Pergamon

Tetrahedron 57 (2001) 2857–2870

TETRAHEDRON

Selective synthesis of natural and unnatural 5,6-disubstituted 2(2*H*)-pyranones via iodolactonization of 5-substituted (*Z*)-2-en-4-ynoic acids

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Received 7 November 2000; revised 11 January 2001; accepted 25 January 2001

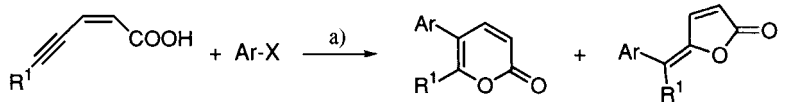
Abstract—Reaction of 5-substituted (*Z*)-2-en-4-ynoic acids with iodine and $NaHCO_3$ in CH_3CN or with ICl in CH_2Cl_2 affords mixtures of (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones and 6-substituted 5-iodo-2(2*H*)-pyranones in which these last compounds are the major products. The 5-iodo-2(2*H*)-pyranones, which are easily separated chromatographically from the corresponding regioisomers, are able to undergo Stille-type reactions with a variety of organotin compounds to give 5,6-disubstituted 2(2*H*)-pyranones in moderate to good yields. One of these compounds, i.e. 5-(1-butynyl)-2(2*H*)-pyranone, has been used as direct precursor to two substances produced by fungal culture LL-11G219, which function as androgen ligands, i.e. (*Z*)-5-(1-butenyl)-6-methyl-2(2*H*)-pyranone and 5-butyl-6-methyl-2(2*H*)-pyranone.

2(2*H*)-Pyranones are useful intermediates for the synthesis of a variety of carbo-[1] and heterocyclic compounds[2] and occur as structural subunits in a large number of natural products, which display a wide range of biological activities including antimicrobial,[3] androgen like,[4] phytotoxic,[5] cardiotonic,[6] antifungal[7] and pheromonal effects.[8] As a consequence, much attention has been paid to the synthesis of 2(2*H*)-pyranone derivatives either by the traditional approaches[9] or by procedures involving transition metal-catalyzed reactions.[10] Nevertheless, despite the plethora of these synthetic processes it is rather disappointing to note that no general procedure has been developed so far for the regioselective synthesis of natural and unnatural unsymmetrically 5,6-disubstituted 2(2*H*)-pyranones.

Recently, we began an investigation on this subject and we found that treatment of (*Z*)-2-en-4-ynoic acids **1** with aryl halides **2** in the presence of K_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$ provides mixtures of 6-substituted 5-aryl-2(2*H*)-pyranones **3** and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]-2(5*H*)-furanones **4** in which, however, these last compounds are the major products (Scheme 1).[11]

More recently, in continuation of our studies on the synthesis of oxygen-containing heterocycles by approaches which involve intramolecular additions of carboxylic acids to alkynes,[12] we developed a new and convenient procedure for the synthesis of 5,6-disubstituted 2(2*H*)-pyranones of general formula **5** (Fig. 1).

We now wish to report that, under suitable reaction conditions, 5-iodo-2(2*H*)-pyranones **6** can be obtained as major products by iodolactonization of (*Z*)-2-en-4-ynoic acids **1** and that these heterocyclic iodides, which represent a not previously reported class of organic electrophiles, are useful precursors to compounds **5**. In fact, we found that compounds **6** are able to undergo palladium-catalyzed reactions with organostannanes **8** such as tetramethylstannane, vinyltributylstannane, aryl- and 1-alkynyltributylstannanes



1 : R^1 = aryl, alkyl — **2** — **3** : R^1 = aryl, alkyl (0 - 7 %) — **4** : R^1 = aryl, alkyl (26 - 38 %)

Scheme 1. (a) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (4 equiv.), CH_3CN, 70–80°C.

Keywords: heterocycles; iodine; cross-coupling; organometallic compounds; natural products.
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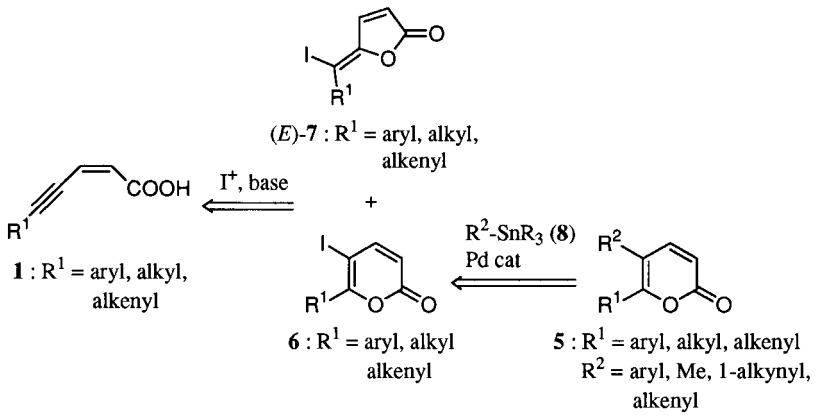


Scheme 2. Retrosynthetic strategy used to prepare compounds **5** and **6**.

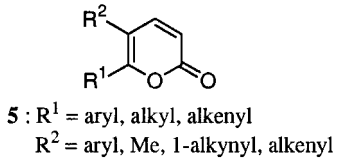


Figure 1. Chemical structures of compounds of general formula **5**.

to give the corresponding 6-substituted 2(2*H*)-pyranones **5** in satisfactory yields (Scheme 2).

Finally, we will show that the 6-substituted 5-(1-alkynyl)-2(2*H*)-pyranones **5a** and **5b**, which can be prepared from the corresponding iodides, **6a** and **6b** respectively, by a Stille-type reaction with 1-butynyltributylstannane, represent the direct precursors to two substances produced by fungal culture LL-11G219, which function as androgen receptor ligands, i.e. compounds **5c** and **5d**,[4] and to two of their analogues, i.e. compounds **5e** and **5f**, respectively (Fig. 2). It must be noted that the synthesis of naturally occurring **5c** has not been reported so far in the literature.

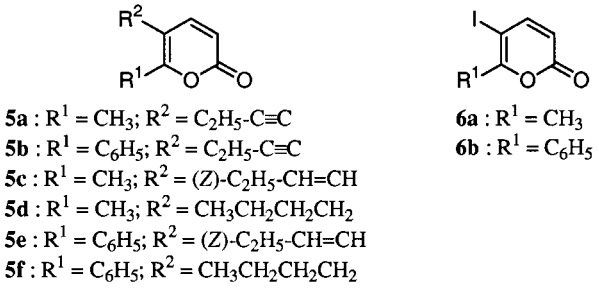


Figure 2. Chemical structures of compounds **5a**–**f** and **6a**–**b**.

1. Results and discussion

1.1. Synthesis of 6-substituted 5-iodo-2(2*H*)-pyranones

The starting materials for our synthesis of 5,6-disubstituted 2(2*H*)-pyranones **5** were (*Z*)-2-en-4-ynoic acids **1a**–**f** (Fig. 3).

The methyl esters corresponding to carboxylic acids **1b**–**1f**, i.e. compounds **9b**–**f**, were prepared as shown in Scheme 3. Thus, methyl (*Z*)-3-bromo-2-propenoate (**10**), which was synthesized in 90% yield by reaction of methyl propiolate with LiBr and acetic acid in CH_3CN,[12a] was reacted with 1.2 equiv. of 1-alkynes **11b**–**f** in Et_3N at room temperature in the presence of 2 mol% $PdCl_2(PPh_3)_2$ and 4 mol% CuI to give compounds **9b**–**f** in yields ranging from 82 to 93%.

Alkynes **11b**–**e** were commercially available and 98% stereoisomerically pure (*E*)-3-hepten-1-yne (**11f**) was diastereoselectively synthesized according to the literature[13] from a diastereoisomeric mixture of 1-bromo-1-pentene. On the other hand, since in the case of the preparation of **9a**, the Sonogashira reaction, which was employed to prepare compounds **9b**–**f**, involved the use of a gaseous 1-alkyne, i.e. 1-propyne (**11a**), we preferred to prepare **9a** by a procedure in which a commercially available 0.5 M THF solution of 1-propynylmagnesium bromide (**12**) was used. Thus, transmetalation between **12** and $ZnCl_2$, followed by treatment of the resulting organozinc halide with 0.83 equiv. of **10** in THF at room temperature in the presence of 5 mol% $Pd(PPh_3)_4$, provided **9a** in 85% yield (Scheme 4).

Esters **9a**–**f** were then treated with a molar excess of 1 M aqueous LiOH solution and THF at room temperature for

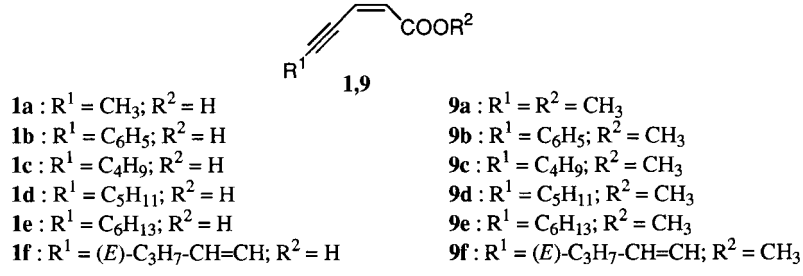
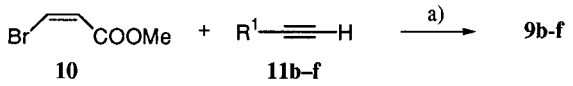
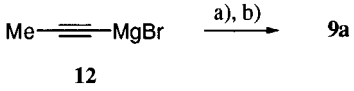


Figure 3. Chemical structures of compounds **1a**–**f** and **9a**–**f**.



Scheme 3. (a) $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), Et_3N, rt, 6–22 h (82–93%).



Scheme 4. (a) $ZnCl_2$ (1.3 equiv.), THF, 0°C; (b) 0.83 equiv. **10**, 5 mol% $Pd(PPh_3)_4$, THF, rt, 20 h (85%).

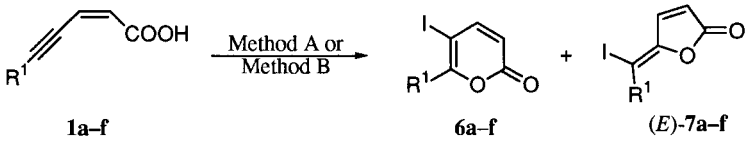
Figure 4. Chemical structures of compounds of general formula **13** and **14**.

24–36 h followed by acidification with diluted H_2SO_4 at 0°C to give the corresponding carboxylic acids **1a–f** in 95–100% yield.

We then examined the possibility to convert regioselectively these carboxylic acids into the corresponding 5-iodo-2(2*H*)-pyranones **6**. No literature data were available for a similar transformation. On the other hand, it has been reported that iodolactonization of 4-ynoic acids **13** by reaction with *N*-iodosuccinimide (NIS) in CH_3CN in the presence of $KHCO_3$[14] or by treatment with NIS utilizing a two-phase system, with 2 mol% Bu_4NOH as a phase transfer agent and $KHCO_3$ as the base,[15] affords regio- and stereoselectively (*E*)-5-(1-iodoalkylidene)tetrahydro-2-furanones **14** (Fig. 4).

Nevertheless, as we had hoped for, compounds **1a–f** proved to be able to undergo reaction with 3 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in CH_3CN at room temperature for 1.5 h (Method A) to provide in high yields mixtures of (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones (*E*)-**7a–f** and 6-substituted 5-iodo-2(2*H*)-pyranones **6a–f** in which these last compounds were the major products (Scheme 5) (entries 1, 2, 4–6 and 10, Table 1).

Interestingly, a similar result was obtained when carboxylic acids **1** were reacted with 1.0 equiv. of ICl in CH_2Cl_2 at room temperature in the absence of a base (Method C). In fact, iodolactonization of **1e** under these conditions provided a mixture of **6e** and (*E*)-**7e** in a ca. 72:28 molar ratio, respectively (entry 7, Table 1). On the contrary, compounds (*E*)-**7** were found to be the major products when carboxylic acids **1** were reacted with 1.1 equiv. of NIS and 1.0 equiv. of $KHCO_3$ in CH_3CN (Method B) (entries 3 and 8, Table 1) or with 1.0 equiv. of NIS in CH_3CN in the absence of a base (Method D) (entry 9, Table 1).



Scheme 5.

Table 1. Synthesis of 6-substituted 5-iodo-2(2*H*)-pyranones **6** and the corresponding (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones (*E*)-**7**

Entry	Carboxylic acid		Method for iodolactonization[a]	Products			
	1	R^1		**6**+(*E*)-**7**	**6**/(*E*)-**7** molar ratio[b]	Yield (%) of **6**[c]	Yield (%) of (*E*)-**7**[c]
1	**1a**	CH_3	A	**6a**+(*E*)-**7a**	66/34	64	32[d]
2	**1b**	C_6H_5	A	**6b**+(*E*)-**7b**	79/21	59	17
3	**1b**	C_6H_5	B[e]	**6b**+(*E*)-**7b**	18/82	15	73
4	**1c**	C_4H_9	A	**6c**+(*E*)-**7c**	66/34	63	32
5	**1d**	C_5H_{11}	A	**6d**+(*E*)-**7d**	69/31	65	30[f]
6	**1e**	C_6H_{13}	A	**6e**+(*E*)-**7e**	68/32	65	31
7	**1e**	C_6H_{13}	C	**6e**+(*E*)-**7e**	72/28	(60)	(27)
8	**1e**	C_6H_{13}	B	**6e**+(*E*)-**7e**	4/96	(3)	(75)
9	**1e**	C_6H_{13}	D	**6e**+(*E*)-**7e**	17/83	(16)	(77)
10	**1f**	(*E*)- C_3H_7–CH=CH	A	**6f**+(*E*)-**7f**	79/21	72	22[g]

[a] Four methods were used for iodolactonization of compounds **1**: Method A involved treatment of **1** with 3.0 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in CH_3CN for 1.5 h. Method B involved reaction of **1** with 1.1 equiv. of NIS and 1.0 equiv. of $KHCO_3$ in CH_3CN for 2.5 h. Method C involved treatment of **1** with 1.0 equiv. of ICl in CH_2Cl_2 for 1 h. Method D involved reaction of **1** with 1.0 equiv. of NIS in CH_3CN for 2.5 h in the absence of a base. Unless otherwise stated, all these reactions were performed at room temperature.

[b] Molar ratio in the crude reaction mixture.

[c] Isolated yield based on **1**. Values in parentheses are referred to GLC yields.

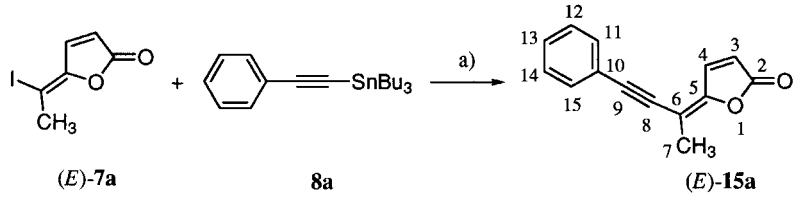
[d] Compound (*E*)-**7a** was contaminated by ca. 15% of the (*Z*)-**7a**.

[e] This reaction was carried out at 0°C for 1.5 h.

[f] Compound (*E*)-**7d** was contaminated by ca. 13% of (*Z*)-**7d**.

[g] Compound (*E*)-**7f** was contaminated by ca. 12% of (*Z*)-**7f**.

Figure 5. Configurational assignment of (*Z*)-**7a** and (*Z*)-**7f** by NOESY experiments.



Scheme 6. (a) $PdCl_2(PPh_3)_2$ (3 mol%), THF, rt, 53 h (76%).

We also observed that the selectivity of the reaction of compounds **1** with 3.0 equiv. of iodine in CH_3CN for 1.0 h at room temperature, in the presence of 3.0 equiv. of a base such as Na_2CO_3 or $KHCO_3$, was lower than that obtained when iodolactonization was carried out according to Method A. In fact, whereas iodolactonization of **1e** according to this last method provided a mixture of **6e** and (*E*)-**7e** in a ca. 68:32 molar ratio, respectively (entry 6, Table 1), a similar reaction performed in the presence of 3.0 equiv. of Na_2CO_3 gave these iodides in a ca. 45:55 molar ratio, respectively. On the other hand, this molar ratio was found to be ca. 54:46 when iodolactonization of **1e** was performed in the presence of 3.0 equiv. of $KHCO_3$.

Compounds **6** were readily separated from the corresponding regioisomers (*E*)-**7** by MPLC on silica gel and were differentiated from these last compounds on the basis of their ^1H NMR spectra. In fact, compounds (*E*)-**7** displayed values of the $^3J_{H3-H4}$ coupling constant in the range 5.3–5.9 Hz[16] and in the 2(2*H*)-pyranones **6** the value of this coupling constant was in the range 9.2–10.0 Hz.[17] Interestingly, compounds (*E*)-**7** underwent partial stereomutation when they were maintained for some hours at room temperature and some of them, i.e (*E*)-**7a**, (*E*)-**7d** and (*E*)-**7f**, could not be isolated in a stereoisomerically pure form (entries 1, 5 and 10, Table 1). The (*E*)-stereochemistry of compounds **7** was deduced from NOESY experiments on (*Z*)-**7a** and (*Z*)-**7f**, which were obtained by partial stereomutation of (*E*)-**7a** and (*E*)-**7f**, respectively. In fact, the NOESY 2D maps of (*Z*)-**7a** and (*Z*)-**7f** exhibited a cross-peak between the resonances of their H-4 and H-7 protons (Fig. 5). On the contrary, NOESY experiments on (*E*)-**7a** and (*E*)-**7f** showed the absence of this cross-peak.

Moreover, when a NOESY experiment was performed on stereoisomerically pure (*E*)-**15a**, which was synthesized in 76% yield by reaction of (*E*)-**7a** with phenylethynyltributylstannane (**8a**) in THF at 20°C in the presence of 3 mol% $PdCl_2(PPh_3)_2$ (Scheme 6), no cross peak was observed between the resonances of its H-4 and H-7 protons.

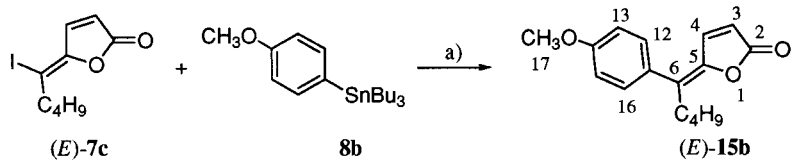
On the other hand, the stereochemistry of (*E*)-**7c** could be assigned on the basis of the stereochemistry of (*E*)-**15b**, which was obtained in 85% yield by reaction of (*E*)-**7c** with 4-methoxyphenyltributylstannane (**8b**) in NMP at 60°C in the presence of 5 mol% of $PdCl_2(PhCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$ (Scheme 7).

In fact, the stereochemistry of (*E*)-**15b**, which we had previously synthesized by treatment of **1b** with 4-methoxyphenyl iodide in CH_3CN in the presence of K_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$,[11] was established to be *E* taking into account that a NOESY 2D map exhibited cross-peaks between the resonances either of its H-4 and H-12 protons or those of its H-4 and H-16 protons.

1.2. Synthesis of 5,6-disubstituted 2(2*H*)-pyranones

With an efficient and selective route to compounds **6** established, the use of these iodo derivatives for the synthesis of 5,6-disubstituted 2(2*H*)-pyranones of general formula **5** was investigated. Thus, it was found that compounds **6** are able to undergo palladium-catalyzed cross-coupling reactions with aryltributylstannanes, vinyltributylstannane, a typical 1-alkynyltributylstannane and tetramethylstannane to give the corresponding 5-aryl-, 5-vinyl-, 5-(1-alkynyl)- and 5-methyl-2(2*H*)-pyranones in moderate to good yields (Scheme 8).

The results of some of these cross-coupling reactions are summarized in Table 2.

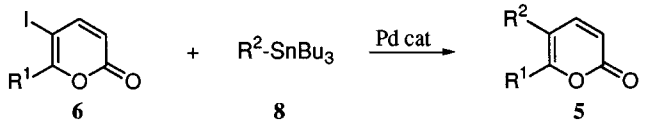


Scheme 7. (a) $PdCl_2(PhCN)_2$ (5 mol%), $AsPh_3$ (10 mol%), CuI (10 mol%), NMP, 60°C, 22 h (85%).

Table 2. Palladium-catalyzed cross-coupling reactions between 5-iodo-2(2*H*)-pyranones **6** and organostannanes **8**

Entry	Reagents				**8/6** molar ratio	Pd cat[a]	Solvent	Reaction conditions (°C h^{-1})	Product	
	Organic iodide		Organotin derivative						**5**	Yield (%)
	6	R^1	**8**[b]	R^2						
1	**6a**	CH_3	**8c**	$C_2H_5C{\equiv}C$	1.2	B	THF	20/19 then 50/21	**5a**	75
2	**6b**	C_6H_5	**8c**	$C_2H_5C{\equiv}C$	1.2	B	THF	20/39 then 50/6	**5b**	82
3	**6c**	C_4H_9	**8b**	4-$CH_3OC_6H_4$	1.2	A	NMP	50/22.5	**5g**	88
4	**6c**	C_4H_9	**8d**	$CH_2{=}CH$	1.2	A	NMP	50/22.0	**5h**	85
5	**6b**	C_6H_5	**8e**	C_6H_5	1.2	A	NMP	50/6.5	**5i**	55
6[c]	**6e**	C_6H_{13}	**8f**	C_4H_9	3.0	C[c]	Dioxane	100/24	**5j**	–
7[d]	**6f**	(*E*)-$C_3H_7CH{=}CH$	**8g**	CH_3	3.0	A	NMP	23/80	**5k**	68

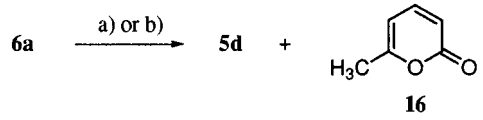
[a] The following catalyst systems were used: catalyst A, which was used in entries 3–5 and 7, was constituted of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$; catalyst B, which was used in entries 1 and 2, was constituted of 3 mol% $PdCl_2(PPh_3)_2$; catalyst C, which was used in entry 6, was constituted of 0.5 mol% $Pd_2(dba)_3$ and 4 mol% PPh_3.
[b] Unless otherwise noted these reactions were performed using organotributylstannanes.
[c] This reaction was performed in the presence of 6.0 equiv. of a 1 M THF solution of TBAF
[d] Tetramethylstannane (**8g**) was the organotin compound used in this reaction.



Scheme 8.

As shown in this table, the cross-coupling reactions involving arylstannanes **8b** and **8e** (entries 3 and 5), vinyltributylstannane **8d** (entry 4) and tetramethylstannane **8g** (entry 7) were performed in NMP in the presence of 5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI and 10 mol% $AsPh_3$.[18] On the other hand, the reactions involving 1-butynyltributylstannane (**8c**) (entries 1 and 2) were carried out in THF in the presence of 3 mol% $PdCl_2(PPh_3)_2$.[19] As shown in entry 6 of Table 2, we also tried to use tetrabutylstannane (**8f**) for a palladium-catalyzed butylation reaction of **6e**. Since the butyl group is typically very reluctant to participate in Stille reactions, we attempted to use the highly coordinated organotin reagent prepared in situ by treatment of **8f** with a large molar excess of TBAF. Unfortunately, even though similar hypervalent organotin species have been successfully employed in palladium-catalyzed reactions between haloanisoles and tetraorganotin reagents,[20] in our case no trace of the expected cross-coupled product was obtained.

Since the failure of this reaction precluded the use of **6a** for the synthesis of naturally-occurring 5-butyl-6-methyl-2(2*H*)-pyranone (**5d**)[4] via a Stille-type reaction, we attempted to prepare **5d** by Ag(I)-promoted palladium-catalyzed butylation of iodide **6a** using a protocol similar

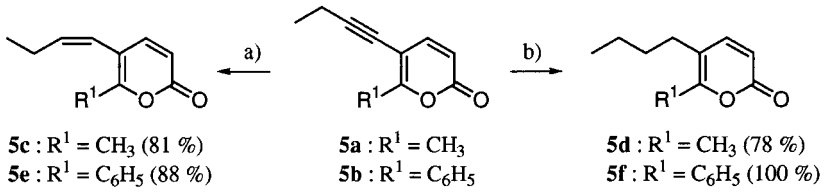


Scheme 9. (a) *n*-$BuB(OH)_2$ (1.1 equiv.), $PdCl_2(CH_3CN)_2$ (5 mol%), $AsPh_3$ (20 mol%), Ag_2O (3 equiv.), THF, reflux, 4 h; (b) *n*-BuZnCl (1.3 equiv.), $PdCl_2$(dppf) (5 mol%), THF, 20°C, 24 h.

to that recently employed for the coupling reaction between β-tetronic acid triflate and alkenyl- or cyclopropylboronic acids.[21] Thus, we found that treatment of **6a** with 1.1 equiv. of butylboronic acid in THF for 4 h at 70°C, in the presence of 3.0 equiv. of Ag_2O, 5 mol% $PdCl_2(CH_3CN)_2$ and 20 mol% $AsPh_3$, provided a mixture of **5d** and a byproduct, which corresponded to 6-methyl-2(2*H*)-pyranone (**16**) in a ca. 1:1 molar ratio (Scheme 9). However, compound **5d** was obtained in only 26% GLC yield. Unfortunately, no improvement of this yield was obtained when **6a** was reacted with 1.3 equiv. of butylzinc chloride in THF at 20°C for 24 h in the presence of 5 mol% $PdCl_2$(dppf) (Scheme 9). This reaction provided too a mixture of **5d** and **16** in which this last compound was largely predominant.

Finally, taking into account that 5-(1-butynyl) substituted 2(2*H*)-pyranones **5a** and **5b** could be prepared in high yield by palladium-catalyzed reaction of **8c** with **6a** and **6b**, respectively (entries 1 and 2, Table 2), we examined the possibility of utilizing either **5a** as direct precursor of **5d** as well as (*Z*)-5-(1-butenyl)-6-methyl-2(2*H*)-pyranone (**5c**)[4] or **5b** as direct precursor to two analogues of these natural products, i.e. **5f** and **5e**, respectively. In the event, we found that partial catalytic hydrogenation of **5b** in toluene at room temperature, using pyridine-poisoned 10% palladium on $BaSO_4$, selectively provided a mixture of **5e** and the corresponding (*E*)-stereoisomer in a ca. 95:5 molar ratio, respectively (Scheme 10). Purification by MPLC on silica gel allowed us to obtain analytically pure **5e** in 88% yield. A procedure very similar to that of this model reaction was then used for the first synthesis of naturally occurring **5c** (Scheme 10). This procedure allowed us to obtain 97% pure **5c** in 81% yield.

On the other hand, when a toluene solution of **5b** was hydrogenated at room temperature in the presence of 10% palladium on $BaSO_4$, chemically pure **5f** was selectively obtained in quantitative yield (Scheme 10). However, hydrogenation of **5a** under similar experimental conditions provided a mixture of three new compounds in a ca. 89:10:1 molar ratio in which the major and the minor components



Scheme 10. (a) H_2, Pd–$BaSO_4$, pyridine (cat), toluene, 20°C; (b) H_2, Pd–$BaSO_4$, toluene, 20°C.

were **5d** and **5c**, respectively, and the third component was not identified. Nevertheless, purification of this mixture by MPLC on silica gel allowed us to obtain chemically pure **5d** in 78% yield.[22]

2. Conclusions

The results summarized above conclusively demonstrate that 6-substituted 5-iodo-2(2*H*)-pyranones **6**, which represent a not previously described class of heterocyclic halides, are selectively available by iodolactonizazion of the corresponding (*Z*)-2-en-4-ynoic acids **1**, and that these iodides are efficient electrophiles for palladium-catalyzed cross-coupling reactions with organostannanes. These reactions allow one to prepare in moderate to high yields a variety of unsymmetrically and symmetrically 5,6-disubstituted 2(2*H*)-pyranones **5** which would be quite difficult to prepare by any other present methodology. One of these 2(2*H*)-pyranone derivatives, i.e. compound **5a**, has been used as direct precursor to two substances produced by fungal culture LL-11G219, which function as androgen ligands, i.e. **5c** and **5d**. The synthesis of the first of these compounds has not been previously reported. Further synthetic applications of compounds **6** are currently under investigation in our laboratory

3. Experimental

Melting points and boiling points are uncorrected. Precoated silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040 mm) were performed on a Büchi instrument using a Bischoff 8110 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer gas-chromatograph. IR spectra were recorded on a Perkin–Elmer 1725 FT-IR spectrophotometer. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or on a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. All reactions of air and water sensitive materials were performed in flame-dried glassware under an atmosphere of nitrogen or argon using standard syringe, cannula and septa techniques. The following compounds were prepared by published procedures: $Pd(PPh_3)_4$,[23] $PdCl_2(PPh_3)_2$,[24] $PdCl_2(CH_3CN)_2$,[25] $PdCl_2$(dppf),[26] methyl (*Z*)-3-bromopropenoate (**10**),[12a] (*E*)-3-hepten-1-yne (**11f**),[13] 4-methoxyphenyl-tributylstannane (**8b**).[27] 1-Butynyltributylstanne (**8c**) [bp 84–85°C/0.04 Torr MS, *m/z* (%): 287 (19), 231 (28), 175 (54), 173 (100), 171 (68), 121 (36), 119 (26). IR (film): ν 2150, 1419, 1377, 1314, 1072, 878, 695, 670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.26 (2H, q, J=7.5 Hz), 1.59–1.47 (6H, m), 1.42–1.24 (6H, m), 1.15 (3H, t, J=7.5 Hz), 0.99–0.83 (15H, m). Anal. Calcd for $C_{16}H_{32}Sn$: C, 56.00.; H, 9.40. Found: C, 56.16; H 9.71] was prepared in 94% yield by reaction of a THF solution of 1-butyne with 0.68 equiv. of a 1.70 M hexane solution of butyllithium at −30°C for 3 h followed by treatment with 0.59 equiv. of chlorotributylstannane at −30°C for 0.5 h, at room temperature for 1 h and under reflux for 17 h.

3.1. General procedure for preparation of methyl (*Z*)-2-en-4-ynoates 9

A mixture of a 1-alkyne **11** (48.0 mmol), methyl (*Z*)-3-bromopropenoate (**10**) (6.60 g, 40.0 mmol), $PdCl_2(PPh_3)_2$ (0.561 g, 0.80 mmol), CuI (0.305 g, 1.60 mmol) and dry Et_3N (100 ml) was stirred at room temperature under a nitrogen atmosphere until a GLC analysis showed that compound **10** had completely reacted. The reaction mixture was then diluted with Et_2O (200 ml), poured into a saturated aqueous NH_4Cl solution (200 ml) and the resulting mixture was stirred open to the atmosphere until the aqueous phase became deep blue. The organic phase was separated and the aqueous phase was extracted with Et_2O (2×50 ml). The collected organic extracts were washed with water (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with hexane (300 ml) and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was fractionally distilled to give the desired methyl (*Z*)-2-en-4-ynoate **9** as a colorless liquid. This procedure was employed to prepare compounds **9b–f**.

3.1.1. Methyl (*Z*)-5-phenyl-2-penten-4-ynoate (9b). This compound, which was prepared in 91% yield from **10** and phenylethyne (**11b**) according to the above mentioned general procedure, had: bp 95–96°C/0.04 Torr MS, *m/z* (%): 186 (31), 171 (21), 155 (14), 127 (17), 115 (27), 63 (27), 51 (100). ^1H NMR (200 MHz, $CDCl_3$): δ 7.58–7.40 (2H, m, Harom), 7.36–7.25 (3H, m, Harom), 6.35 (1H, d, J=11.8 Hz, H-3 or H-2), 6.13 (1H, d, J=11.8 Hz, H-2 or H-3), 3.78 (3H, s, OCH_3). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H 5.41. Found: C, 77.18; H 5.55.

3.1.2. Methyl (*Z*)-2-nonen-4-ynoate (9c). This compound,[28] which was prepared in 91% yield from **10** and 1-hexyne (**11c**) according to the above mentioned general procedure, had: bp 60–62°C/0.05 Torr MS, *m/z*

(%): 166 (1), 124 (15), 109 (16), 95 (8), 63 (35), 55 (43), 51 (100). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.16 (1H, dt, J=11.6 and 2.2 Hz, H-3), 6.03 (1H, d, J=11.6 Hz, H-2), 3.76 (3H, s, OCH_3), 2.46 (2H, td, J=7.0 and 2.2 Hz, H-6), 1.66–1.36 (4H, m, H-7 and H-8), 0.93 (3H, t, J=7.0 Hz, H-9). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.43; H 8.51.

3.1.3. Methyl (*Z*)-2-decen-4-ynoate (9d). This compound, which was prepared in 82% yield from **10** and 1-heptyne (**11d**) according to the above mentioned general procedure, had: bp 76–78°C/0.2 Torr MS, *m/z* (%): 180 (3), 149 (14), 137 (67), 124 (60), 109 (100), 105 (46), 95 (28). IR (film): ν 1730, 1718, 1611, 1438, 1196, 1176, 818 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.16 (1H, dt, J=11.5 and 2.1 Hz, H-3), 6.02 (1H, d, J=11.5 Hz, H-2), 3.75 (3H, s, OCH_3), 2.45 (2H, td, J=7.0 and 2.1 Hz, H-6), 1.65–1.32 (6H, m, H-7, H-8 and H-9), 0.90 (3H, t, J=7.0 Hz, H-10). These NMR data were in agreement with those previously reported.[29]

3.1.4. Methyl (*Z*)-2-undecen-4-ynoate (9e). This compound, which was prepared in 93% yield from **10** and 1-octyne (**11e**) according to the above mentioned general procedure, had: bp 72°C/0.04 Torr MS, *m/z* (%): 194 (5), 137 (93), 124 (94), 111 (80), 108 (100), 95 (85), 79 (71). IR (film): ν 1732, 1718, 1611, 1438, 1195, 1176, 818 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.19 (1H, dt, J=11.3 and 2.2 Hz, H-3), 6.03 (1H, d, J=11.3 Hz, H-2), 3.76 (3H, s, OCH_3), 2.45 (2H, td, J=6.9 and 2.2 Hz, H-6), 1.65–1.28 (8H, m, H-7, H-8, H-9 and H-10), 0.89 (3H, t, J=6.7 Hz, H-11). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.33. Found: C, 73.99; H 9.39.

3.1.5. Methyl (2*Z*,6*E*)-2,6-decadien-4-ynoate (9f). This compound, which was prepared in 86% yield from **10** and (*E*)-3-hepten-1-yne (**11f**) according to the above mentioned general procedure, had: bp 84–85°C/0.2 Torr MS, *m/z* (%): 178 (10), 163 (44), 131 (59), 105 (72), 91 (100), 77 (82). IR (film): ν 1728, 1600, 1438, 1235, 1197, 1178, 816 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.33 (1H, dt, J=15.7 and 6.9 Hz, H-7), 6.27 (1H, dd, J=11.3 and 2.6 Hz, H-3), 6.05 (1H, d, J=11.3 Hz, H-2), 5.72 (1H, ddt, J=15.7, 2.6 and 1.5 Hz, H-6), 3.76 (3H, s, OCH_3), 2.15 (2H, dtd, J=7.3, 7.3 and 1.5 Hz, H-8), 1.45 (2H, tq, J=7.3 and 7.3 Hz, H-9), 0.93 (3H, t, J=7.3 Hz, H-10). Anal. Calcd for $C_{11}H_{14}O_2$: C,74.13; H 7.92. Found: C, 74.25; H 7.94.

3.1.6. Methyl (*Z*)-2-hexen-4-ynoate (9a). A 0.50 M THF solution of 1-propynylmagnesium bromide (**12**) (192 ml, 96 mmol) was added dropwise to a slurry of dry $ZnCl_2$ (17.00 g, 124.8 mmol) in THF (230 ml), which was stirred under argon at 0°C. After stirring for 15 min at 0°C a solution of **10** (13.20 g, 80.0 mmol) in THF (20 ml) and $Pd(PPh_3)_4$ (4.62 g, 4.0 mmol) were sequentially added and the resulting mixture was stirred for 20 h at room temperature. It was then poured into a saturated aqueous NH_4Cl solution (300 ml) and extracted with Et_2O (4×100 ml). The collected organic extracts were washed with brine (100 ml), dried over Na_2SO_4 and concentrated. The residue was diluted with pentane (300 ml) and filtered over Celite. The filtrate was concentrated and the residue was fractionally distilled to give **9a** (8.50 g, 85% yield) as a colorless liquid: bp 79°C/17 Torr. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.15 (1H, dq, J=11.4 and 2.6 Hz, H-3), 6.04 (1H, d, J=11.4 Hz, H-2), 3.76 (3H, s, OCH_3), 2.10 (3H, d, J=2.6 Hz, H-6). The spectral properties of this compound were in satisfactory agreement with those previously reported.[30]

3.1.7. (*Z*)-2-Hexen-4-ynoic acid (1a). Compound **9a** (8.42 g, 67.87 mmol) was dissolved in THF (250 ml) and the resulting solution was added to an aqueous 1.0 M LiOH solution (203 ml, 203 mmol). The resulting mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure at 20°C. The residue was diluted with water (100 ml) and extracted with Et_2O (3×50 ml). The aqueous phase was cooled to 0°C, acidified with cold 10% H_2SO_4 and extracted with Et_2O (350 ml). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to give **1a** (7.20 g, 97% yield) as a colorless solid. Mp 108–112°C (lit. 30 mp 113–114.5°C). ^{1}H NMR (200 MHz, $CDCl_3$): δ=10.76 (1H, br s, COOH), 6.25 (1H, dq, J=11.5 and 2.4 Hz, H-3), 6.07 (1H, d, J=11.5 Hz, H-2), 2.11 (3H, d, J=2.4 Hz, H-6). These NMR data were in satisfactory agreement with those previously reported.[30] This crude product was used in the next step without any further purification and characterization.

3.1.8. (*Z*)-5-Phenyl-2-penten-4-ynoic acid (1b). Compound **9b** was converted in quantitative yield into **1b** according to the same procedure used to prepare **1a** from **9a**. Crude **1b**, which was a pale yellow solid, had: mp 127–128°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.30 (1H, br s, COOH), 7.60–7.45 (2H, m, Harom), 7.40–7.27 (3H, m, Harom), 6.48 (1H, d, J=11.4 Hz, H-3 or H-2), 6.17 (1H, d, J=11.4 Hz, H-2 or H-3. This crude product was used in the next step without any further purification and characterization.

3.1.9. (*Z*)-2-Nonen-4-ynoic acid (1c). Compound **9c** was converted in 98% yield into **1c** according to the same procedure used to prepare **1a** from **9a**. Crude **1c** was a pale yellow liquid which had: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.76 (1H, br s, COOH), 6.27 (1H, dt, J=11.3 and 2.2 Hz, H-3), 6.07 (1H, dd, J=11.3 and 0.7 Hz, H-2), 2.46 (2H, td, J=6.8 and 2.2 Hz, H-6), 1.66–1.36 (4H, m, H-7 and H-8), 0.93 (3H, t, J=7.0 Hz, H-9). This crude carboxylic acid was used in the next step without any further purification and characterization.

3.1.10. (*Z*)-2-Decen-4-ynoic acid (1d). Compound **9d** was converted in quantitative yield into **1d** according to the same procedure used to prepare **1a** from **9a**. Crude **1d**, which was a pale yellow liquid, had: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.75 (1H, br s, COOH), 6.26 (1H, dt, J=11.6 and 2.2 Hz, H-3), 6.06 (1H, d, J=11.6 Hz, H-2), 2.45 (2H, td, J=7.0 and 2.2 Hz, H-6), 1.59–1.32 (6H, m, H-7, H-8 and H-9), 0.91 (3H, t, J=6.9 Hz, H-10). The spectral properties of this compound were in satisfactory agreement with those previously reported.[31] This crude carboxylic acid was used in the next step without any further purification and characterization.

3.1.11. (*Z*)-2-Undecen-4-ynoic acid (1e). Compound **9e** was converted in 98% yield into **1e** according to the same procedure used to prepare **1a** from **9a**. Crude **1e**, which was

a pale yellow liquid, had: ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.10 (1H, br s, COOH), 6.27 (1H, dt, J=11.4 and 2.3 Hz, H-3), 6.06 (1H, d, J=11.4 Hz, H-2), 2.44 (2H, dt, J=6.7 and 2.3 Hz, H-6), 1.70–1.20 (8H, m, H-7, H-8, H-9 and H-10), 0.89 (3H, t, J=6.7 Hz, H-11). These NMR data were in agreement with those previously reported.[32] This crude carboxylic acid was used in the next step without any further purification and characterization.

3.1.12. (2*Z*,6*E*)-2,6-Decadien-4-ynoic acid (1f). Compound **9f** was converted in 95% yield into **1f** according to the same procedure used to prepare **1a** from **9a**. Crude **1f**, which was a yellow solid, had: mp 30°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.90 (1H, br s, COOH), 6.37 (1H, dd, J=11.4 and 2.5 Hz, H-3), 6.34 (1H, dt, J=15.7 and 6.9 Hz, H-7), 6.07 (1H, d, J=11.4 Hz, H-2), 5.72 (1H, ddt, J=15.7, 2.5 and 1.5 Hz, H-6), 2.15 (2H, dtd, J=7.0, 7.0 and 1.4 Hz, H-8), 1.44 (2H, tq, J=7.3 and 7.3 Hz, H-9), 0.92 (3H, t, J=7.3 Hz, H-10). This crude carboxylic acid was used in the next step without any further purification and characterization.

3.2. General procedures for the synthesis of 6-substituted 5-iodo-2(2*H*)-pyranones 6 and the corresponding (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones (E)-7

The iodolactonization of carboxylic acids **1** was performed according to four different methods. (Method A) To a suspension of $NaHCO_3$ (8.06 g, 96.0 mmol)) in CH_3CN (150 ml) were added sequentially a solution of a (*Z*)-2-en-4-ynoic acid **1** (32.0 mmol) in CH_3CN (50 ml) and iodine (24.36 g, 96.0 mmol) and the mixture was stirred vigorously under nitrogen at room temperature for 1.5 h at which time the reaction was complete as shown by GLC and TLC analyses. The reaction mixture was then diluted with AcOEt (150 ml) and washed with a 10% aqueous $Na_2S_2O_3$ solution (50 ml) and water (50 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude mixture of a 6-substituted 5-iodo-2(2*H*)-pyranone **6** and the corresponding (*E*)-5-(1-iodoylidene)-2(5*H*)-furanones (*E*)-**7**, where compound **6** was the major component. Compounds **6** and (*E*)-**7** were separated by MPLC on silica gel. This procedure was employed for iodolactonization of (*Z*)-2-en-4-ynoic acids **1a**–**f**. Table 1 summarizes the **6**/(*E*)-**7** molar ratio found in the crude reaction mixtures which were obtained from these carboxylic acids as well as the isolated yields of compounds **6a**–**f** and (*E*)-**7a**–**f** prepared by this procedure (entries 1, 2, 4–6 and 10, Table 1). It must be noted that compounds (*E*)-**7** underwent a partial stereomutation at room temperature and that some of these substances, i.e. (*E*)-**7a**, (*E*)-**7d** and (*E*)-**7f**, could not be isolated in stereoisomerically pure form.

Method B. This method was used for iodolactonization of **1b** and **1e** (entries 3 and 8, Table 1). In particular, to a deareated solution of **1b** (5.0 g, 29.04 mmol) in CH_3CN (150 ml), which was maintained at 0°C under nitrogen in the dark, were added sequentially *N*-iodosuccinimide (7.23 g, 32.26 mmol) and $KHCO_3$ (2.91 g, 29.04 mmol) and the resulting mixture was stirred at 0°C for 1.5 h. After usual work up a ^{1}H NMR analysis of the crude reaction product showed the presence of two compounds, which were subsequently identified as **6b** and (*E*)-**7b** in a ca. 18:82 molar ratio, respectively (entry 3, Table 1). These crude compounds were separated by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate stereoisomerically pure (*E*)-**7b** (6.30 g, 73% yield) as a crystalline solid. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate pure **6b** (1.30 g, 15% yield) as a crystalline solid. A similar procedure was used for iodolactonization of **1e**, but the reaction was carried out at room temperature for 3.5 h (entry 8, Table 1). Compounds **6e** and (*E*)-**7e**, which were present in the crude reaction mixture in a ca. 4:96 molar ratio, were obtained in 3 and 75% GLC yield, respectively.

Method C. To a solution of a compound **1** (1.95 mmol) in CH_2Cl_2 (6 ml) was added a solution of ICl (1.95 mmol) in CH_2Cl_2 (4 ml) and the reaction mixture was stirred in the dark at room temperature for 5.0 h. It was then poured into a 10% aqueous $NaHCO_3$ solution (10 ml) and extracted with AcOEt (2×8 ml). The organic extract was washed with a 10% aqueous $Na_2S_2O_3$ solution (15 ml) and water (20 ml), dried and analyzed by GLC using biphenyl as an internal standard. This method was used for iodolactonization of **1e** (entry 7, Table 1).

Method D. *N*-Iodosuccinimide (0.443 g, 1.95 mmol) was added to a solution of a compound **1** (1.95 mmol) in CH_3CN (13 ml) and the mixture was stirred in the dark at room temperature for 2.5 h. It was then poured into a 10% aqueous $Na_2S_2O_3$ solution (15 ml) and extracted with AcOEt (2×10 ml). The organic extract was washed with water, dried and analyzed by GLC using biphenyl as an internal standard. This method was used for iodolactonization of **1e** (entry 9, Table 1).

The physical and spectral properties of compounds **6a**–**f** and (*E*)-**7a**–**f** as well as the chromatographic conditions which were used for their isolation are reported below.

3.2.1. 5-Iodo-6-methyl-2(2*H*)-pyranone (6a) and (*E*)-5-(1-iodoethylidene)-2(5*H*)-furanone [(*E*)-7a]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1a** according to Method A, showed the presence of two compounds in a ca. 66:34 molar ratio, which were subsequently identified as **6a** and (*E*)-**7a**, respectively (entry 1, Table 1). This mixture was purified by MPLC on silica gel using a mixture of hexane, CH_2Cl_2 and AcOEt (80:15:5) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 32% yield (*E*)-**7a** as a crystalline solid. Mp 75–76°C. MS, *m*/*z* (%): 236 (65), 127 (26), 109 (72), 81 (39), 63 (9), 55 (40), 53 (100). IR (KBr): ν 1741, 1080, 1044, 914, 875, 823 cm^{-1}. GLC and NMR analyses showed that (*E*)-**7a** was contaminated by ca. 15% of the corresponding (*Z*)-stereoisomer. The NMR parameters for (*E*)-**7a** were as follows. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (1H, d, J=5.5 Hz, H-4), 6.27 (1H, d, J=5.5 Hz, H-3), 2.74 (3H, s, H-7). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.77 (C-2), 150.16 (C-5), 144.69 (C-4), 122.53 (C-3), 85.86 (C-6), 27.08 (C-7). The NMR parameters for (*Z*)-**7a** were as follows. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (1H, d, J=5.5 Hz, H-4), 6.32 (1H, d, J=5.5 Hz, H-3), 2.71 (3H, s, H-7). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.68 (C-2), 152.16 (C-5), 136.59

(C-4), 120.55 (C-3), 84.28 (C-6), 26.60 (C-7). A NOESY experiment showed a cross-peak between the resonances of the H-4 and H-7 protons. Anal. Calcd for $C_6H_5IO_2$: C, 40.67; H, 2.13. Found: C, 40.82; H 2.19. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 64% yield pure **6a** as a crystalline solid. Mp 72–73°C. MS, *m/z* (%): 236 (49), 208 (100), 165 (33), 127 (19), 81 (48), 66 (11), 53 (28). IR (KBr): ν 1735, 1715, 1599, 1541, 1010, 828, 599 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.43 (1H, d, J=9.6 Hz, H-4), 5.99 (1H, d, J=9.6 Hz, H-3), 2.47 (3H, s, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.58 (C-6), 161.24 (C-2), 151.62 (C-4), 114.68 (C-3), 67.96 (C-5), 23.48 (C-7). Anal. Calcd for $C_6H_5IO_2$: C, 40.67; H, 2.13. Found: C, 40.83; H 2.28.

3.2.2. 5-Iodo-6-phenyl-2(2*H*)-pyranone (6b) and (*E*)-5-[1-iodobenzylidene)-2(5*H*)-furanone [(*E*)-7b]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1b** according to Method A, showed the presence of two compounds in a ca. 79:21 molar ratio, which were subsequently identified as **6b** and (*E*)-**7b**, respectively (entry 2, Table 1). This mixture was purified by MPLC on silica gel using a mixture of benzene and hexane (95:5) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 17% yield (*E*)-**7b** as an orange solid. Mp 64–67°C. MS, *m/z* (%): 298 (76), 171 (100), 143 (14), 115 (77), 89 (41), 77 (15), 63 (27). IR (KBr): ν 1774, 1766, 1749, 948, 899, 760, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (1H, d, J=5.6 Hz, H-4), 7.72–7.63 (2H, m, Harom), 7.44–7.32 (3H, m, Harom), 6.34 (1H, d, J=5.6 Hz, H-3). Anal. Calcd for $C_{11}H_7IO_2$: C, 44.32; H 2.37. Found: C, 44.45; H 2.48. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 59% yield **6b** as a pale yellow solid. Mp 101–103°C. MS, *m/z* (%): 298 (100), 270 (83), 143 (12), 115 (33), 105 (55), 77 (62), 63 (8). IR (KBr): ν 1717, 1601, 1539, 1486, 1024, 834, 706 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.78–7.69 (2H, m, Harom), 7.64 (1H, d, J=9.9 Hz, H-4), 7.52–7.44 (3H, m, Harom), 6.11 (1H, d, J=9.9 Hz, H-3). Anal. Calcd for $C_{11}H_7IO_2$: C,44.32; H 2.37. Found: C, 44.37; H, 2.41.

3.2.3. 6-Butyl-5-iodo-2(2*H*)-pyranone (6c) and (*E*)-5-(1-iodopentylidene)-2(5*H*)-furanone [(*E*)-7c]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1c** according to Method A, showed the presence of two compounds in a ca. 66:34 molar ratio, which were subsequently identified as **6c** and (*E*)-**7c**, respectively (entry 4, Table 1). This mixture was purified by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 32% yield stereoisomerically pure (*E*)-**7c** as a red liquid. MS, *m/z* (%): 278 (40), 235 (15), 179 (9), 153 (7), 109 (100), 81 (10), 54 (15). IR (film): ν 1777, 1754, 1105, 959, 915, 881, 814 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (1H, d, J=5.4 Hz, H-4), 6.29 (1H, d, J=5.4 Hz, H-3), 2.82 (2H, t, J=7.0 Hz, H-7), 1.63–1.28 (4H, m, H-8 and H-9), 0.94 (3H, t, J=7.0 Hz, H-10). Anal. Calcd for $C_9H_{11}IO_2$:C, 38.87; H, 3.99. Found: C, 39.01; H 4.09. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 63% yield chemically pure **6c** as an orange liquid. MS, *m/z* (%): 278 (88), 236 (49), 221 (100), 207 (54), 165 (53), 109 (24), 95 (39), 81 (69). IR (film): ν 1735, 1601, 1542, 1189, 1012, 822, 599 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (1H, d, J=9.8 Hz, H-4), 5.98 (1H, d, J=9.8 Hz, H-3), 2.71 (2H, t, J=7.7 Hz, H-6a), 1.66 (2H, quint, J=7.7 Hz, H-6b), 1.39 (2H, sext, J=7.7 Hz, H-6c), 0.94 (3H, t, J=7.7 Hz, H-6d). Anal. Calcd for $C_9H_{11}IO_2$: C 38.87; H, 3.99. Found: C, 39.09; H 4.18.

3.2.4. 5-Iodo-6-pentyl-2(2*H*)-pyranone (6d) and (*E*)-5-(1-iodohexylidene)-2(5*H*)-furanone [(*E*)-7d]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1d** according to Method A, showed the presence of two compounds in a ca. 69:31 molar ratio, which were subsequently identified as **6d** and (*E*)-**7d**, respectively (entry 5, Table 1). This mixture was purified by MPLC on silica gel using a mixture of toluene and hexane (90:10) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 30% yield stereoisomerically pure (*E*)-**6d** as a red liquid. MS, *m/z* (%): 292 (4), 147 (10), 109 (100), 81 (28), 50 (10). IR (film): ν 1779, 1751, 1632, 1553, 1379, 1196, 728 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (1H, d, J=5.5 Hz, H-4), 6.28 (1H, d, J=5.5 Hz, H-3), 2.81 (2H, t, J=7.3 Hz, H-6a), 1.61–1.54 (2H, m, H-6b), 1.35–1.27 (4H, m, H-6c and H-6d), 0.90 (3H, t, J=6.6 Hz, H-6f). Anal. Calcd for $C_{10}H_{13}IO_2$: C, 41.11. H 4.49. Found: C, 40.95; H 4.61. ^1H NMR analysis showed that (*E*)-**7d** was contaminated by ca. 13% of the corresponding (*Z*)-stereoisomer. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 65% yield pure **6d** as a red liquid. MS, *m/z* (%): 292 (18), 221 (36), 165 (60), 119 (24), 109 (30), 95 (56), 81 (100). IR (film): ν 1735, 1600, 1541, 1465, 1189, 1011, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (1H, d, J=9.8 Hz, H-4), 5.99 (1H, d, J=9.8 Hz, H-3), 2.71 (2H, t, J=7.7 Hz, H-7), 1.72–1.65 (2H, m, H-8), 1.38–1.31 (4H, m, H-9 and H-10), 0.91 (3H, t, J=5.5 Hz, H-11). Anal. Calcd for $C_{10}H_{13}IO_2$: C 41.11; H 4.49. Found: C, 41.26; H 4.65.

3.2.5. 6-Hexyl-5-iodo-2(2*H*)-pyranone (6e) and (*E*)-5-(1-iodoheptylidene)-2(5*H*)-furanone [(*E*)-7e]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1e** according to Method A, showed the presence of two compounds in a ca. 68:32 molar ratio, which were subsequently identified as **6e** and (*E*)-**7e**, respectively (entry 6, Table 1). This mixture was purified by MPLC on silica gel using a mixture of toluene and hexane (90:10) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 31% yield stereoisomerically pure (*E*)-**7e** as a red liquid. MS, *m/z* (%): 306 (2), 133 (8), 109 (100), 95 (15), 82 (12), 81 (17), 55 (16). IR (film): ν 1781, 1755, 1554, 1242, 1106, 936, 811 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.65 (1H, d, J=5.4 Hz, H-4), 6.28 (1H, d, J=5.4 Hz, H-3), 2.80 (2H, t, J=7.4 Hz, H-7), 1.60–1.20 (8H, m, H-8, H-9, H-10 and H-11), 0.89 (3H, t, J=6.4 Hz, H-12). Anal. Calcd for $C_{12}H_{15}IO_2$: C, 43.15; H 4.94. Found: C, 43.32; H 5.12. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 65% yield pure **6e** as a red liquid. MS, *m/z* (%): 306 (17), 236 (20), 221 (29), 165 (31), 133 (35), 109 (22), 95 (47), 81 (100). IR (film): ν 1739, 1599, 1542, 1465, 1189, 1012, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.43 (1H, d, J=9.7 Hz, H-4), 5.98 (1H, d, J=9.7 Hz, H-3), 2.70 (2H, t,

J=7.7 Hz, H-6a), 1.71–1.59 (2H, m, H-6b), 1.45–1.20 (6H, m, H-6c, H-6d and H-6e), 0.89 (3H, t, J=6.6 Hz, H-6f). Anal. Calcd for $C_{12}H_{15}IO_2$: C, 43.15; H 4.94. Found: C, 43.17; H 5.23.

3.2.6. 5-Iodo-6-[(*E*)-1-pentenyl]-2(2*H*)-pyranone (6f) and (*E*)-5-[1-iodo-(*E*)-2-hexenylidene)-2(5*H*)-furanone [(*E*)-7f]. A GLC analysis of the crude reaction mixture, which was obtained by iodolactonization of **1f** according to Method A, showed the presence of two compounds in a ca. 79:21 molar ratio, which were subsequently identified as **6f** and (*E*)-**7f**, respectively (entry 10, Table 1). This mixture was purified by MPLC on silica gel using toluene as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate in 22% yield stereoisomerically pure (*E*)-**7f** as an orange liquid. A GLC analysis showed that (*E*)-**7f** was contaminated by ca. 12% of (*Z*)-**7f**. Stereoisomerically pure (*E*)-**7f** had: MS, *m/z* (%): 290 (19), 248 (40), 121 (95), 117 (44), 91 (52), 71 (100), 55 (40). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (1H, d, J=5.5 Hz, H-4), 6.42 (1H, dt, J=14.4 and 1.4 Hz, H-7), 6.25 (1H, d, J=5.5 Hz, H-3), 6.24 (1H, dt, J=14.4 and 7.3 Hz, H-8), 2.30 (2H, dquart, J=7.3 and 1.4 Hz, H-9), 1.52 (2H, sext, J=7.3 Hz, H-10), 0.94 (3H, t, J=7.3 Hz, H-11). ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.32 (C-2), 148.91 (C-5), 147.65 (C-8), 145.34 (C-4), 125.61 (C-7), 121.42 (C-3), 90.92 (C-6), 34.87 (C-9), 22.18 (C-10), 13.74 (C-11). A NOESY experiment showed a cross-peak between the resonance of the H-4 and H-7 protons. Some spectral data for (*Z*)-**7f** are as follows. MS, *m/z* (%): 290 (16), 248 (30), 121 (83), 117 (36), 91 (55), 70 (100), 65 (56). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (1H, d, J=5.5 Hz, H-4), 6.34 (1H, d, J=5.5 Hz, H-3), 6.29 (1H, dt, J=14.4 and 7.3 Hz, H-8), 6.06 (1H, dt, J=14.4 and 1.4 Hz, H-7), 2.29 (2H, dquart, J=7.3 and 1.4 Hz, H-9), 1.51 (2H, sext, J=7.3 Hz, H-10), 0.95 (3H, t, J=7.3 Hz, H-11). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.05 (C-2), 152.24 (C-5), 146.12 (C-8), 136.91 (C-4), 124.45 (C-7), 119.99 (C-3), 91.03 (C-6), 34.86 (C-9), 22.28 (C-10), 13.74 (C-11). The IR and elemental analysis data for (*E*)-**7f** contaminated by (*Z*)-**7f** were as follows. IR (film): ν 1782, 1751, 1623, 1542, 1107, 944, 885 cm^{-1}. Anal. Calcd for $C_{10}H_{11}IO_2$: C, 41.40; H 3.82. Found: C, 41.78; H 3.81. On the other hand, concentration of the last eluted chromatographic fractions allowed to isolate in 72% yield **6f** as a red oil. MS, *m/z* (%): 290 (12), 236 (35), 106 (52), 91 (27), 79 (29), 78 (47), 55 (100). IR (film): ν 1740, 1637, 1515, 1192, 1015, 964, 816 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 (1H, d, J=9.5 Hz, H-4), 6.80 (1H, dt, J=15.4 and 7.3 Hz, H-8), 6.38 (1H, dt, J=15.4 and 1.5 Hz, H-7), 5.99 (1H, d, J=9.5 Hz, H-3), 2.26 (2H, dtd, J=7.3, 7.3 and 1.5 Hz, H-9), 1.52 (2H, tq, J=7.3 and 7.3 Hz, H-10), 0.96 (3H, t, J=7.3 Hz, H-11). Anal. Calcd for $C_{10}H_{11}IO_2$: C, 41.40; H 3.82. Found: C, 41.65; H 4.01.

3.2.7. (*E*)-5-[1-(Phenylethynyl)ethylidene]-2(5*H*)-furanone ((*E*)-15a). A flame-dried reaction vessel, which was maintained under an argon atmosphere, was charged with (*E*)-**7a** (2.24 g, 9.51 mmol), $PdCl_2(PPh_3)_2$ (0.20 g, 0.28 mmol) and deareated THF (40 ml) and the mixture was stirred. A deaerated solution of phenylethynyltributylstannane (**8a**) (4.46 g, 11.42 mmol) in THF (10 ml) was then added and the mixture was stirred at 20°C for 53 h. It was then poured into an aqueous NH_4Cl solution (200 ml) and extracted with AcOEt (2×100 ml). The organic extract was stirred at 20°C with an aqueous 8 M solution of KF (150 ml) for 4 h. The mixture was then filtered over Celite and the filtrate was extracted with AcOEt (3×60 ml). The organic extract was washed with water (80 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel using a mixture of toluene and hexane (80:20) as eluant to give (*E*)-**15a** (1.52 g, 76% yield) as a crystalline solid. Mp 71–72°C. MS, *m/z* (%): 210 (93), 181 (50), 153 (100), 128 (74), 127 (39), 102 (41), 77 (32). IR (KBr): ν 1785, 1757, 1545, 1256, 1111, 1097, 886, 764 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (1H, d, J=5.4 Hz, H-4), 7.48 (2H, m, H-11 and H-15), 7.37 (2H, m, H-12 and H-14), 7.36 (1H, m, H-13), 6.22 (1H, d, J=5.4 Hz, H-3), 2.20 (3H, s, H-7). ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.23 (C-2), 153.85 (C-5), 141.125 (C-4), 131.61 (C-11 and C-15), 129.11 (C-13), 128.54 (C-12 and C-14), 122.29 (C-10), 119.52 (C-3), 107.14 (C-6), 96.55 (C-9), 86.57 (C-8), 17.37 (C-7). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.12; H 5.04.

3.2.8. (*E*)-5-[1-(4-Methoxyphenyl)pentylidene]-2(5*H*)-furanone ((*E*)-15b). A flame-dried reaction vessel, which was maintained under an argon atmosphere, was charged with $PdCl_2(PhCN)_2$ (0.25 g, 0.66 mmol), $AsPh_3$ (0.40 g, 1.32 mmol), CuI (0.25 g, 1.32 mmol), compound (*E*)-**7c** (3.68 g, 13.23 mmol) and *N*-methylpyrrolidinone (NMP) (15 ml). A deaerated solution of 4-methoxyphenyltributylstannane (**8b**) (6.31 g, 15.88 mmol) in NMP (5 ml) was then added and the mixture was stirred at 60°C for 22 h. It was then cooled to 20°C, poured into an aqueous NH_4Cl solution (150 ml) and extracted with AcOEt (4×50 ml). The organic extract was stirred for 4 h with an aqueous 8 M solution of KF (100 ml) and the resulting mixture was filtered over Celite. The filtrate was extracted with AcOEt (4×30 ml) and the organic extract was washed with water (50 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by MPLC on silica gel using a mixture of toluene and Et_2O (97:3) as eluant to give (*E*)-**15b** (2.91 g, 85% yield) as a pale yellow liquid. MS, *m/z* (%): 258 (100), 215 (71), 201 (23), 187 (43), 133 (27), 91 (17), 77 (16). IR (film): ν 1777, 1756, 1752, 1606, 1512, 1251, 1106 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (1H, d, J=5.6 Hz, H-4), 7.21 (2H, d, J=8.7 Hz, H-12 and H-16), 6.93 (2H, d, J=8.7 Hz, H-13 and H-15), 6.13 (1H, d, J=5.6 Hz, H-3), 3.85 (3H, s, OCH_3), 2.77 (2H, t, J=7.4 Hz, H-7), 1.38 (2H, quint, J=7.4 Hz, H-8), 1.32 (2H, sext, J=7.4 Hz, H-9), 0.86 (3H, t, J=7.4 Hz, H-10). A NOESY experiment showed the presence of a cross-peak between the resonances of the H-4 and H-12 (H-16) protons. ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.38 (C-2), 159.99 (C-12 and C-16), 147.10 (C-5), 142.29 (C-4), 131.78 (C-11), 130.30 (C-14), 129.09 (C-6), 118.68 (C-3), 114.06 (C-13 and C-15), 55.35 (OCH_3), 31.95 (C-7), 30.31 (C-8), 22.56 (C-9), 13.80 (C-10). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.51; H 7.24. The spectral properties of this compound were in agreement with those of a sample of (*E*)-**15b** prepared by reaction of **1c** with 4-methoxyphenyl iodide in CH_3CN in the presence of 4 equiv. of K_2CO_3 and 5 mol% $Pd(PPh_3)_4$.[11]

3.3. Procedures for the palladium-catalyzed cross-coupling reactions of 5-iodo-2(2*H*)-pyranones 6 with organostannanes 8

The palladium-catalyzed reactions between compounds **6**

and **8** were carried out using three different procedures. The first of these (Procedure A) was used for reactions involving aryltributylstannanes, i.e. compounds **8b** and phenyltributylstannane (**8e**), vinyltributylstannane (**8d**), and tetramethylstannane (**8g**). According to this procedure, a flame-dried flask flushed with argon was charged with $PdCl_2(PhCN)_2$ (0.16 g, 0.41 mmol), CuI (0.16 g, 0.83 mmol), $AsPh_3$ (0.25 g, 0.83 mmol), a 5-iodo-2(2*H*)-pyranone **6** (8.27 mmol) and deaerated NMP (55 ml). A deaerated solution of an organostannane **8** in NMP (15 ml) was then added and the mixture was stirred at the temperature and for the period of time reported in Table 2. The reaction involving **8g** (entry 7) was carried out using a 3:1 molar ratio between this organometallic reagent and **6**, but the coupling reactions involving **8b**, **8d** and **8e** (entries 3–5) were performed using a 1.2:1 molar ratio between these organometallics and compounds **6**. After completion of the reaction, which was periodically monitored by GLC, the reaction mixture was allowed to cool to 20°C and poured into a saturated aqueous NH_4Cl solution (150 ml). After stirring for 0.5 h the mixture was extracted with AcOEt (4×50 ml). The organic extracts derived from reactions involving organotributylstannanes were stirred for 3–4 h with an aqueous 8 M solution of KF (150 ml), filtered over Celite and the filtrate was extracted with AcOEt. The organic extract was washed with brine, dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel. Procedure A was used for the synthesis of compounds **5g**, **5h**, **5i** and **5k** (entries 3, 4, 5 and 7, Table 2). The second procedure (Procedure B), which was used for the cross-coupling reactions involving 1-butynyltributylstannane (**8c**), was very similar to that employed for the synthesis of (*E*)-**15a** from (*E*)-**7a** and **8a**. This procedure was used for the synthesis of compounds **5a** and **5b** (entries 1 and 2, Table 2). Table 2 summarizes the reaction conditions used for the preparation of these 5,6-disubstituted 2(2*H*)-pyranones. Finally a third procedure (Procedure C) was employed in an attempt to use tetrabutylstannane (**8f**) in a palladium-catalyzed reaction with **6e**. Thus, a deaerated solution of $Pd_2(dba)_3$ (0.039 g, 0.042 mmol) and PPh_3 (0.089 g, 0.338 mmol) in dioxane (45 ml), which was stirred under argon, were added sequentially **6e** (2.59 g, 8.46 mmol), **8f** (2.93 g, 8.46 mmol) and a 1 M THF solution of TBAF (50.8 ml, 50.80 mmol) and the resulting mixture was refluxed under stirring for 22 h. After this period of time GLC and GLC/MS analyses of a sample of the reaction mixture, which was washed with water, showed that **6e** had completely reacted. However, no trace of the expected cross-coupled product was present. Thus, this trial was interrupted.

3.3.1. 5-(1-Butynyl)-6-methyl-2(2*H*)-pyranone (5a). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6a** and **8c** according to Procedure B (entry 1, Table 2), was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (95:5) as eluant, to give in 75% yield **5a** as a crystalline solid. Mp 48–50°C. MS, *m/z* (%): 162 (63), 147, (54), 119 (83), 105 (18), 91 (100), 65 (39), 43 (43). IR (KBr): ν 1733, 1633, 1547, 1305, 1073, 857, 823 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.24 (1H, d, *J*=9.6 Hz, H-4), 6.13 (1H, d, *J*=9.6 Hz, H-3), 2.40 (2H, q, *J*=7.5 Hz, H-5c), 2.39 (3H, s, H-6a), 1.21 (3H, t, *J*=7.5 Hz, H-5d). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H 6.21. Found: C, 74.21; H, 6.48.

3.3.2. 5-(1-Butynyl)-6-phenyl-2(2*H*)-pyranone (5b). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6b** and **8c** according to Procedure B (entry 2, Table 2), was purified by MPLC on silica gel, using a mixture of petroleum ether and AcOEt (90:10) as eluant, to give in 82% yield **5b** as a yellow crystalline solid. Mp 70–72°C. MS, *m/z* (%): 224 (24), 181 (11), 153 (13), 105 (80), 77 (100), 65 (10). IR (KBr): ν 2235, 1726, 1528, 1138, 853, 820, 694 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.19–8.14 (2H, m, Harom), 7.47–7.41 (3H, m, Harom), 7.39 (1H, d, *J*=9.5 Hz, H-4), 6.25 (1H, d, *J*=9.5 Hz, H-3), 2.42 (2H, q, *J*=7.5 Hz, H-5c), 1.22 (3H, t, *J*=7.5 Hz, H-5d). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H 5.39. Found: C, 80.36; H, 5.47.

3.3.3. 6-Butyl-5-(4-methoxyphenyl)-2(2*H*)-pyranone (5g). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6c** and **8b** according to Procedure A (entry 3, Table 2), was purified by MPLC on silica gel, using a mixture of toluene and Et_2O (90:10) as eluant, to give in 88% yield **5g** as a yellow liquid. MS, *m/z* (%): 258 (55), 201 (100), 187 (30), 173 (13), 159 (5), 145 (50), 102 (11). IR (film): ν 1732, 1610, 1544, 1513, 1249, 1179, 826 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ7.30 (1H, d, *J*=9.5 Hz, H-4), 7.16 (2H, dt, *J*=9.0 and 2.2 Hz, Harom), 6.95 (2H, dt, *J*=9.0 and 2.2 Hz, Harom), 6.22 (1H, d, *J*=9.5 Hz, H-3), 3.85 (3H, s, OCH_3), 2.50 (2H, t, *J*=7.7 Hz, H-6a), 1.78–1.57 (2H, m, H-6b), 1.28 (2H, sext, *J*=7.3 Hz, H-6c), 0.85 (3H, t, *J*=7.3 Hz, H-6d). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H 7.02. Found: C, 74.09; H, 6.92. The spectral properties of this compound were in agreement with those of **5g** prepared by treatment of **1c** with 4-methoxyphenyl iodide in CH_3CN in the presence of K_2CO_3 and a catalytic quantity of $Pd(PPh_3)_4$.[11]

3.3.4. 5-Ethenyl-6-butyl-2(2*H*)-pyranone (5h). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6c** and **8d** according to Procedure A (entry 4, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and AcOEt (85:15) as eluant, to give in 85% yield **5h** as an orange liquid. MS, *m/z* (%): 178 (82), 163 (23), 149 (24), 136 (56), 121 (100), 70 (70), 65 (34). IR (film): ν 1734, 1551, 1091, 1065, 985, 907, 829 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.57 (1H, d, *J*=9.7 Hz, H-4), 6.58 (1H, dd, *J*=17.7 and 11.0 Hz, H-5a), 6.24 (1H, d, *J*=9.7 Hz, H-3), 5.47 (1H, d, *J*=17.3 Hz, H-5b(*E*)), 5.26 (1H, d, *J*=11.0 Hz, H-5b(*Z*)), 2.61 (2H, t, *J*=7.5 Hz, H-6a), 1.75–1.57 (2H, m, H-6b), 1.38 (2H, sext, *J*=7.1 Hz, H-6c), 0.93 (3H, t, *J*=7.1 Hz, H-6d). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H 7.92. Found: C, 74.25; H, 7.99.

3.3.5. 5,6-Diphenyl-2(2*H*)-pyranone (5i). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6b** and **8e** according to Procedure A (entry 5, Table 2), was purified by MPLC on silica gel, using a mixture of hexane and AcOEt (85:15) as eluant, to give in 55% yield **5i** as a pale yellow crystalline solid. Mp 93–96°C. MS, *m/z* (%): 248 (100), 220 (96), 207 (19), 191 (38), 115 (34), 105 (39), 77 (61). IR (KBr): ν 1730, 1535,

1486, 1010, 839, 770, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, d, J=9.5 Hz, H-4), 7.40–7.15 (10, m, Harom), 6.38 (1H, d, J=9.5 Hz, H-3). The spectral properties of **5i** were in good agreement with those previously reported.[9f]

3.3.6. 5-Methyl-6-[(*E*)-1-pentenyl]-2(2*H*)-pyranone (5k). The crude reaction mixture, which was obtained from the palladium-catalyzed reaction between **6f** and **8g** according to Procedure A (entry 7, Table 2), was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (90: 10) as eluant, to give in 68% yield **5k** as a pale yellow liquid. MS, *m/z* (%): 178 (32), 136 (42), 124 (64), 121 (100), 108 (64), 93 (32), 77 (44). IR (film): ν 1729, 1646, 1533, 1098, 963, 940, 820 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.15 (1H, d, J=9.2 Hz, H-4), 6.71 (1H, dt, J=15.4 and 7.4 Hz, H-6b), 6.17 (1H, d, J=15.4 Hz, H-6a), 6.14 (1H, d, J=9.2 Hz, H-3), 2.23 (2H, q, J=7.2 Hz, H-6c), 2.05 (3H, s, H-5a), 1.50 (2H, sext, J=7.3 Hz, H-6d), 0.95 (3H, t, J=7.3 Hz, H-6e). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H 7.92. Found: C, 73.94; H 8.06.

3.3.7. (*Z*)-5-(1-Butenyl)-6-phenyl-2(2*H*)-pyranone (5e). A deaerated solution of **5b** (0.35 g, 1.56 mmol) in toluene (10 ml) was added to a suspension of 10% palladium on $BaSO_4$ (35.71 mg) in toluene (10 ml), poisoned by addition of pyridine (25 drops) followed by stirring for 5 min. The mixture was vigorously stirred under a hydrogen atmosphere and the uptake of gas monitored. After 2 h uptake had ceased and the reaction mixture was filtered and the filtrate concentrated in vacuo. A GLC/MS analysis of the residue showed the presence of two compounds in a ca. 95:5 molar ratio. The first of these was subsequently identified as **5b** and the minor component of this mixture, which had a MS spectrum very similar to that of **5b**, corresponded likely to the (*E*)-stereoisomer of this substance. The residue was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (92.5:7.5) as eluant, to give stereoisomerically pure **5e** (0.31 g, 88% yield) as a colorless solid. Mp 50–52°C. MS, *m/z* (%): 226 (6), 197 (31), 169 (12), 141 (17), 105 (97), 91 (14), 77 (100). IR (KBr): ν 1736, 1526, 1109, 1079, 996, 825, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.70–7.60 (2H, m, Harom), 7.50–7.35 (3H, m, Harom), 7.37 (1H, d, J=9.3 Hz, H-4), 6.29 (1H, d, J=9.3 Hz, H-3), 6.09 (1H, d, J=11.4 Hz, H-5a), 5.68 (1H, dt, J=11.4 and 7.3 Hz, H-5b), 2.13 (2H, dquint, J=7.5 and 1.6 Hz, H-5c), 1.00 (3H, t, J=7.5 Hz, H-5d). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H 6.24. Found: C, 79.68; H 6.31.

3.3.8. (*Z*)-5-(1-Butenyl)-6-methyl-2(2*H*)-pyranone (5c). A deaerated solution of **5a** (0.50 g, 3.08 mmol) in toluene (20 ml) was added to a suspension of 10% palladium on $BaSO_4$ (67.63 mg) poisoned by addition of pyridine (47 drops) followed by stirring for 10 min. The mixture was vigorously stirred under a hydrogen atmosphere and the uptake of gas monitored. After 3.5 h uptake had ceased and the reaction mixture was filtered and concentrated under reduced pressure. A GLC analysis of the residue showed the presence of unreacted **5a** and three new compounds in a ca. 8:88:2:2 molar ratio, respectively. The residue was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (90:10) as eluant, to give 97% pure **5c** (0.41 g, 81% yield) as a colorless oil. MS, *m/z* (%): 164 (35), 135 (13), 121 (86), 107 (46), 93 (20), 78 (46), 44 (100). IR (film): ν 1740, 1546, 1191, 1123, 1067, 864, 829 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (1H, d, J=9.5 Hz, H-4), 6.16 (1H, d, J=9.5 Hz, H-3), 6.00 (1H, d, J=11.1 Hz, H-5a), 5.71 (1H, dt, J=11.1 and 7.4 Hz, H-5b), 2.20 (3H, s, H-6a), 2.18–1.97 (2H, m, H-5c), 1.01 (3H, t, J=7.5 Hz, H-5d). These NMR data were in good agreement with those of the natural product.[4]

3.3.9. 5-Butyl-6-phenyl-2(2*H*)-pyranone (5f). A deaerated solution of **5b** (0.37 g, 1.60 mmol) in toluene (10 ml) was added to a suspension of 10% palladium on $BaSO_4$ (35.71 mg) in toluene (10 ml). The mixture was vigorously stirred under a hydrogen atmosphere and the uptake of gas monitored. After 1 h and 45 min uptake had ceased and the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (92.5:7.5) as eluant, to give **5f** (0.37 g, 100% yield) as a colorless liquid. MS, *m/z* (%): 228 (11), 185 (28), 157 (34), 129 (23), 105 (100), 77 (81), 51 (8). IR (film): ν 1736, 1632, 1546, 1491, 1099, 827, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.58–7.40 (5H, m, Harom), 7.35 (1H, d, J=9.6 Hz, H-4), 6.30 (1H, d, J=9.6 Hz, H-3), 2.43 (2H, t, J=7.6 Hz, H-5a), 1.60–1.49 (2H, m, H-5b), 1.40–1.21 (2H, m, H-5c), 0.87 (3H, t, J=7.3 Hz, H-5d). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.05; H 7.12.

3.3.10. 5-Butyl-6-methyl-2(2*H*)-pyranone (5d). A deaerated solution of **5a** (0.35 g, 2.16 mmol) in toluene (13 ml) was added to a suspension of 10% palladium on $BaSO_4$ (47.34 mg) in toluene (14 ml) and the mixture was vigorously stirred under a hydrogen atmosphere and the uptake of gas monitored. After 25 min uptake of gas, which was not complete, had ceased and 10% palladium on $BaSO_4$ (47.34 mg) was added to the mixture which was stirred under a hydrogen atmosphere. After 0.5 h uptake of gas was complete and the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. A GLC analysis of the residue showed the presence of three compounds in a ca. 89:10:1 molar ratio, in which the major and the minor component corresponded to compounds **5d** and **5c**, respectively, and the third component was not identified. The residue was purified by MPLC on silica gel, using a mixture of petroleum ether, CH_2Cl_2 and AcOEt (80:15:5) as eluant, to give **5d** (0.28 g, 78% yield) as a colorless liquid. MS, *m/z* (%): 166 (22), 138 (12), 123 (100), 95 (92), 82 (12), 68 (7), 44 (77). IR (film): ν 1740, 1642, 1557, 1466, 1104, 867, 827 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.17 (1H, d, J=9.6 Hz, H-4), 6.14 (1H, d, J=9.6 Hz, H-3), 2.29 (2H, t, J=7.5 Hz, H-5a), 2.23 (3H, s, H-6a), 1.51–1.21 (4H, m, H-5b and H-5c), 0.93 (3H, t, J=7.2 Hz, H-5d). These NMR data were in agreement with those of the natural product.[4]

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the University of Pisa. We thank Dr Luisa Mannina of the University of Molise for obtaining the ^1H NMR spectra at

600 MHz and the ^{13}C NMR spectra at 150 MHz and Professor Annalaura Segre for the use of NMR facilities of the Servizio NMR dell'Area della Ricerca di Roma (CNR). We wish also to thank Dr Jean-Luc Parrain (C.N.R.S.—Marseille) for useful suggestions and comments.

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