C_{18}H_{12}Cl_2O_2$: C, 65.28; H, 3.65. Found: C, 65.35; H, 3.81.

*(E)-3-[1-(3,5-Dichlorophenyl)methylidene]-5-propyl-3H-furan-2-one, (E)-**9d**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11d** in the presence of *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino)benzyl]dipalladium (Entry 5, Table)], was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (80 : 20) as eluent, to give in 67 % yield pure (*E*)-**9d** as a yellow crystalline solid. M.p. 57-58 °C. MS, *m/z* (%): 284 (5), 185 (3), 183 (3), 148 (3), 71 (100), 43 (48). IR (KBr): 1773, 1628, 1613, 1030, 925, 847, 671 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.38 (3H, br s, Harom), 7.11 (1H, s, H-α), 6.20 (1H, s, H-4), 2.49 (2H, t, J = 7.3 Hz, H-1'), 1.70 (2H, sext, J = 7.3 Hz, H-2"), 1.01 ppm (3H, t, J = 7.3 Hz, H-3"). Anal.

Calc for $C_{14}H_{12}Cl_2O_2$: C, 59.38; H, 4.27. Found: C, 59.27; H, 4.22.

*(E)-5-Phenyl-3-[1-(phenyl)methylidene]-3H-furan-2-one, (E)-**9e**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11e** in the presence of $PdCl_2(CH_3CN)_2$ and Et_3N (Entry 8, Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give in 42 % yield stereoisomerically pure (*E*)-**9e** as a yellow crystalline solid. M.p. 149 °C. Lit. m.p. 149-150 °C;[28] 155 °C.[29] MS, *m/z* (%): 248 (58), 207 (3), 115 (7), 105 (100), 77 (59), 63 (11), 51 (42). IR (KBr): 1765, 1625, 1451, 1278, 1004, 996, 883, 752, 680 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.80-7.70 (2H, br m, Harom), 7.70-7.57 (2H, br m, Harom), 7.52-7.36 (7H, br m, Harom and H-α), 6.93 ppm (1H, br s, H-4). Anal. Calc for $C_7H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.12; H, 4.95. It must be noted that this same product was obtained in 87 % yield by cyclization of (*E*)-**11e** in the presence of *trans*-di(μ-acetato)bis[(di-*o*-tolylphosphino]benzyl]dipalladium (Entry 6, Table).

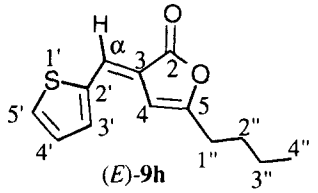
*(E)-3-[1-(4-Fluorophenyl)methylidene]-5-hexyl-3H-furan-2-one, (E)-**9g**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11g** in the presence of Et_3N and $PdCl_2(CH_3CN)_2$ (Entry 7, Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give in 79 % yield pure (*E*)-**9g** as a yellow crystalline solid. M.p. 62 °C. MS, m/z (%): 274 (100), 204 (42), 203 (36), 162 (54), 134 (71), 113 (50), 85 (32), 43 (61). IR (KBr): 1763, 1636, 1596, 1508, 1146, 930, 835, 507 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.54 (2H, ddd, J_{H-H} = 8.7 and 2.9 Hz, J_{H-F} = 5.4 Hz, H-2'and H-6'), 7.25 (1H, br s, H-α), 7.12 (2H, ddd, J_{H-H} = 8.7 and 2.9 Hz, J_{H-F} = 8.7 Hz, H-3' and H-5'), 6.21 (1H, dt, J = 1.1 and 1.1 Hz, H-4), 2.48 (2H, dt, J = 7.3 and 1.1 Hz, H-1"), 1.64 (2H, quint, J = 7.3 Hz, H-2"), 1.38 (2H, quint, J = 7.3 Hz, H-3"), 1.32 (4H, m, H-4" and H-5"), 0.90 ppm (3H, t, J = 7.3 Hz, H-6"). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.83 (C-2), 162.58 (C-5), 163.43 (C-4'), 132.58 (C-α), 131.83 (C-2' and C-6'), 131.44 (C-1'), 125.02 (C-3), 116.26 (C-3' and C-5'), 100.70 (C-4), 31.45 (C-4"), 28.95 (C-1"), 28.77 (C-3"), 25.89 (C-2"), 22.48 (C-5"), 14.02 ppm (C-6"). Anal. Calc for $C_{17}H_{19}FO_2$: C, 74.43; H, 6.98. Found: C, 74.58; H, 7.12. The structure of this compound was confirmed by of NMR techniques which included a 1D-NOE selective experiment and ^1H-^{13}C heteronuclear multiple-quantum coherence (HMQC) experiments.



(*E*)-**9g**

*(E)-5-Butyl-3-[1-(2-thienyl)methylidene]-3H-furan-2-one, (E)-**9h**.* The crude reaction product, which was obtained by cyclization of crude (*E*)-**11h** in the presence of $AgNO_3$ (Entry 10, Table), was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give in 72 % yield pure (*E*)-**9h** as a yellow crystalline solid. M.p. 60-62 °C. MS, m/z (%): 235 (18), 234 (100), 150 (32), 121 (44), 85 (79), 57 (41), 41 (34). IR (KBr): 1760, 1625, 1605, 1248, 1150, 1025, 928, 852, 714 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (1H, ddd, J = 4.9, 1.1 and 1.1 Hz, H-5'), 7.43 (1H, ddd, 1.1, 1.1 and 1.1 Hz, H-α), 7.35 (1H, ddd, J = 3.6, 1.1 and 1.1 Hz, H-3'), 7.12 (1H, dd, J = 4.9 and 3.6 Hz, H-4'), 6.62 (1H, dt, J = 1.1 and 1.1 Hz, H-4), 2.49 (2H,

dt, J = 7.4 and 1.1 Hz, H-1"), 1.65 (2H, quint, J = 7.4 Hz, H-2"), 1.42 (2H, sext, J = 7.4 Hz, H-3"), 0.96 ppm (3H, t, J = 7.4 Hz, H-4"). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.88 (C-2), 161.42 (C-5), 139.33 (C-2'), 133.32 (C-3'), 130.45 (C-5'), 128.15 (C-4'), 125.95 (C-α), 122.78 (C-3), 101.54 (C-4), 28.65 (C-1"), 28.07 (C-2"), 22.22 (C-3"), 13.73 ppm (C-4"). Anal. Calc for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.84; H, 6.32. The structure of this compound was confirmed by NMR techniques which included 2D-NOESY and ^1H-^{13}C heteronuclear multiple-quantum coherence experiments.



(*E*)-**9h**

Alternatively, this same compound was prepared in 39 % yield by cylization of crude (*E*)-**11h** in the presence of Et_3N and $PdCl_2(CH_3CN)_2$ (Entry 9, Table).

*(Z)-2-Bromo-3-(4-chlorophenyl)propenoic acid, (Z)-**12h***. This compound was prepared in 97 % yield from (Z)-**17h** by a procedure similar to that used for the synthesis of compound (*E*)-**11a**, in which, however, the base used was 1N LiOH. Compound (Z)-**12h** had: m.p. 200-201 °C. MS, *m/z* (%): 263 (14), 262 (81), 261 (16), 185 (11), 184 (21), 183 (100), 152 (11), 108 (51), 107 (22). ^1H NMR (200 MHz, DMSO-d^6): δ 8.24 (1H, s, H-3), 7.93 (2H, d, J = 8.5 Hz, H-3' and H-5'), 7.56 ppm (2H, d, J = 8.5 Hz, H-2' and H-6'). This crude compound was used in the next step without any further purification and characterization.

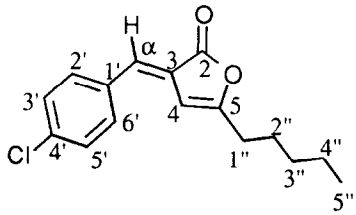
*Palladium-catalyzed cross couplin-cyclization of (Z)-**12h** with phenylacetylene, **13a**: synthesis of (E)-3-[1-(4-chlorophenyl)methylidene]-5-phenyl-3H-furan-2-one, (E)-**9i***. Deareated CH_3CN (150 ml), phenylacetylene, **13a**, (2.34 g, 22.94 mmol) and Et_3N (8.5 ml, 51.2 mmol) were sequentially added to a mixture of crude (Z)-**12h** (3.04 g, 11.6 mmol), CuI (0.146 g, 0.76 mmol) and $Pd(PPh_3)_4$ (0.88 g, 0.76 mmol) and the resulting mixture was stirred under argon at 20 °C for 23 h and for 23 h at 85 °C. It was the concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 and washed with diluted H_2SO_4 and water. The organic extact was filtered over Celite, dried and concentrated *in vacuo*. The residue was diluted with a mixture of hexane and CH_2Cl_2 (60 : 40) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give pure (*E*)-**9i** (0.74 g, 22.5 % yield) as a yellow crystalline solid. M.p. 230 °C (from benzene and hexane). MS, *m/z* (%): 284 (7), 282 (20), 114 (3), 106 (7), 105 (100), 77 (36). IR (KBr): 1759, 1623, 1490, 1091, 1004, 818, 739, 681, 542 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.82-7.70 (2H, br m, Harom), 7.62-7.40 (7H, br m, Harom), 7.37 (1H, s, H-α), 6.88 ppm (1H, s, H-4). Anal. Calc for $C_{17}H_{11}ClO_2$: C, 72.22; H, 4.04. Found: C, 72.35; H, 4.04.

*Palladium-catalyzed cross coupling-cyclization of (Z)-**12h** with 1-hexyne, **13c**: synthesis of (E)-5-butyl-3-[1-(4-chlorophenyl)methylidene]-3H-furan-2-one, **(E)-9j**, and (E)/(Z)-3-[1-(4-chlorophenyl)methyl]-5-(1-propylidene)-5H-furan-2-one, (E)/(Z)-**20***. 1-Hexyne, **13c**, (3.43 ml, 29.9 mmol) and Et_3N (11.1 ml, 79.7 mmol) were sequentially added to a deareated mixture of crude (Z)-**12h** (5.20 g, 19.9 mmol), $Pd(PPh_3)_4$ (1.15 g, 0.996 mmol) and CuI (0.19 g, 0.996 mmol) in CH_3CN (200 ml) and the resulting mixture was stirred for 70 h at 20 °C and for 24 h at 80 °C. It was then concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 and

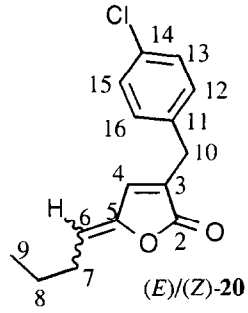
washed repeatedly with diluted H_2SO_4 and water. The collected organic extracts were filtered over Celite, dried and concentrated *in vacuo*. The residue was diluted with a large excess of a mixture of hexane and CH_2Cl_2 (60 : 40) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent. Concentration of the first eluted chromatographic fractions yielded a yellow crystalline solid, which was diluted with a mixture of hexane and CH_2Cl_2 (60 : 40) and filtered. Concentration of the filtrate yielded chemically and stereoisomerically pure (*E*)-**9j** (0.57 g, 10.9 % yield) as a yellow crystalline solid. M.p. 85-87 °C. MS, *m/z* (%): 264 (9), 262 (30), 178 (18), 149 (16), 114 (11), 85 (100), 57 (34). IR (KBr): 1765, 1632, 1276, 1172, 1010, 931, 820, 670, 517 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.48 (2H, d, J = 8.7 Hz, H-3" and H-5"), 7.39 (2H, d, J = 8.7 Hz, H-2" and H-6"), 7.23 (1H, s, H-α), 6.21 (1H, s, H-4), 2.49 (2H, t, J = 7.4 Hz, H-1'), 1.65 (2H, quint, J = 7.4 Hz, H-2'), 1.41 (2H, sext, J = 7.4 Hz, H-3'), 0.99 ppm (3H, t, J = 7.4 Hz, H-4'). Anal. Calc for $C_{15}H_{15}ClO_2$: C, 67.57; H, 5.75. Found: C, 67.61; H, 5.85.

Concentration of the intermediate chromatographic fractions yielded a solid residue, which was purified by MPLC on silica gel using a mixture of hexane and Et_2O (90 : 10) as eluent. Concentration of the first eluted fractions gave stereoisomerically pure (*Z*)-**20** (0.37 g, 7.1 % yield) as a pale yellow oil. MS, *m/z* (%): 264 (19), 262 (61), 233 (24), 220 (32), 185 (68), 171 (33), 141 (24), 115 (69), 55 (100). IR (film): 1774 , 1493, 1267, 1092, 1042, 1016, 983, 895, 806 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.276 (2H, d, J = 8.5 Hz, H-13 and H-15), 7.141 (2H, d, J = 8.5 Hz, H-16 and H-12), 6.184 (1H, m, H-4), 5.152 (1H, t, J = 8.0 Hz, H-6), 3.620 (2H, s, H-10), 2.326 (2H, dt, J = 7.5 and 7.5 Hz, H-7), 1.464 (2H, sext, H-8), 0.919 ppm (3H, t, J = 7.5 Hz, H-9). ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.14 (C-2), 148.38 (C-5), 138.03 (C-4), 135.76 (C-3), 133.80 (C-14), 130.21 (C-13 and C-15), 129.37 (C-11), 128.86 (C-12 and C-16), 115.94 (C-6), 30.92 (C-10), 28.16 (C-7), 22.27 (C-8), 13.67 ppm (C-9). Anal. Calc for $C_{15}H_{15}ClO_2$: C, 67.57; H, 5.75. Found: C, 67.51; H, 5.90. Concentration of the last eluted fractions of this second chromatography gave a mixture of (*Z*)- and (*E*)-**20** (0.13 g, 2.5 % yield) ina *ca.* 1 : 1 ratio. On the other hand, concentration of the last eluted fractions of the first chromatography gave a 97.6 % chemically pure mixture of (*Z*)- and (*E*)-**20** (1.27 g, 24.3 % yield) in a 17.2 : 82.8 ratio, respectively. This mixture was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give a new mixture of (*Z*)- and (*E*)-**20** in a *ca.* 10 : 90 ratio, respectively. Compound (*E*)-**20** had MS, *m/z* (%): 264 (15), 262 (47), 233 (17), 220 (22), 185 (55), 171 (23), 141 (15), 115 (48), 55 (100). ^1H NMR (600 MHz, $CDCl_3$):δ 7.29 (2H, d, J = 8.5 Hz, H-15 and H-13), 7.17 (2H, d, J = 8.5 Hz, H-12 and H-16), 7.08 (1H, m, H-4), 5.65 (1H, t, J = 8.5 Hz, H-6), 2.16 (2H, q, J = 7.5 Hz, H-7), 1.48 (2H, sext, J = 7.5 Hz, H-8), 0.91 ppm (3H, t, J = 7.5 Hz, H-9). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.01 (C-2), 148.64 (C-5), 135.62 (C-3), 133.47 (C-14), 132.30 (C-4), 130.25 (C-13 and C-15), 129.53 (C-11), 128.92 (C-12 and C-16), 115.16 (C-6), 31.14 (C-10), 28.36 (C-7), 22.81 (C-8), 13.49 ppm (C-9). Selective 1D-NOE experiments allowed to confirm the stereochemistry of compounds (*Z*)- and (*E*)-**20**. In particular, by selective excitation of the resonance at 5.152 ppm attributed to H-6 in (*Z*)-**20** (negative signal), it was observed a positive signal at 6.814 ppm, which was attributed to H-4. On the other contrary, no NOE contact was observed by selective excitation of the resonance at 5.651 ppm (negative signal), which was attributed to H-6 in (*E*)-**20**.

It must also be mentioned that when compound (*E*)-**9j** was reacted with 3 equiv of Et_3N in CH_3CN under reflux for 5 h, a mixture of (*E*)- and (*Z*)-**20** in a *ca.* 60 : 40 ratio, respectively, was obtained.

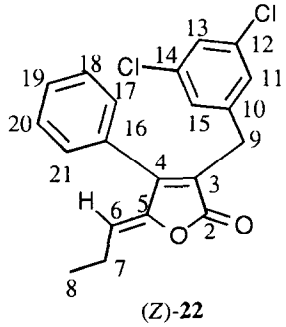


(*E*)-**9j**



(*E*)/(*Z*)-**20**

*(Z)-3-(3,5-Dichlorophenyl)methyl-4-phenyl-5-(1-propylidene)-5H-furan-2-one, (Z)-**22***. $Pd(PPh_3)_4$ (2.04 g, 1.76 mmol) was added to a deareated mixture of crude (*E*)-**11d** (1.0 g, 3.53 mmol), iodobenzene, **21**, (0.77 ml, 7.01 mmol), *n*-Bu_4NCl (0.98 g, 3.53 mlmol) and Et_3N (17.4 ml, 124.8 mmol) in DMSO (30 ml) and the resulting mixture was stirred at 85 °C for 22 h under argon. It was then cooled to room temperature, poured into a large excess of water and extracted repeatedly with $CHCl_3$. The collected organic extracts were washed with water, dried, filtered and concentrated *in vacuo*. The residue was diluted with a large excess of a mixture of hexane and CH_2Cl_2 (65 : 35) and filtered over Celite.The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel using a mixture of hexane and CH_2Cl_2 (65 : 35) as eluent. GLC/MS analysis of the chromatographic fractions which contained the reaction product showed that it was contaminated by PPh_3 and PPh_3O. Thus, these fractions were collected and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (60 : 40) as eluent, to give pure (*Z*)-**22** (0.29 g, 22.8 % yield) as a yellow oil. MS, *m/z* (%): 362 (11), 361 (10), 360 (49), 359 (21), 358 (74), 225 (100), 189 (85), 94 (50), 55 (57). IR (film): 1763, 1569, 1432, 1058, 795, 767, 702 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.50 (3H, , H-18, H-19 and H-20), 7.25 (2H, m , H-17 and H-21), 7.16 (1H, dd, J = 1.8 and 1.8 Hz, H-13), 6.98 (2H, d, J = 1.8 Hz, H-11 and H-15), 5.23 (1H, t, J = 7.6 Hz, H-6), 3.64 (2H, s, H-9), 2.43 (2H, quint, J = 7.6 Hz, H-7), 1.07 ppm (3H, t, J = 7.6 Hz, H-8). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.50 (C-2), 152.01 (C-4), 148.71 (C-5), 141.19 (C-3), 134.95 (C-12 and C-14), 129.81 (C-19), 129.74 (C-16), 128.92 (C-18 and C-20), 128.66 (C-17 and C-21), 127.00 (C-11 and C-15), 126.88 (C-13), 125.50 (C-10), 118.16 (C-6), 29.18 (C-9), 19.99 (C-7), 13.54 ppm (C-8). Anal. Calc for $C_{20}H_{16}Cl_2O_2$: C, 66.87; H, 4.49. Found: C, 66.95; H, 4.63. The structure and stereochemistry of this compound were confirmed by NMR experiments which included ^1H-^1H NOESY and ^1H-^{13}C heteronuclear long range shift correlation.



(*Z*)-**22**

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