Selective Synthesis of 5,6-Disubstituted 3-Methyl-2(2*H*)-pyranones and 6-Substituted 3-Methyl-2(2*H*)-pyranones, Including Fusalanipyrone and Gibepyrone A

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Keywords: C−C coupling / Lactones / Natural products / Cyclizations / Synthetic methods

The 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranones **11**, prepared by iodolactonization of the corresponding 5-substituted (*E*)-2-bromo-2-en-4-ynoic acids **10**, were used as precursors to 5,6-disubstituted 3-methyl-2(2*H*)-pyranones **8** and 6-substituted 3-methyl-2(2*H*)-pyranones **7**. The synthesis of compounds **8** involved two consecutive Stille-type reactions, whereas the approach followed to prepare compounds **7** consisted of the selective reduction of the dihalogen derivatives **11** to the corresponding 6-substituted 3-bromo-2(2*H*)-pyranones **12**, followed by a Pd/Cu-catalysed reaction with tetramethyltin. However, this synthetic approach to compounds **7** proved to be unsuitable for preparing stereoisomerically pure fusalanipyrone (**7a**), a natural product isolated from *Fusarium solani*. Nevertheless, **7a** and gibepyrone A (**7b**), which is a natural product isolated from *Gibberella fujikuroi*, could be synthesized in stereoisomerically pure form by reaction sequences involving iodolactonization of easily available (2*Z*,6*Z*)- and (2*Z*,6*E*)-2,6-dimethyl-2,6-octadien-4-ynoic acids (**16a**) and (**16b**), respectively, followed by Pd-catalysed triethylammonium formate reduction of the thus obtained 6-substituted 5-iodo-3-methyl-2(2*H*)-pyranones **17a** and **17b**, respectively.

Introduction

Over the past few decades, many 2(2*H*)-pyranone derivatives have been isolated from natural sources. These compounds include 2(2*H*)-pyranones that are 6-substituted,[1] 3,5-,[2] 3,6-,[3] 4,6-,[4] and 5,6-disubstituted,[5] 3,4,6-[6] and 4,5,6-trisubstituted,[7] and 3,4,5,6-tetrasubstituted,[8] and many of them have been shown to display a wide range of biological activities including antifungal,[9] antimicrobial,[3b] androgen-like,[5b] phytotoxic,[10] cardiotonic,[1e] and pheromonal effects[2] and the ability to induce morphological and physiological differentiation of tumour cells.[1f] 2(2*H*)-Pyranones have also been shown to be useful synthetic intermediates.[11] As a consequence, numerous reports on the preparation of these heterocycles have been published.[12]

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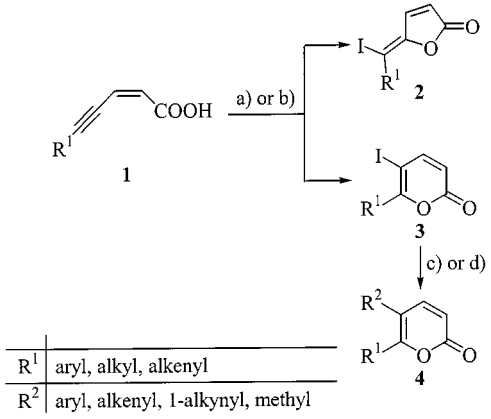
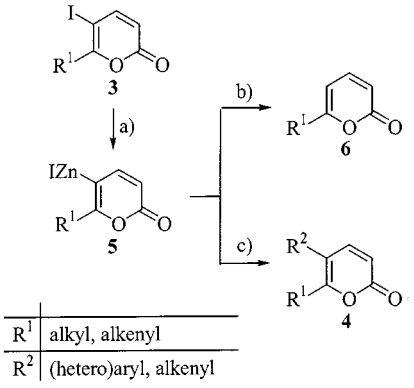
Recently, in the course of our studies on the synthesis of biologically active, naturally occurring oxygen-containing heterocycles and their analogues,[13] we became interested in developing a regioselective route to unsymmetrically 5,6-disubstituted 2(2*H*)-pyranones **4**. In fact, no general procedure to prepare these compounds had been reported in the literature. We succeeded in developing a convenient two-step procedure for the synthesis of these derivatives.[14] In particular, we found that treatment of 5-substituted (*Z*)-2-en-4-ynoic acids **1** with iodine and $NaHCO_3$ in acetonitrile or with ICl in CH_2Cl_2 afforded mixtures of compounds **2** and **3** in which these derivatives were the major products and that compounds **3**, easily separated chromatographically from iodides **2**, were able to undergo Stille-type reactions with a variety of organotin derivatives to give the desired 5,6-disubstituted 2(2*H*)-pyranones **4** in moderate to good yields (Scheme 1).[14]

We also searched for an alternative and practical route to compounds **4**, and we found that 6-alkyl-5-iodozinc-2(2*H*)-pyranones **5**, available from the corresponding iodides **3** by insertion of activated zinc metal into their carbon−iodine bonds, underwent Pd-catalysed reaction either with activated alkenyl halides or with activated and deactivated (hetero)aryl halides to provide compounds **4** in fair to good yields (Scheme 2).[15] Moreover, we observed that acidic hydrolysis of the organometallic derivatives **5** gave 6-substi-



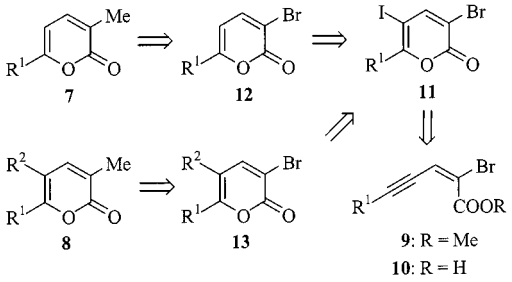
Scheme 1. Synthesis of 5,6-disubstituted 2(2*H*)-pyranones; reagents: a) I_2 (3 equiv.), $NaHCO_3$ (3 equiv.), MeCN, 1.5 h, room temp.; b) ICl (1 equiv.), CH_2Cl_2, 1.5 h, room temp.; c) R^2SnBu_3 or R^2SnMe_3 (1.2−3.0 equiv.), NMP, $PdCl_2(PhCN)_2$ (5 mol %), CuI (10 mol %), $AsPh_3$ (10 mol %), 20−80 °C, 22−80 h; d) R^2SnBu_3 (1.2 equiv.), THF, $PdCl_2(PPh_3)_2$ (3 mol %), 20−50 °C, 40−46 h



Scheme 2. Synthesis of 6-substituted and 5,6-disubstituted 2(2*H*)-pyranones; reagents: a) activated zinc dust (3 equiv.), THF, room temp., 3−3.5 h; b) 5% HCl, 0 °C; c) R^2X (X = Br, I) (0.83−1.43 equiv.), $Pd_2(dba)_3$ (2 mol %), PPh_3 (8 mol %), THF, 20−70 °C; 15−63 h

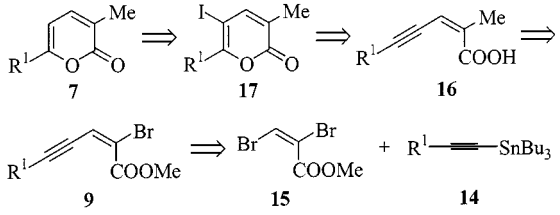
tuted 2(2*H*)-pyranones **6**, including two natural products, in satisfactory yields (Scheme 2).[15]

More recently, we examined the possibility of accessing 3,6-disubstituted and 3,5,6-trisubstituted 2(2*H*)-pyranones of general formula **7** and **8**, respectively, through chemistry similar to that successfully used to prepare compounds **4** and **6**. In particular, we speculated that carboxylic acids **10**, corresponding to the readily available methyl esters **9**,[16] might be regioselectively converted into 3-bromo-5-iodo-2(2*H*)-pyranones **11** and that these dihalogen derivatives might be useful starting materials to prepare compounds **7** if it was possible to reduce compounds **11** selectively to the corresponding 3-bromo derivatives **12** and then to perform a transition metal-catalysed methylation reaction on these last compounds, as illustrated in the retrosynthetic analysis shown in Scheme 3. The trisubstituted 2(2*H*)-pyranones **8**, on the other hand, we imagined might be prepared from **11**, if it was possible to achieve a regioselective Pd-catalysed carbon−carbon bond-forming reaction at the iodine-bearing carbon atom 5 of these dihalogen derivatives, followed by a methylation reaction of the resultant 5,6-disubstituted 3-bromo-2(2*H*)-pyranones **13** (Scheme 3).



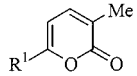
Scheme 3. Retrosynthetic analysis of compounds **7** and **8**

Moreover, we also considered the alternative possibility of synthesizing compounds **7** from methyl esters **9** by a reaction sequence based on the retrosynthetic analysis depicted in Scheme 4, involving the preparation and use of 3,6-disubstituted 5-iodo-2(2*H*)-pyranones **17**.



Scheme 4. Alternative retrosynthetic analysis of compounds **7**

We now wish to describe and comment on the results of these studies. In particular, we show that compounds **11** were useful intermediates for the selective synthesis of compounds **8**, characterized by an alkyl or an aryl group at C-6. We also report that, whereas compounds of general formula **7**, characterized by an alkyl group at C-6, could be selectively synthesized in satisfactory yields by a reaction sequence involving the preparation and use of a 6-alkyl-3-bromo-5-iodo-2(2*H*)-pyranone **11** (R^1 = alkyl), a similar reaction sequence involving stereodefined 6-(alkenyl)-3-bromo-5-iodo-2(2*H*)-pyranones **11** [R^1 = (*Z*)- or (*E*)-alkenyl] was not suitable for the synthesis of two stereoisomerically pure 3,6-disubstituted 2(2*H*)-pyranones isolated from fungi: 6-[(*Z*)-2-butenyl]-3-methyl-2(2*H*)-pyranone (fusalanipyrone, **7a**)[3a] and 6-[(*E*)-2-butenyl]-3-methyl-2(2*H*)-pyranone (gibepyrone A, **7b**)[3b] (Figure 1). Finally, we report that these naturally occurring compounds could be regioselectively synthesized in stereoisomerically pure form and in satisfactory overall yields by seven-step reaction sequences based on the retrosynthetic analysis depicted in Scheme 4.



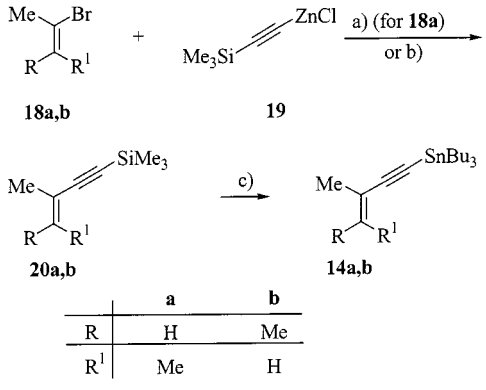
7a: R^1 = (*Z*)-Me-C=CH-Me
7b: R^1 = (*E*)-Me-C=CH-Me

Figure 1. Chemical structures of compounds **7a** and **7b**

Results and Discussion

6-Substituted 3-Bromo-5-iodo-2(2*H*)-pyranones and 6-Substituted 5-Iodo-3-methyl-2(2*H*)-pyranones

The starting materials for the synthesis of the possible precursors to 6-substituted 3-methyl-2(2*H*)-pyranones **7** and 5,6-disubstituted 3-methyl-2(2*H*)-pyranones **8**, compounds **11** and **17**, were methyl (*E*)-2,3-dibromopropenoate (**15**)[17] and the organotin derivatives **14** (Scheme 4). Whereas one of these *organometallics* − phenylethynyltributyltin (**14d**) − was commercially available, and 1-hexynyltributyltin (**14c**) could be prepared according to the literature,[18] (*Z*)- and (*E*)-3-methyl-3-penten-1-ynyltributyltin (**14a** and **14b**) were synthesized by a two-step reaction sequence that did not involve the use of the corresponding volatile enynes (Scheme 5). The first step of this sequence used to prepare **14a**, involved treatment of stereoisomerically pure (*Z*)-2-bromo-2-butene (**18a**) with a THF solution of 1.25 equiv. of **19** in the presence of 5 mol % $Pd(PPh_3)_4$. This reaction furnished 95% stereoisomerically pure **20a** in 51% yield after 6 d at 65 °C. However, when the coupling was performed at 60 °C for 24 h in a 1:1 mixture of THF and DMF in the presence of 5 mol % $Pd(PPh_3)_4$, it provided 97% stereoisomerically pure **20a** in 71% yield. In the second step of the reaction sequence, **20a** was converted into the corresponding tributyltin derivative **14a** by means of a catalytic method for the conversion of 1-alkynylsilanes into the corresponding tributylstannanes (Scheme 5).[19]

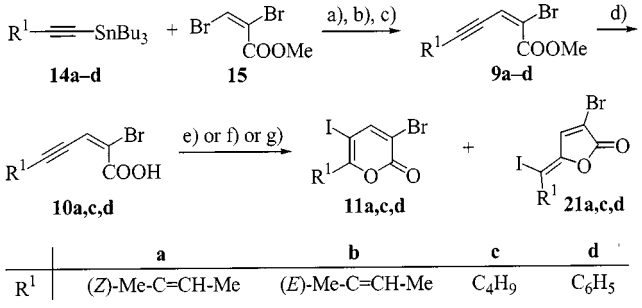


Scheme 5. Synthesis of (*Z*)- and (*E*)-(3-methyl-3-penten-1-ynyl)tributyltin (**14a**) and (**14b**); reagents: a) **19** (1.25 equiv.), $Pd(PPh_3)_4$ (5 mol %), THF, 65 °C, 6 days; b) **19** (1.25 equiv.), $Pd(PPh_3)_4$ (5 mol %), THF and DMF (1:1), 60 °C, 24 h (for **18a**) and 3 h (for **18b**); c) $(Bu_3Sn)_2O$ (0.47 equiv.), TBAF (0.02 equiv.), THF, 65 °C, 2.5 h

In particular, a mixture of **20a** and 0.47 equiv. of bis(tributyltin) oxide in dry THF was treated with 0.02 equiv. of TBAF and the resulting mixture was heated to 65 °C for 2.5 h. The volatiles were then removed under reduced pressure to give a quantitative yield of crude **14a** with 97% stereoisomeric purity and a chemical purity higher than 92%.

A similar reaction sequence was then used to prepare **14b** from **18b** in 74% overall yield (Scheme 5). Compound **14b** was stereoisomerically pure and had a chemical purity higher than 95%.

The subsequent regioselective and stereospecific reactions between **15** and 1.1 equiv. of the organotin derivatives **14a**−**d**, in *N*-methylpyrrolidinone (NMP) at room temperature in the presence of 5 mol % $PdCl_2(PhCN)_2$ and 10 mol % $AsPh_3$, allowed stereoisomerically pure compounds **9a**, **9b**, **9c**, and **9d** to be prepared in 66, 54, 67, and 69% yields, respectively (Scheme 6).



Scheme 6. Synthesis of 5-substituted (*E*)-2-bromo-2-en-4-ynoic acids **10** and their iodolactonization; reagents: a) **14** (1.1 equiv.), $PdCl_2(PhCN)_2$ (5 mol %), $AsPh_3$ (10 mol %), NMP, room temp., 20−24 h; b) 8 M aq. KF, Et_2O; c) MPLC on silica gel; d) for compounds **9a**,**c**,**d**: 1 M LiOH, THF, 24 h, then 10% H_2SO_4, 0 °C; e) *Method A:* I_2 (3.0 equiv.), $NaHCO_3$ (3.0 equiv.), MeCN, room temp., 1 h; f) *Method B:* ICl (1.0 equiv.), CH_2Cl_2, 0 °C, 1 h; g) *Method C:* NIS (1.1 equiv.), $KHCO_3$ (1.0 equiv.), MeCN, room temp., 1 h

We then examined the possibility of preparing the 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranones **11a**, **11c**, and **11d** by conversion of **9a**, **9c**, and **9d**, respectively, into the corresponding carboxylic acids **10**, followed by iodolactonization of these compounds by one of the procedures that we had previously employed to prepare 5-iodo-2(2*H*)-pyranones **3** from the corresponding acids **1**.[14] Thus, THF solutions of **9a**, **9c**, and **9d** were treated with molar excesses of 1 M LiOH solutions for 24−36 h, followed by acidification at 0 °C to give the corresponding carboxylic acids **10a**, **10c**, and **10d** in 80, 100, and 73% yields, respectively. Three procedures for iodolactonization of these carboxylic acids were then investigated (Scheme 6 and Table 1). The first of these (*Method A*) involved treatment of the carboxylic acid with 3.0 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in CH_3CN at room temperature for 1 h. The second procedure (*Method B*) consisted of treatment of the carboxylic acid with 1.0 equiv. of ICl in CH_2Cl_2 at 0 °C, while the last procedure (*Method C*) involved treatment of the carboxylic acid with 1.1 equiv. of *N*-iodosuccinimide (NIS) and 1.0 equiv. of $KHCO_3$ in CH_3CN at room temperature for 1 h.

Table 1. Synthesis of 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranones **11** and the corresponding (*E*)-3-bromo-5-(1-iodoylidene)-2(5*H*)-furanones **21**

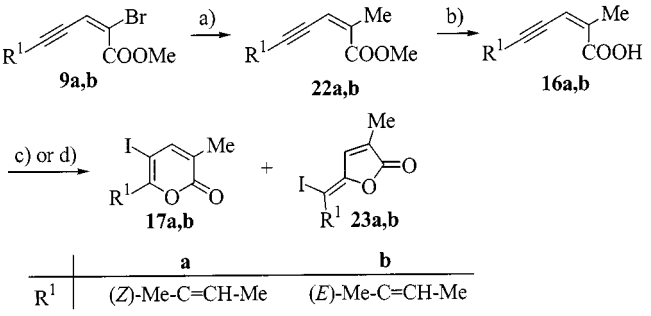
Entry	Carboxylic acid **10**	Method for iodo lactonization[a]	Products **11** + **21**	**11**/**21** molar ratio[b]	Yield of **11**	Yield of **21**
1	**10a**	A	**11a** + **21a**	97.5:2.5	75	n.d
2	**10a**	B	**11a** + **21a**	> 99.0:< 1.0	52	n.d.
3	**10a**	C	**11a** + **21a**	53.0:47.0	38	40[c]
4	**10c**	A	**11c** + **21c**	40.0:60.0	30	50[d]
5	**10c**	B	**11c** + **21c**	57.0:43.0	n.d.	n.d.
6	**10c**	C	**11c** + **21c**	1.5:98.5	n.d.	n.d.
7	**10d**	A	**11d** + **21d**	49.0:51.0	40	43
8	**10d**	B	**11d** + **21d**	92.8:7.2	70	7
9	**10d**	C	**21d**	0:100	n.d.	n.d.

[a] *Methods A*, *B*, and *C* were used for iodolactonization of compounds **10**. [b] Molar ratio in the crude reaction mixture. [c] This compound was isolated as a mixture of four stereoisomers. [d] Compound **21c** was contaminated with ca. 30% of the corresponding (*Z*) stereoisomer.

As shown in Table 1, where the results of these reactions are summarized, our attempts to prepare **11c** with high selectivity by *Methods A* or *B* met with no success (Entries 4 and 5). In fact, these methods gave **11c** and the corresponding isomer **21c** in comparable amounts. On the other hand, *Method C* furnished a crude reaction mixture in which **21c** was the major product (Entry 6). However, we were able to obtain isomerically pure **11c** in 30% isolated yield by chromatographic purification of the crude reaction mixture obtained in Entry 4. This purification also allowed **21c** to be isolated in 50% yield. This latter compound, however, which had been stereoisomerically pure in the crude reaction mixture, underwent partial stereomutation during the chromatographic purification and was isolated as a mixture of (*E*) and (*Z*) stereoisomers in ca. 70:30 molar ratio.

In contrast, both *Methods A* and *B* proved to be suitable for the selective preparation of stereoisomerically pure **11a** (Entries 1 and 2), although a higher isolated yield of this compound could be obtained by the first of these procedures (Entry 1). Finally, we found that compound **11d** could also be regioselectively prepared in satisfactory yield by iodolactonization of **10d** by *Method B* (Entry 8). In contrast, *Method A* unexpectedly furnished a crude mixture of **11d** and **21d** in 49:51 molar ratio (Entry 7). It should also be noted that, whereas compounds **21c** and **21d** could be regioselectively obtained by iodolactonization of **10c** and **10d**, respectively, by *Method C* (Entries 6 and 9, Table 1), a crude mixture of **11a** and **21a** in 53:47 molar ratio was unexpectedly obtained when this same method was used for iodolactonization of **10a** (Entry 3, Table 1).

Next, we completed our studies on the preparation of possible precursors to 6-substituted 3-methyl-2(2*H*)-pyranones **7** by investigating the synthesis of two stereodefined 6-alkenyl-5-iodo-3-methyl-2(2*H*)-pyranones: compounds **17a** and **17b**. Thus, **9a** and **9b** were treated with 3.0 equiv. of tetramethyltin in the presence of 5 mol % $PdCl_2[P(o\text{-tolyl})_3]_2$ and 10 mol % CuI[20] in NMP at 70 °C for 2.5 h to give stereoisomerically pure **22a** and **22b**, in 74 and 84% yields, respectively (Scheme 7).



Scheme 7. Synthesis of 5-substituted (*Z*)-2-methyl-2-en-4-ynoic acids **16** and their iodolactonization; reagents: a) Me_4Sn (3.0 equiv.), $PdCl_2[P(o\text{-tolyl})_3]_2$ (5 mol %), CuI (10 mol %), NMP, 70 °C, 2.5 h; b) 1 M LiOH, THF, room temp., 24 h, then 10% H_2SO_4, 0 °C; c) *Method A:* I_2 (3.0 equiv.), $NaHCO_3$ (3.0 equiv.), MeCN, room temp., 1 h; d) *Method B:* ICl (1.0 equiv.), CH_2Cl_2, 0 °C, 1 h

Saponification of these esters with 1 M LiOH at room temperature, followed by acidification at 0 °C, provided the corresponding crude carboxylic acids **16a** and **16b** in 100 and 92% yields, respectively. Interestingly, iodolactonization of these carboxylic acids by *Method A*, which we had used to prepare the dihalogen derivatives **11**, allowed us to obtain mixtures of compounds **23** and the required 6-alkenyl-5-iodo-3-methyl-2(2*H*)-pyranones **17** with these last iodides as the major products (Scheme 7, Table 2).

It should be noted that the regioselectivity of iodolactonization of **16a** was different from that of the analogous reaction involving **16b**. In fact, whereas treatment of **16a** with iodine and $NaHCO_3$ in CH_3CN gave a crude reaction mixture in which **17a** and the corresponding stereoisomerically pure regioisomer **23a** were in a ca. 92:8 molar ratio (Entry 1, Table 2), iodolactonization of **16b** by this procedure afforded a mixture of **17b** and stereoisomerically pure **23b** in a ca. 80:20 molar ratio (Entry 3, Table 2). Chromatographic

Table 2. Synthesis of 6-substituted 5-iodo-3-methyl-2(2*H*)-pyranones **17** and the corresponding (*E*)-5-(1-iodoylidene)-3-methyl-2(5*H*)-furanones **23**

Entry	Carboxylic acid **16**	Method for iodo lactonization[a]	Products **17** + **23**	**17**/**23** molar ratio[b]	Yield of **17**	Yield of **23**
1	**16a**	A	**17a** + **23a**	92.0:8.0	78	7[c]
2	**16a**	B	**17a**	> 99.0:< 1.0	88	–
3	**16b**	A	**17b** + **23b**	80.0:20.0	59	17[d]

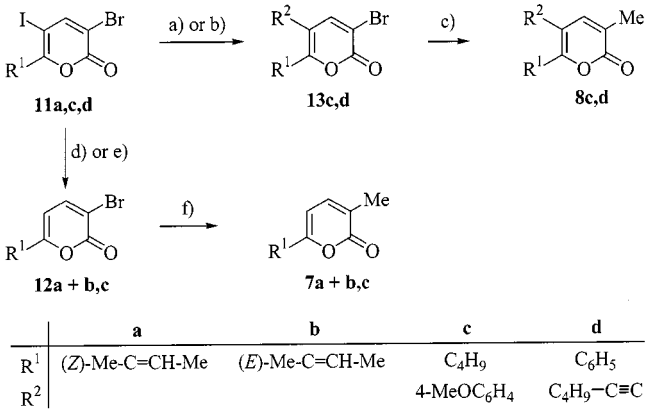
[a] *Methods A* and *B* were used for iodolactonization of compounds **16**. [b] Molar ratio in the crude reaction mixture. [c] **23a** underwent stereomutation during purification by MPLC on silica gel to give a mixture of (5*E*)- and (5*Z*)-**23a** in a ca. 70:30 molar ratio. [d] **23b** underwent isomerization during the purification by MPLC on silica gel to give a complex mixture of compounds.

purification of the crude reaction mixture deriving from **16a** furnished regio- and stereoisomerically pure **17a** and **23a** in 78 and 7% yields, respectively. During this purification, however, **23a** underwent partial stereomutation and the isolated product proved to consist of a mixture of two stereoisomers in ca. 70:30 molar ratio. On the other hand, chromatographic purification of the crude reaction mixture derived from **16b** allowed us to isolate regio- and stereoisomerically pure **17b** and a complex mixture of stereoisomers of the corresponding 5-[(*E*)-1-iodoylidene]-3-methyl-2(5*H*)-furanone, in which the major component was presumably **23b**, in 59 and 17% yields, respectively.

Finally, it is worth mentioning that iodolactonization of **16a** with ICl in CH_2Cl_2 at room temperature for 2 h furnished stereoisomerically pure **17a** in 88% isolated yield with complete regioselectivity (Entry 2, Table 2).

5,6-Disubstituted and 6-Substituted 3-Methyl-2(2*H*)-pyranones

Encouraged by the successful outcome of the reaction sequences affording 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranones **11** and 6-substituted 5-iodo-3-methyl-2(2*H*)-pyranones **17**, we first of all decided to investigate the use of compounds **11** in the selective synthesis of 5,6-disubstituted 3-methyl-2(2*H*)-pyranones **8**. Our attempt to synthesize these compounds through preparation of 5,6-disubstituted 3-bromo-2(2*H*)-pyranones **13** by selective Stille-type reactions involving the dihalogen derivatives **11** was based on the assumptions that: (i) oxidative addition of compounds **11** to Pd^0 would be the selectivity-determining step, and (ii) the reactivity for this oxidative addition of the carbon−iodine bond at C-5 of **11** would be higher than that of the carbon−bromine bond at C-3 of these derivatives. Indeed, we were gratified to find that treatment of **11c** with 1.1 equiv. of 4-methoxyphenyltributyltin in NMP at 45 °C for 23 h, in the presence of 5 mol % $PdCl_2(PhCN)_2$, 10 mol % $AsPh_3$ and 10 mol % CuI,[20] was highly selective and gave the required cross-coupled product **13c** in 89% yield (Scheme 8).



Scheme 8. Synthesis of 5,6-disubstituted 3-bromo-2(2*H*)-pyranones **13**, 5,6-disubstituted 3-methyl-2(2*H*)-pyranones **8**, 6-substituted 3-bromo-2(2*H*)-pyranones **12** and 6-substituted 3-methyl-2(2*H*)-pyranones **7**; reagents: a) for **11c**: 4-$MeOC_6H_4SnBu_3$ (**24**) (1.1 equiv.), $PdCl_2(PhCN)_2$ (5 mol %), CuI (10 mol %), $AsPh_3$ (10 mol %), NMP, 23 h, 45 °C; b) for **11d**: **14c** (1.1 equiv.), $PdCl_2(PPh_3)_2$ (3 mol %), THF, 22 h, 20 °C, then 44 h, 45 °C; c) Me_4Sn (3.0 equiv.), $PdCl_2[P(o\text{-tolyl})_3]_2$ (5 mol %), CuI (10 mol %), NMP, 80 °C, 22 h; d) for **11a**: $Pd(OAc)_2$ (2 mol %), Et_3N (3.0 equiv.), PPh_3 (4 mol %), HCOOH (1.5 equiv.), DMF, 60 °C, 5 h; e) activated zinc dust (5.0 equiv.), THF, 2.5−13.5 h, then H_3O^+; f) Me_4Sn (3.0 equiv.), $PdCl_2[P(o\text{-tolyl})_3]_2$ (5 mol %), CuI (10 mol %), NMP, 80 °C, 22 h

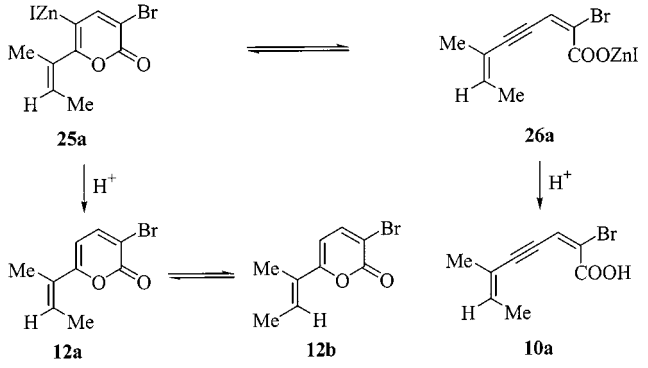
On the other hand, the cross-coupling reaction between **13c** and 3 equiv. of tetramethyltin in NMP at 80 °C for 22 h, in the presence of catalytic amounts of $PdCl_2[P(o\text{-tolyl})_3]_2$ and CuI, gave **8c** in 94% yield (Scheme 8). Similarly, treatment of **11d** with 1.1 equiv. of **14c** in THF, in the presence of 3 mol % $PdCl_2(PPh_3)_2$, proved to be highly selective and furnished **13d** in 74% yield. This last compound then underwent a Pd-catalysed reaction with tetramethyltin to give **8d** in 83% yield (Scheme 8).

We next examined the possibility of using compounds **11** as precursors to 6-substituted 3-methyl-2(2*H*)-pyranones **7**. In particular, we investigated a reaction sequence involving the selective reduction of **11** to the corresponding 3-bromo derivatives **12** and the Pd/Cu-catalysed methylation of these compounds. The procedure initially used to reduce **11** was similar to that that we had recently developed to prepare 6-

substituted 2(2*H*)-pyranones from the corresponding 5-iodo derivatives, and involved the formation of 5-(iodozinc)-2(2*H*)-pyranones.[15] Thus, we found that **11c** was selectively converted into **12c** in 74% yield by treatment with a large molar excess of activated zinc dust,[21] followed by acidic hydrolysis of the obtained organometallic. Compound **12c** then underwent a Pd/Cu-catalysed reaction with tetramethyltin to give 6-butyl-3-methyl-2(2*H*)-pyranone (**7c**) in 91% yield (Scheme 8).

Interestingly, we observed that the reaction between **11a** and activated zinc dust was slower than that for insertion of activated zinc metal into the carbon−iodine bond of **11c** (13.5 h instead of 2.5 h) and provided a crude reaction product consisting of stereoisomerically pure **12a** and **10a** in a ca. 1:2.5 molar ratio. However, **12a** underwent stereomutation during its isolation by MPLC on silica gel. In fact, chromatographic purification of the crude reaction product furnished a stereoisomeric mixture of **12b** and **12a** in a ca. 83:17 molar ratio, in 36% yield.

A possible explanation for the formation of **10a** and the mixture of **12a** and **12b** is summarized in Scheme 9.



Scheme 9. Possible explanation for the formation of compounds **10a**, **12a**, and **12b** in the reaction between **11a** and activated zinc dust, followed by acidic hydrolysis

This proposal involves: (i) partial conversion of the organozinc derivative **25a**, which derives from insertion of activated zinc metal into the carbon−iodine bond of **11a**, into the iodozinc carboxylate **26a**,[22] and (ii) room-temperature stereomutation of compound **12a**, derived from acidic hydrolysis of **25a**.

A similar explanation could be put forward to explain the previously observed formation of a mixture of (*Z*)-5-phenyl-2-buten-4-ynoic acid and 6-phenyl-2(2*H*)-pyranone in the reaction between 5-iodo-6-phenyl-2(2*H*)-pyranone and activated zinc dust, followed by acidic hydrolysis.[15]

It should also be noted that we were unsuccessful in preparing stereoisomerically pure **12a** by Pd-catalysed triethylammonium formate reduction[23] of **11a** (Scheme 8). In fact, the crude product of this reaction consisted of a mixture of 93% stereoisomerically pure **12a** and two other major components, which − on the basis of their MS spectra − presumably corresponded to the overreduction product **27** and **28** (Figure 2). Moreover, significant stereomutation occurred during the chromatographic purification of crude **12a**. In fact, this compound was isolated in 34% yield as a mixture of **12a** and **12b**, in which the **12a:12b** ratio was 38:62.

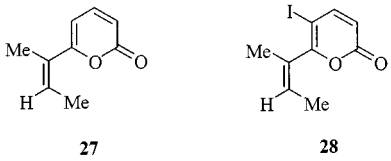
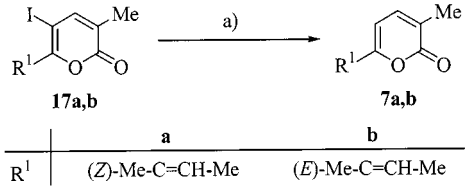


Figure 2. Chemical structures of compounds **27** and **28**

Despite these unsatisfactory results, however, we attempted to prepare fusalanipyrone (**7a**) and gibepyrone A (**7b**) from a stereoisomeric mixture of **12a** and **12b**. Thus, we performed a Pd/Cu-catalysed reaction between tetramethyltin and a 46:54 mixture of **12a** and **12b** (Scheme 8). This reaction proved to be stereospecific and provided a mixture of **7a** and **7b** in quantitative yield. Unfortunately, the chromatographic separation of these compounds was difficult, and **7a** and **7b** isolated in this way were in fact judged by GLC analysis to be only 85% stereoisomerically pure.

Nevertheless, we succeeded in preparing stereoisomerically pure **7a** and **7b** cleanly in 87 and 81% yields, respectively, by Pd-catalysed triethylammonium formate reduction of **17a** and **17b**, respectively (Scheme 10).



Scheme 10. Synthesis of stereoisomerically pure **7a** and **7b**; reagents: a) $Pd(OAc)_2$ (2 mol %), Et_3N (3.0 equiv.), PPh_3 (4 mol %), HCOOH (1.5 equiv.), DMF, 55−60 °C, 2−3 h

The ^1H NMR parameters of **7a**, with the exception of the chemical shift of the olefinic proton 6b-H were in agreement with those reported for naturally occurring fusalanipyrone.[3a] It should also be noted that, whereas gibepyrone A was reported to be an oil,[3b] our sample of stereoisomerically pure **7b** proved to be a colourless solid with m.p. 39−41 °C.

Conclusion

In this study we have demonstrated that: (i) iodolactonization of carboxylic acids **10** affords mixtures of the required 3-bromo-5-iodo-2(2*H*)-pyranones **11** and the corresponding 3-bromo-5-[(*E*)-1-iodoylidene]-2(5*H*)-furanones **21**, and (ii) the selectivity of this reaction is dependent either on the nature of the substituent present at C-5 of **10** or on the

procedure used for iodolactonization (*Methods A*, *B*, or *C*). We also showed that compounds **11** are useful synthetic intermediates. In fact, they proved to be able to undergo selective Stille-type reactions to give, in satisfactory yields, 5,6-disubstituted 3-bromo-2(2*H*)-pyranones **13**, which are direct precursors to 5,6-disubstituted 3-methyl-2(2*H*)-pyranones **8**.

Compounds **11** could also be selectively reduced to the corresponding 3-bromo derivatives **12**, and these last compounds proved to be useful precursors for 6-substituted 3-methyl-2(2*H*)-pyranones **7**. However, a serious disadvantage of this procedure was that it was not suitable for the preparation of stereoisomerically pure fusalanipyrone (**7a**). In fact, reduction of **11a** by Pd-catalysed triethylammonium formate or by treatment with a large excess of activated zinc dust in THF followed by acidic hydrolysis provided a stereoisomeric mixture of **12a** and **12b**. Moreover, the chromatographic separation of **7a** and **7b**, prepared by means of a Pd-catalysed reaction between a mixture of **12a** and **12b** and tetramethyltin, proved to be difficult and these natural products were isolated only in 85% stereoisomerically pure form.

Nevertheless, we then succeeded in preparing stereoisomerically pure **7a** in 26% overall yield from (*Z*)-2-bromo-2-butene (**18a**) by a seven-step reaction sequence involving the highly regioselective iodolactonization of carboxylic acid **16a**, followed by the Pd-catalysed triethylammonium formate reduction of the obtained compound **17a**. An analogous reaction sequence involving carboxylic acid **16b** and the derived iodolactone **17b** was then used to synthesize stereoisomerically pure **7b** in 15% overall yield starting from **18b**.

Studies on the use of some of these compounds as intermediates for the synthesis of some natural product hybrids, which are characterized by two different pharmacophoric subunits and are pharmacologically and/or agrochemically important, are in progress.

Experimental Section

General Remarks: Melting points and boiling points are uncorrected. Precoated Merck 60 F_{254} aluminium silica gel sheets were used for TLC analyses. GLC analyses were performed with a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani 86.01 data station. 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 60 silica gel, particle size 0.015−0.040 mm) were performed with a Büchi B-680 system with a Knauer K-2400 differential refractometer as detector. GLC/MS analyses were performed with a Q-mass 910 spectrometer, interfaced with a Perkin−Elmer 8500 gas chromatograph or an HP 6890 Plus GC system equipped with a mass-selective detector HP 5973. IR spectra were recorded with a Perkin−Elmer 1725 FT-IR spectrophotometer. NMR spectra were recorded with a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer, with TMS and $CDCl_3$, respectively, as internal standards. The structures of compounds **20a**, **20b**, **11a**, **22a**, **22b**, **7a**, and **7b** were assigned by a combination of NMR techniques, which included ^{11}H COSY, NOESY (mixing time: 400 ms), HMQC (Heteronuclear Multiple Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation). All reactions of air- and water-sensitive materials were performed in flame-dried glassware under argon or nitrogen, by standard syringe, cannula and septa techniques. The following compounds were prepared by published procedures: $Pd(PPh_3)_4$,[24] $PdCl_2(PhCN)_2$,[25] methyl (*E*)-2,3-dibromopropenoate (**15**),[17] tributyl(1-hexynyl)tin (**14c**)[18] and tributyl(4-methoxyphenyl)tin (**24**).[26]

(*Z*)-Trimethyl(3-methyl-3-penten-1-ynyl)silane (20a)

First Procedure: Trimethylsilylacetylene (8.65 g, 88.1 mmol) was added dropwise to a solution of ethylmagnesium bromide (88.1 mmol) in THF (100 mL), and the mixture was heated under reflux for 1 h. The resulting solution was then cooled to 20 °C and slowly added with stirring to a slurry of dry $ZnCl_2$ (15.60 g, 114.5 mmol) in THF (150 mL), cooled to 0 °C. The resulting mixture was maintained at room temperature for 0.5 h. $Pd(PPh_3)_4$ (4.07 g, 3.52 mmol) and (*Z*)-2-bromo-2-butene (**18a**) (9.55 g, 70.5 mmol) were then added sequentially, and the mixture, which was periodically monitored by GLC analysis of samples hydrolysed with aqueous NH_4Cl solution, was heated under reflux for 6 d. It was then cooled to room temperature, poured into a saturated aqueous NH_4Cl solution (300 mL) and extracted with diethyl ether (4 × 100 mL). The extracts were washed with brine (100 mL), dried, and concentrated. The residue was diluted with pentane (250 mL), filtered through Celite and concentrated. Fractional distillation of the residue gave **20a** (5.47 g, 51%) as a colourless liquid. B.p. 77−79 °C/99 mbar. MS: *m*/*z* (%) = 152 (28) [M^+], 138 (14), 137 (100), 109 (10), 97 (8), 83 (16), 59 (16). IR (film): $\tilde{\nu}$ = 2135 cm^{-1}, 1340, 1251, 1042, 961, 864, 843, 760, 633. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.76 (m, 1 H, 4-H), 1.82 (m, 3 H, 3a-H), 1.81 (m, 3 H, 5-H), 0.20 (s, 9 H, $SiMe_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 133.91, 118.78, 104.62, 97.73, 22.75, 16.29, 0.15. An NOESY experiment showed the presence of a cross-peak between the resonances of protons 4-H and 3a-H. $C_9H_{16}Si$ (152.31): calcd. C 70.97, H 10.59; found C 71.19, H 10.75. ^{1}H NMR and GLC analyses showed that **20a** had 95% stereoisomeric purity.

Second Procedure: A solution of trimethylsilylethynylmagnesium bromide (44.2 mmol) in THF (50 mL), prepared according to the procedure described above, was added at 0 °C to a slurry of dry $ZnCl_2$ (7.83 g, 57.5 mmol) in THF (40 mL), and the mixture was stirred at 20 °C for 0.5 h. $Pd(PPh_3)_4$ (2.00 g, 1.77 mmol) and a solution of **18a** (4.77 g, 35.4 mmol) in DMF (90 mL) were then added sequentially and the resulting mixture was stirred at 60 °C for 24 h. After this period of time, the reaction was complete, and so it was worked up as usual. The crude reaction product was diluted with pentane (150 mL) and filtered through Celite. Fractional distillation of the filtrate gave **20a** (3.82 g, 71%) as a colourless liquid. ^{1}H NMR and GLC analyses showed that **20a** had stereoisomeric purity higher than 97%.

(*E*)-Trimethyl(3-methyl-3-penten-1-ynyl)silane (20b): (*E*)-2-Bromo-2-butene (**18b**, 5.18 g, 38.4 mmol) was converted into **20b** (4.32 g, 74%) by the second procedure used for the synthesis of **20a**. Interestingly, the Pd-catalysed reaction between **18b** and trimethylsilylethynylzinc chloride **19** was complete after 3 h at 60 °C. GLC analysis showed that **20b**, which was obtained as a pale yellow liquid, was stereoisomerically pure. B.p. 91−92 °C/100 mbar (ref.[27] b.p. 56 °C/20 mbar). MS: *m*/*z* (%) = 152 (23) [M^+], 138 (45), 137 (100), 109 (6), 97 (7), 83 (12), 59 (8). IR (film): $\tilde{\nu}$ = 2144 cm^{-1}, 1250, 1220, 1094, 960, 842, 760, 698, 643. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.00 (qq, *J* = 7.0, 1.2 Hz, 1 H, 4-H), 1.77 (quint, *J* = 1.2 Hz, 3 H, 5-H), 1.67 (dq, *J* = 7.0, 1.2 Hz, 3 H, 3a-H), 0.17 (s, 9 H,

$SiMe_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 133.91, 118.76, 108.73, 97.73, 16.77, 14.12, 0.11. The spectral properties of this compound were in satisfactory agreement with those previously reported.[27]

(*Z*)-Tributyl(3-methyl-3-penten-1-ynyl)tin (14a): A flame-dried reaction vessel, maintained under argon, was charged with a deaerated solution of **20a** (5.20 g, 34.1 mmol) in THF (60 mL) and bis(tributyltin) oxide (9.50 g, 15.9 mmol). A THF solution of TBAF (1 M, 0.68 mL, 0.68 mmol) was added, and the mixture was stirred at 65 °C for 2.5 h, after which the volatiles were removed under reduced pressure to give **14a** (11.77 g, 100%) as an orange liquid. MS: *m*/*z* (%) = 313 (100), 311 (77), 257 (41), 255 (33), 199 (63), 177 (7), 121 (17). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.74 (m, 1 H, 4-H), 1.84−1.80 (m, 6 H, 5-H and 3a-H), 1.63−1.25 (m, 12 H, Sn−*CH*$_2$−*CH*$_2$), 1.00 (t, *J* = 7.8 Hz, 6 H, Sn−*CH*$_2$), 0.90 (t, *J* = 7.1 Hz, 9 H, Sn−C−C−C−*CH*$_3$). GLC and GLC/MS analyses showed that **14a** had 97% stereoisomeric purity and a chemical purity higher than 92%. This crude product was used in the next step without any further purification and characterization.

(*E*)-Tributyl(3-methyl-3-penten-1-ynyl)tin (14b): Compound **20b** (4.20 g, 27.6 mmol) was converted into crude **14b** (9.50 g, 100%) by the procedure used to prepare the corresponding stereoisomer. GLC analysis showed that crude **14b**, which was an orange liquid, was stereoisomerically pure and had a chemical purity higher than 95%. MS: *m*/*z* (%) = 313 (100), 311 (77), 257 (43), 255 (34), 199 (71), 197 (51), 121 (14). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.93 (qq, *J* = 7.3, 1.5 Hz, 1 H, 4-H), 1.77 (pseudo-quint, *J* = 1.1 Hz, 3 H, 3a-H), 1.66 (dq, *J* = 7.3, 1.1 Hz, 3 H, 5-H), 1.61−0.90 (m, 27 H, $SnBu_3$). This crude product was used in the next step without any further purification and characterization.

General Procedure for the Pd-Catalysed Cross-Coupling Reactions between 15 and Tributyl(1-ynyl)tin Derivatives of General Formula 14: A flame-dried reaction vessel, flushed with argon, was charged with $PdCl_2(PhCN)_2$ (0.54 g, 1.4 mmol), $AsPh_3$ (0.86 g, 2.8 mmol), **15** (6.83 g, 28.0 mmol), and NMP (25 mL). A deaerated solution of a tributyl(1-ynyl)tin derivative **14** in NMP (25 mL) was then added and the mixture was stirred at room temperature until the reaction was complete (18−24 h). Reactions involving **14a** and **14c** were carried out with a 1:1 molar ratio between the organometallics and **15**, but coupling reactions involving **14b** and **14d** were performed with 1.10:1 and 1.05:1 molar ratios, respectively, between the organometallics and **15**. After completion of the reaction, which was periodically monitored by GLC, the reaction mixture was poured into a saturated aqueous NH_4Cl solution (200 mL) and extracted with diethyl ether (4 × 60 mL). The organic extract was then stirred for 3 h with aqueous KF (8 M, 120 mL) and filtered through Celite, and the filtrate was extracted with diethyl ether (4 × 50 mL). The organic extract was washed with brine (50 mL), dried, filtered, and concentrated under reduced pressure, and the residue was analysed by GLC/MS and TLC. It was then diluted with the solvent used for TLC analysis (200 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel. Compounds **9a**−**d** were prepared by this procedure.

Methyl (2*E*,6*Z*)-2-Bromo-6-methylocta-2,6-dien-4-ynoate (9a): The crude reaction product obtained by the Pd-catalysed reaction between **15** and **14a** (20 h at room temperature) was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (60:40) as eluent, to give **9a** (4.49 g, 66%) as a pale yellow liquid. MS: *m*/*z* (%) = 244 (42) [M^+], 242 (44) [M^+], 163 (100), 131 (78), 120 (40), 103 (76), 91 (49). IR (film): $\tilde{\nu}$ = 2175 cm^{-1}, 1724, 1570, 1435, 1329, 1218, 1037, 882, 762. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.85 (s, 1 H, 3-H), 5.89−5.69 (m, 1 H, 7-H), 3.86 (s, 3 H, OCH_3), 1.89 (br s, 3 H, 6a-H), 1.92−1.85 (m, 3 H, 8-H). $C_{10}H_{11}BrO_2$ (243.10): calcd. C 49.40, H 4.56; found C 49.65, H 4.61. GLC and ^1H NMR analyses showed that **9a** was stereoisomerically pure.

Methyl (2*E*,6*E*)-2-Bromo-6-methylocta-2,6-dien-4-ynoate (9b): The crude reaction product obtained by the Pd-catalysed reaction between **15** and **14b** (22 h at room temperature) was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (60:40) as eluent, to give **9b** (3.68 g, 54%) as a pale yellow liquid. MS: *m*/*z* (%) = 244 (43) [M^+], 242 (43) [M^+], 163 (100), 131 (81), 120 (39), 103 (80), 91 (51). IR (film): $\tilde{\nu}$ = 1724 cm^{-1}, 1568, 1435, 1342, 1330, 1221, 1031, 881, 762. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.85 (s, 1 H, 3-H), 6.11 (qq, *J* = 7.3, 1.5 Hz, 1 H, 7-H), 3.86 (s, 3 H, OCH_3), 1.93 (pseudo-quint, *J* = 1.5 Hz, 3 H, 6a-H), 1.73 (dq, *J* = 7.3, 1.1 Hz, 3 H, 8-H). $C_{10}H_{11}BrO_2$ (243.10): calcd. C 49.40, H 4.56; found C 49.55, H 4.69. GLC and ^1H NMR analyses showed that **9b** was stereoisomerically pure.

Methyl (*E*)-2-Bromonon-2-en-4-ynoate (9c): The crude reaction product obtained by the Pd-catalysed reaction between **15** and **14c** (24 h at room temperature) was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (70:30) as eluent, to yield **9c** (4.60 g, 67%) as an orange liquid. MS: *m*/*z* (%) = 246 (1) [M^+], 244 (1) [M^+], 189 (9), 105 (11), 63 (16), 51 (37), 41 (100). IR (film): $\tilde{\nu}$ = 2213 cm^{-1}, 1727, 1435, 1337, 1223, 1168, 1031, 1010, 763. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.66 (t, *J* = 2.6 Hz, 1 H, 3-H), 3.85 (s, 3 H, OCH_3), 2.39 (dt, *J* = 6.8, 2.6 Hz, 2 H, 6-H), 1.65−1.39 (m, 4 H, 7-H and 8-H), 0.93 (t, *J* = 7.2 Hz, 3 H, 9-H). $C_{10}H_{13}BrO_2$ (245.11): calcd. C 49.00, H 5.34; found C 49.22, H 5.16. GLC and ^1H NMR analyses showed that **9c** was stereoisomerically pure.

Methyl (*E*)-2-Bromo-5-phenylpent-2-en-4-ynoate (9d): The crude reaction product obtained from the Pd-catalysed reaction between **15** and **14d** (18 h at room temperature) was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (60:40) as eluent, to give **9d** (5.12 g, 69%) as an orange liquid. MS: *m*/*z* (%) = 266 (21) [M^+], 264 (22) [M^+], 195 (9), 185 (100), 153 (42), 74 (13), 63 (16). IR (film): $\tilde{\nu}$ = 2194 cm^{-1}, 1723, 1490, 1435, 1336, 1224, 1049, 758, 690. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.51−7.20 (m, 5 H, $H_{arom.}$), 6.87 (s, 1 H, 3-H), 3.89 (s, 3 H, OCH_3). $C_{12}H_9BrO_2$ (265.11): calcd. C 54.37, H 3.42; found C 54.56, H 3.68. GLC and ^1H NMR analyses showed that **9d** was stereoisomerically pure.

(2*E*,6*Z*)-2-Bromo-6-methylocta-2,6-dien-4-ynoic Acid (10a): An aqueous LiOH solution (1 M, 55.5 mL, 55.5 mmol) was added to a solution of **9a** (4.50 g, 18.5 mmol) in THF (115 mL), and the resulting mixture was stirred at room temperature for 24 h. It was then diluted with water (100 mL) and extracted with diethyl ether (3 × 50 mL). The aqueous phase was cooled to 0 °C, acidified with cold 10% H_2SO_4 and extracted with diethyl ether (3 × 50 mL). The organic extract was dried and concentrated under reduced pressure to give crude **10a** (3.39 g, 80%) as a pale yellow solid. M.p. 57−60 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.40 (br s, 1 H, COOH), 6.97 (s, 1 H, 3-H), 5.90 (qq, *J* = 6.0, 1.1 Hz, 1 H, 7-H), 1.87 (br s, 3 H, 6a-H), 1.88−1.81 (m, 3 H, 8-H). This crude product was used in the next step without any further purification and characterization.

(*E*)-2-Bromonon-2-en-4-ynoic Acid (10c): Compound **9c** (4.95 g, 20.2 mmol) was converted into crude **10c** (4.66 g, 100%) by the same procedure as employed to prepare **10a**. Crude **10c** was a colourless solid. M.p. 56−60 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H, COOH), 6.79 (t, *J* = 2.7 Hz, 1 H, 3-H), 2.40 (dt,

J = 6.8, 2.7 Hz, 2 H, 6-H), 1.63−1.34 (m, 4 H, 7-H and 8-H), 0.95 (t, J = 7.0 Hz, 3 H, 9-H). This crude product was used in the next step without any further purification and characterization.

(*E*)-2-Bromo-5-phenylpent-2-en-4-ynoic (10d): Compound **9d** (7.27 g, 27.4 mmol) was converted into crude **10d** (5.02 g, 73%) by the same procedure as used to prepare **10a**. Crude **10d** was a colourless solid. M.p. 87−90 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.35 (br s, 1 H, COOH), 7.51−7.25 (m, 5 H, $H_{arom.}$), 7.02 (s, 1 H, 3-H). This crude product was used in the next step without any further purification and characterization.

General Procedures for the Iodolactonization of Carboxylic Acids 10

Synthesis of 6-Substituted 3-Bromo-5-iodo-2(2*H*)-pyranones 11 and the Corresponding 3-Bromo-5-[(*E*)-1-iodoylidene]-2(5*H*)-furanones 21: The iodolactonization of carboxylic acids **10** was performed by three different procedures (*Methods A*−*C*).

Method A: A solution of the carboxylic acid **10** (14.54 mmol) in CH_3CN (40 mL) and iodine (11.07 g, 43.6 mmol) were added sequentially to a suspension of $NaHCO_3$ (3.66 g, 43.6 mmol) in CH_3CN (60 mL), and the mixture was stirred in the dark under nitrogen at room temperature for 1 h, at which point the reaction was complete by TLC and GLC analyses. The reaction mixture was then diluted with EtOAc (200 mL) and washed with a 10% aqueous $Na_2S_2O_3$ solution (50 mL) and water (50 mL). The organic phase was dried and concentrated under reduced pressure to give a mixture of a 6-substituted 3-bromo-5-iodo-2(2*H*)-pyranone **11** and the corresponding 5-[(*E*)-1-iodoylidene]-2(5*H*)-furanone **21**. Compounds **11** and **21** were separated by MPLC on silica gel. In all cases examined, the more rapidly eluting regioisomers were compounds **21**. This procedure was employed for iodolactonization of **10a**, **10c**, and **10d**. Table 1 summarizes the **11/21** molar ratio found in the crude reaction mixtures obtained from these reactions and the isolated yields of compounds **11a**, **11c**, **11d**, **21c**, and **21d** prepared by this procedure (Entries 1, 4, and 7). It must be noted that compound **21c** underwent partial stereomutation during its isolation.

Method B: This procedure was used for iodolactonization of **10a**, **10c**, and **10d** (Entries 2, 5, and 8, Table 1). A solution of ICl (177 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) was added to a deaerated solution of a carboxylic acid **10** (1.1 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred in the dark at 0 °C for 1 h. It was then poured into an aqueous $NaHCO_3$ solution (10%, 15 mL) and extracted with EtOAc (3 × 10 mL). The organic extract was washed with a 10% aqueous $Na_2S_2O_3$ solution (10 mL) and water (15 mL), dried, and analysed by GLC, with biphenyl as an internal standard. Compounds **11a**, **11d**, and **21d** were isolated by chromatographic purification of the crude reaction mixtures derived from **10a** and **10d**, respectively, according to this procedure (Entries 2 and 8, Table 1). However, no attempt was made to isolate the iodolactonization products derived from **10c** (Entry 5, Table 1).

Method C: *N*-Iodosuccinimide (246 mg, 1.2 mmol) was added to stirred mixture of a carboxylic acid **10** (1.1 mmol) and $KHCO_3$ (108 mg, 1.1 mmol) in CH_3CN (5 mL), and the mixture was stirred in the dark at room temperature for 1 h. It was then poured into an aqueous $Na_2S_2O_3$ solution (10%, 15 mL) and extracted with EtOAc (3 × 8 mL). The organic extract was washed with water (5 mL), dried, and analysed by GLC, with biphenyl as an internal standard. This method for used for iodolactonization of **10a**, **10c** and **10d** (Entries 3, 6, 9, Table 1). However, no attempt was made to isolate the products of iodolactonization of **10c** and **10d**.

3-Bromo-6-[(*Z*)-2-butenyl]-5-iodo-2(2*H*)-pyranone (11a): GLC analysis of the crude reaction mixture obtained by iodolactonization of **10a** by *Method A* showed the presence of two isomeric compounds in a 97.5:2.5 molar ratio (Entry 1, Table 1). The major product was subsequently identified as **11a**. The structure of 5-[(5*E*,7*Z*)-1-iodo-2-methylbutylidene]-2(5*H*)-furanone (**21a**), on the other hand, was tentatively assigned to the minor product. The mixture was purified by MPLC on silica gel, with toluene as eluent. Concentration of the intermediate chromatographic fractions allowed pure **11a** (3.87 g, 75%) to be isolated as a colourless solid. M.p. 102−104 °C. MS: *m*/*z* (%) = 356 (97) [M^+], 354 (100) [M^+], 201 (20), 199 (21), 173 (33), 171 (34), 91 (74). IR (KBr): $\tilde{\nu}$ = 1718 cm^{-1}, 1594, 1530, 1196, 1009, 950, 909, 742, 712. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (s, 1 H, 4-H), 5.70 (qq, J = 7.0, 1.5 Hz, 1 H, 6b-H), 1.93 (pseudo-quint, J = 1.5 Hz, 3 H, 6a′-H), 1.64 (dq, J = 7.0, 1.5 Hz, 3 H, 6c-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.41, 157.98, 151.84, 130.53, 129.69, 110.56, 67.29, 20.84, 15.72. $C_9H_8BrIO_2$ (354.97): calcd. C 30.45, H 2.27; found C 30.78, H 2.45. The MS spectrum of **21a** was as follows. MS: *m*/*z* (%) = 356 (100) [M^+], 354 (100) [M^+], 201 (26), 199 (29), 173 (53), 171 (49), 92 (84). Purification of the crude reaction mixtures obtained by iodolactonization of **10a** by *Methods B* and *C* provided **11a** in 52 and 38% isolated yields, respectively (Entries 2 and 3, Table 1). GLC analysis showed that the crude reaction mixture obtained in Entry 3 contained stereoisomerically pure **21a** and **11a** in a 47.0:53.0 molar ratio. Nevertheless, **21a** underwent significant stereomutation during its isolation by MPLC on silica gel, with a mixture of toluene and petroleum ether (50:50) as eluent. The IR spectrum of the stereoisomeric mixture derived from **21a** was as follows. IR (film): $\tilde{\nu}$ = 1777 cm^{-1}, 1623, 1552, 1246, 1110, 969, 848, 749, 728. $C_9H_8BrIO_2$ (354.97): calcd. C 30.45, H 2.27; found C 30.65, H 2.38.

3-Bromo-6-butyl-5-iodo-2(2*H*)-pyranone (11c) and 3-Bromo-5-[(*E*)-1-iodopentylidene]-2(5*H*)-furanone (21c): GLC analysis of the crude reaction mixture obtained by iodolactonization of **10c** by *Method A* showed the presence of two compounds in a 40.0:60.0 molar ratio (Entry 4, Table 1). This mixture was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (70:30) as eluent. Concentration of the first eluted chromatographic fractions allowed **21c** (2.59 g, 50%) to be isolated as an orange liquid. MS: *m*/*z* (%) = 358 (1) [M^+], 356 (3) [M^+], 285 (2), 173 (3), 119 (3), 43 (37), 41 (100). IR (film): $\tilde{\nu}$ = 1782 cm^{-1}, 1556, 1464, 1113, 1072, 980, 906, 870, 749. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (s, 1 H, 4-H), 2.78 (t, J = 7.3 Hz, 2 H, 7-H), 1.55 (m, 2 H, 8-H), 1.34 (sext, J = 7.4 Hz, 2 H, 9-H), 0.93 (t, J = 7.4 Hz, 3 H, 10-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.33, 148.27, 142.91, 115.75, 96.46, 37.60, 31.26, 21.36, 13.76. NMR analysis showed that **21c** was contaminated by ca. 30% of the corresponding (*Z*) stereoisomer. The NMR parameters of the (*Z*) stereoisomer were as follows. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (s, 1 H, 4-H), 2.67 (t, J = 7.3 Hz, 2 H, 7-H), 1.59 (m, 2 H, 8-H), 1.35 (m, 2 H, 9-H), 0.93 (m, 3 H, 10-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.48, 150.05, 135.29, 114.42, 94.82, 37.90, 32.05, 21.58, 13.78. A NOESY experiment showed the presence of a cross-peak between the resonances of the 4-H and 7-H protons and those of the 4-H and 8-H protons. These cross-peaks were not observed for **21c**. $C_9H_{10}BrIO_2$ (356.98): calcd. C 30.28, H 2.82; found C 30.35, H 3.04. On the other hand, concentration of the last eluted chromatographic fractions allowed pure **11c** (1.56 g, 30%) to be isolated as an orange solid. M.p. 42−44 °C. MS: *m*/*z* (%) = 358(3) [M^+], 356 (2) [M^+], 189 (13), 187 (18), 55 (19), 53 (38), 41 (100). IR (KBr): $\tilde{\nu}$ = 1719 cm^{-1}, 1599, 1527, 1294, 1087, 1016, 967, 802, 743. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (s, 1 H, 4-H), 2.71 (t, J = 7.7 Hz, 2 H, 6a-H), 1.66 (m, 2 H, 6b-

H), 1.40 (sext, J = 7.4 Hz, 2 H, 6c-H), 0.95 (t, J = 7.4 Hz, 3 H, 6d-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.28, 158.14, 151.99, 109.47, 66.41, 35.98, 29.04, 22.17, 13.70. $C_9H_{10}BrIO_2$ (356.98): calcd. C 30.28, H 2.82; found C 30.45, H 2.99.

3-Bromo-5-iodo-6-phenyl-2(2*H*)-pyranone (11d) and 3-Bromo-5-[(*E*)-1-iodobenzylidene]-2(5*H*)-furanone (21d): GLC analysis of the crude reaction mixture obtained by iodolactonization of **11d** by *Method A* (Entry 7, Table 1) showed the presence of two compounds in a 49.0:51.0 molar ratio. This mixture was purified by MPLC on silica gel, with toluene as eluent. Concentration of the first eluted chromatographic fractions allowed **21d** (2.36 g, 43%) to be isolated as an orange solid. M.p. 108−111 °C. MS: *m*/*z* (%) = 378 (64) [M$^+$], 376 (66) [M$^+$], 251 (85), 249 (87), 196 (98), 193 (100), 142 (40), 114 (57), 89 (91). IR (KBr): $\tilde{\nu}$ = 1784 cm^{-1}, 1772, 1441, 1108, 984, 942, 866, 762, 722. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00 (s, 1 H, 4-H), 7.66−7.34 (m, 5 H, $H_{arom.}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.70, 147.68, 144.39, 136.84, 130.79, 130.04, 128.33, 115.85, 89.65. $C_{11}H_6BrO_2$ (376.97): calcd. C 35.04, H 1.60; found C 35.39, H 1.97. Concentration of the last eluted chromatographic fractions allowed **11d** (2.19 g, 40%) to be isolated as a pale yellow solid. M.p. 117−119 °C. MS: *m*/*z* (%) = 378 (49) [M$^+$], 376 (51) [M$^+$], 350 (27), 348 (28), 241 (18), 195 (40), 193 (41), 105 (100), 77 (95). IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1601, 1198, 1050, 981, 906, 769, 744, 706. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02 (s, 1 H, 4-H), 7.76−7.71 (m, 2 H, $H_{arom.}$), 7.51−7.45 (m, 3 H, $H_{arom.}$). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.12, 157.50, 153.14, 132.49, 131.07, 129.16, 128.28, 110.70, 65.27. $C_{11}H_6BrO_2$ (376.97): calcd. C 35.04, H 1.60; found C 35.38, H 1.87.

Methyl (2*Z*,6*Z*)-2,6-Dimethylocta-2,6-dien-4-ynoate (22a): A flame-dried reaction vessel was charged with $PdCl_2[P(o\text{-tolyl})_3]_2$ (524 mg, 0.7 mmol) and CuI (253 mg, 1.3 mmol) and flushed with argon. A deaerated solution of **9a** (3.23 g, 13.3 mmol) in dry NMP (60 mL) and deaerated tetramethyltin (7.13 g, 39.8 mmol) were then added sequentially, and the mixture was stirred at 70 °C for 2.5 h. After this period of time, the reaction was complete. The mixture was cooled to room temperature, poured into a saturated aqueous NH_4Cl solution (200 mL) and extracted with EtOAc (4 × 50 mL). The organic extract was washed with brine (2 × 30 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of petroleum ether and toluene (70:30) as eluent, to give chemically and stereoisomerically pure **22a** (1.75 g, 74%) as a pale yellow liquid. MS: *m*/*z* (%) =178 (79) [M$^+$], 146 (45), 135 (48), 117 (54), 107 (58), 91 (100), 77 (55). IR (KBr): $\tilde{\nu}$ = 2179 cm^{-1}, 1709, 1605, 1434, 1343, 1224, 1134, 1069, 771. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.16 (q, J = 1.8 Hz, 1 H, 3-H), 5.86−5.75 (m, 1 H, 7-H), 3.78 (s, 3 H, OCH_3), 2.02 (d, J = 1.8 Hz, 3 H, 2′-H), 1.91−1.84 (m, 6 H, 6′-H and 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.66, 136.23, 134.10, 118.74, 117.93, 97.10, 90.56, 51.49, 22.61, 19.96, 16.27. $C_{11}H_{14}O_2$ (178.23): calcd. C 74.13, H 7.92; found C 74.15, H 7.98.

Methyl (2*Z*,6*E*)-2,6-Dimethylocta-2,6-dien-4-ynoate (22b): Compound **9b** (2.70 g, 11.1 mmol) was converted into pure **22b** (1.66 g, 84%) by the same procedure as used to prepare **22a** from **9a**. Compound **22b**, which was a pale yellow liquid, had the following spectral properties. MS: *m*/*z* (%) =178 (68) [M$^+$], 146 (39), 135 (44), 117 (51), 107 (54), 91 (100), 77 (57). IR (KBr): $\tilde{\nu}$ = 2184 cm^{-1}, 1709, 1603, 1434, 1250, 1224, 1134, 836, 770. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.04 (q, J = 1.4 Hz, 1 H, 3-H), 5.98 (qq, J = 7.0, 1.4 Hz, 1 H, 7-H), 3.74 (s, 3 H, OCH_3), 1.95 (d, J = 1.4 Hz, 3 H, 2′-H), 1.78 (pseudo-quint, J = 1.2 Hz, 3 H, 6′-H), 1.68 (dq, J = 7.0, 1.4 Hz, 3 H, 8-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.67, 136.08, 134.28, 118.71, 118.33, 101.21, 83.63, 51.46, 19.85, 16.57, 14.22. $C_{11}H_{14}O_2$ (178.23): calcd. C 74.13, H 7.92; found C 74.27, H 8.06.

(2*Z*,6*Z*)-2,6-Dimethylocta-2,6-dien-4-ynoic Acid (16a): By the same procedure as was used to prepare **10a** from **9a**, saponification of **22a** (1.54 g, 8.6 mmol) followed by acidification gave crude **16a** (1.41 g, 100%) as a pale yellow solid. M.p. 36 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.61 (br s, 1 H, COOH), 6.25 (q, J = 1.5 Hz, 1 H, 3-H), 5.87−5.75 (m, 1 H, 7-H), 2.02 (d, J = 1.5 Hz, 3 H, 2′-H), 1.85 (br s, 3 H, 6′-H), 1.85−1.78 (m, 3 H, 8-H). This crude product was used in the next step without any further purification and characterization.

(2*Z*,6*E*)-2,6-Dimethylocta-2,6-dien-4-ynoic Acid (16b): By the same procedure as was used to prepare **10a** from **9b**, saponification of **22b** (1.48 g, 8.3 mmol) followed by acidification gave crude **16b** (1.25 g, 92%) as a pale yellow solid. M.p. 70 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.73 (br s, 1 H, COOH), 6.22 (q, J = 1.4 Hz, 1 H, 3-H), 6.04 (qq, J = 7.0, 1.4 Hz, 1 H, 7-H), 2.03 (d, J = 1.4 Hz, 3 H, 2′-H), 1.82 (pseudo-quint, J = 1.4 Hz, 3 H, 6′-H), 1.75−1.70 (m, 3 H, 8-H). This crude product was used in the next step without any further purification and characterization.

6-[(*Z*)-2-Butenyl]-5-iodo-3-methyl-2(2*H*)-pyranone (17a) and 5-[(5*Z*/*E*,7*Z*)-1-Iodo-2-methylbutylidene]-3-methyl-2(5*H*)-furanone [(5*Z*/*E*)-23a]: GLC analysis of the crude reaction mixture obtained by iodolactonization of **16a** (1.05 g, 6.4 mmol) by the procedure used to prepare **11a** and **21a** from **10a** (*Method A*) showed the presence of two compounds in a 92.0:8.0 molar ratio (Entry 1, Table 2). During the purification of this mixture by MPLC on silica gel, with toluene as eluent, the minor component of this mixture underwent partial isomerization to give a mixture of two compounds in a ca. 70:30 molar ratio. The structures (5*E*)-**23a** and (5*Z*)-**23a** were tentatively assigned to these compounds. Concentration of the first eluted chromatographic fractions allowed this mixture of stereoisomers (0.13 g, 7%) to be obtained as a red solid. M.p. 30 °C. The MS and ^{1}H NMR parameters of the minor component of this mixture were as follows. MS: *m*/*z* (%) = 290 (100) [M$^+$], 262 (79), 247 (15), 163 (21), 135 (30), 107 (25), 91 (62). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 (q, J = 1.4 Hz, 1 H, 4-H), 5.50 (dq, J = 7.0, 1.4 Hz, 1 H, 8-H), 1.98 (d, J = 1.4 Hz, 3 H, 3a-H), 1.84 (pseudo-quint, J = 1.4 Hz, 3 H, 7a-H), 1.71 (dq, J = 7.0, 1.4 Hz, 3 H, 9-H). The MS and ^{1}H NMR parameters of the major component of this mixture were as follows. MS: *m*/*z* (%) = 290 (100) [M$^+$], 262 (72), 247 (13), 163 (19), 135 (29), 107 (25), 91 (62). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.95 (q, J = 1.4 Hz, 1 H, 4-H), 5.57 (dq, J = 7.0, 1.4 Hz, 1 H, 8-H), 1.90 (d, J = 1.4 Hz, 3 H, 3a-H), 1.86 (pseudo-quint, J = 1.4 Hz, 3 H, 7a-H), 1.47 (dq, J = 7.0, 1.4 Hz, 3 H, 9-H). The IR parameters of the stereoisomeric mixture of (5*E*)-**23a** and (5*Z*)-**23a** were as follows. IR (film): $\tilde{\nu}$ = 1769 cm^{-1}, 1629, 1447, 1376, 1048, 1001, 943, 850, 753. $C_{10}H_{11}IO_2$ (290.10): calcd. C 41.40, H 3.82; found C 41.65, H 3.95. Concentration of the last eluted chromatographic fractions allowed **17a** (1.44 g, 78%) to be isolated as a colourless solid. M.p. 41−43 °C. MS: *m*/*z* (%) = 290 (100) [M$^+$], 262 (32), 247 (17), 179 (11), 135 (20), 107 (35), 91 (31). IR (KBr): $\tilde{\nu}$ = 1709 cm^{-1}, 1614, 1559, 1165, 1056, 971, 899, 833, 752. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33 (q, J = 1.5 Hz, 1 H, 4-H), 5.64 (qq, J = 7.0, 1.5 Hz, 1 H, 6b-H), 2.08 (d, J = 1.5 Hz, 3 H, 3a-H), 1.91 (pseudo-quint, J = 1.5 Hz, 3 H, 6a′-H), 1.61 (dq, J = 7.0, 1.5 Hz, 3 H, 6c-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.54, 160.18, 147.24, 130.40, 129.45, 125.19, 68.64, 20.92, 16.24, 15.48. $C_{10}H_{11}IO_2$ (290.10): calcd. C 41.40, H 3.82; found C 41.59, H 4.01.

6-[(*E*)-2-Butenyl]-5-iodo-3-methyl-2(2*H*)-pyranone (17b) and 5-[(5*E*,7*E*)-1-Iodo-2-methylbutylidene]-3-methyl-2(5*H*)-furanone

(23b): GLC analysis of the crude reaction mixture obtained by iodolactonization of **16b** (1.14 g, 6.9 mmol) by *Method A* (Entry 3, Table 2) showed the presence of two compounds in a ca. 80:20 molar ratio. During the purification of this mixture by MPLC on silica gel, with toluene as eluent, the minor component of this mixture underwent partial stereomutation to give a complex mixture of compounds. We tentatively assigned the structure **23b** to the major component of this stereoisomeric mixture. Concentration of the first eluted chromatographic fractions allowed this mixture of stereoisomers (0.34 g, 17%) to be obtained as a yellow liquid. IR (film): $\tilde{\nu}$ = 1768 cm^{-1}, 1627, 1611, 1438, 1046, 992, 922, 795, 753. The MS and ^1H NMR parameters of the major component of this mixture were as follows. MS: *m*/*z* (%) = 290 (100) [M^+], 262 (71), 163 (19), 135 (27), 107 (24), 91 (42), 67 (39). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20 (q, *J* = 1.4 Hz, 1 H, 4-H), 5.67 (qq, *J* = 7.0, 1.4 Hz, 1 H, 5c-H), 1.95 (d, *J* = 1.4 Hz, 3 H, 3a-H), 1.87 (pseudo-quint, *J* = 1.4 Hz, 3 H, 7a-H), 1.76 (dq, *J* = 7.0, 1.2 Hz, 3 H, 9-H). $C_{10}H_{11}IO_2$ (290.10): calcd. C 41.40, H 3.82; found C 41.60, H 4.02. Concentration of the last eluted chromatographic fractions allowed **17b** (1.19 g, 59%) to be isolated as a pale yellow liquid. MS: *m*/*z* (%) = 290 (100) [M^+], 262 (31), 135 (25), 107 (49), 91 (44). 83 (27), 55 (55) − IR (film): $\tilde{\nu}$ = 1720 cm^{-1}, 1613, 1551, 1444, 1218, 1169, 1049, 969, 754. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.37 (q, *J* = 1.3 Hz, 1 H, 4-H), 6.04 (qq, *J* = 6.9, 1.5 Hz, 1 H, 6b-H), 2.07 (d, *J* = 1.0 Hz, 3 H, 3a-H), 1.91 (pseudo-quint, *J* = 1.0 Hz, 3 H, 6a′-H), 1.79 (dq, *J* = 6.9, 1.0 Hz, 3 H, 6c-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.28, 161.53, 148.52, 133.14, 130.02, 124.55, 65.69, 16.10, 14.22, 13.69. $C_{10}H_{11}IO_2$ (290.10): calcd. C 41.40, H 3.82; found C 41.62, H 4.03.

3-Bromo-6-butyl-5-(4-methoxyphenyl)-2(2*H*)-pyranone (13c): A flame-dried reaction vessel, flushed with argon, was charged with $PdCl_2(PhCN)_2$ (37.6 mg, 0.1 mmol), $AsPh_3$ (60.0 mg, 0.2 mmol), CuI (37.3 mg, 0.2 mmol), compound **11c** (0.70 g, 2.0 mmol), and deaerated NMP (5 mL). A deaerated solution of **24** (0.86 g, 2.2 mmol) in NMP (15 mL) was then added, and the mixture was stirred at 45 °C for 23 h. It was then cooled to 20 °C, poured into a saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (4 × 30 mL). The organic extract was stirred for 4 h at 20 °C with an aqueous KF solution (8 M, 200 mL) and the reaction mixture was filtered through Celite. The filtrate was extracted with EtOAc (4 × 30 mL) and the organic extract was dried, filtered, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with benzene as eluent, to give **13c** (0.59 g, 89%) as a pale yellow liquid. MS, *m*/*z* (%) = 338 (41) [M^+], 336 (49) [M^+], 280 (65), 278 (64), 115 (44), 57 (79), 41 (100). IR (film): $\tilde{\nu}$ = 1737 cm^{-1}, 1628, 1513, 1281, 1249, 1179, 1035, 967, 835. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.66 (s, 1 H, 4-H), 7.17 (d, *J* = 8.8 Hz, 2 H, $H_{arom.}$), 6.95 (d, *J* = 8.8 Hz, 2 H, $H_{arom.}$), 3.85 (s, 3 H, OCH_3), 2.48 (t, *J* = 7.7 Hz, 2 H, 6a-H), 1.72−1.57 (m, 2 H, 6b-H), 1.28 (sext, *J* = 7.3 Hz, 2 H, 6c-H), 0.82 (t, *J* = 7.3 Hz, 3 H, 6d-H). $C_{16}H_{17}BrO_3$ (337.21): calcd. C 56.99, H 5.08; found C 57.12, H 5.16.

6-Butyl-5-(4-methoxyphenyl)-3-methyl-2(2*H*)-pyranone (8c): Compound **13c** (0.50 g, 1.5 mmol) was treated with tetramethyltin (0.79 g, 4.4 mmol) in NMP (20 mL) in the presence of $PdCl_2[P(o\text{-tolyl})_3]_2$ (58.8 mg, 0.07 mmol) and CuI (28.1 mg, 0.15 mmol) at 80 °C for 22 h, by the same procedure as employed to prepare **22a** from **9a**. After the usual workup, the crude reaction product was purified by MPLC on silica gel, with benzene as eluent, to give **8c** (0.38 g, 94%) as a pale yellow liquid. MS, *m*/*z* (%) = 272 (52) [M^+], 230 (7), 215 (100), 201 (32), 188 (13), 159 (38), 115 (17). IR (film): $\tilde{\nu}$ = 1719 cm^{-1}, 1514, 1464, 1287, 1248, 1176, 981, 836, 763. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.9 Hz, 2 H, $H_{arom.}$), 7.10 (q, *J* = 1.1 Hz, 1 H, 4-H), 6.93 (d, *J* = 8.9 Hz, 2 H, $H_{arom.}$), 3.84 (s, 3 H, OCH_3), 2.47 (t, *J* = 7.7 Hz, 2 H, 6a-H), 2.10 (d, *J* = 1.1 Hz, 3 H, 3a-H), 1.72−1.57 (m, 2 H, 6b-H), 1.27 (sext, *J* = 7.4 Hz, 2 H, 6c-H), 0.84 (t, *J* = 7.4 Hz, 3 H, 6d-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 163.75, 159.76, 158.95, 143.30, 129.82, 128.32, 121.97, 117.39, 113.94, 55.20, 30.74, 29.80, 22.21, 16.64, 16.32 − $C_{17}H_{20}O_3$ (272.34): calcd. C 74.97, H 7.40; found C 75.01, H 7.38.

3-Bromo-5-(1-hexynyl)-6-phenyl-2(2*H*)-pyranone (13d): A flame-dried reaction vessel, flushed with argon, was charged with $PdCl_2(PPh_3)_2$ (50.0 mg, 0.07 mmol), **11d** (0.90 g, 2.84 mmol) and THF (10 mL). A deaerated solution of **14c** (1.10 g, 2.9 mmol) in THF (10 mL) was then added, and the mixture was stirred for 22 h at room temperature and for 44 h at 45 °C. After this period of time, GLC analysis showed that **11d** had reacted completely. The reaction mixture was then cooled to 20 °C, poured into a saturated aqueous NH_4Cl solution (100 mL), and extracted with diethyl ether (4 × 50 mL). The organic extract was then stirred for 3 h with an aqueous KF solution (8 M, 80 mL) and filtered through Celite, and the filtrate was extracted with diethyl ether (4 × 50 mL). The organic extract was washed with brine (50 mL), dried, filtered, and concentrated under reduced pressure, and the residue was purified by MPLC on silica gel, with a mixture of CH_2Cl_2 and petroleum ether (50:50) as eluent, to give **13d** (0.58 g,74%) as a yellow solid. M.p. 68−70 °C. MS, *m*/*z* (%) = 332 (33) [M^+], 330 (34) [M^+], 290 (25), 288 (24), 152 (49), 105 (84), 77 (100). IR (KBr): $\tilde{\nu}$ = 2229 cm^{-1}, 1736, 1607, 1442, 1325, 1180, 920, 907, 688. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.16−8.11 (m, 2 H, $H_{arom.}$), 7.76 (s, 1 H, 4-H), 7.49−7.38 (m, 3 H, $H_{arom.}$), 2.41 (t, *J* = 6.7 Hz, 2 H, 5c-H), 1.69−1.25 (m, 4 H, 5d-H and 5e-H), 0.94 (t, *J* = 7.0 Hz, 3 H, 5f-H). $C_{17}H_{15}BrO_2$ (331.21): calcd. C 61.65, H 4.56; found C 61.78, H 4.76.

5-(1-Hexynyl)-3-methyl-6-phenyl-2(2*H*)-pyranone (8d): Compound **13d** (0.46 g, 1.4 mmol) was treated with tetramethyltin (0.74 g, 4.3 mmol) in NMP (20 mL) in the presence of $PdCl_2[P(o\text{-tolyl})_3]_2$ (54 mg, 0.07 mmol) and CuI (26 mg, 0.14 mmol) at 80 °C for 20 h, by the same procedure as used to prepare **22a** from **9a**. After the usual workup, the crude reaction product was purified by MPLC on silica gel, with benzene as eluent, to give **8d** (0.30 g, 83%) as a yellow solid. M.p. 50−52 °C. MS: *m*/*z* (%) = 266 (100) [M^+], 224 (62), 223 (63), 165 (36), 152 (28), 105 (64), 77 (66). IR (KBr): $\tilde{\nu}$ = 1723 cm^{-1}, 1546, 1180, 1056, 1000, 914, 775, 754, 695. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.15−8.11 (m, 2 H, $H_{arom.}$), 7.44−7.37 (m, 3 H, $H_{arom.}$), 7.18 (q, *J* = 1.0 Hz, 1 H, 4-H), 2.39 (t, *J* = 7.0 Hz, 2 H, 5c-H), 2.11 (d, *J* = 1.0 Hz, 3 H, 3a-H), 1.63−1.34 (m, 4 H, 5d-H and 5e-H), 0.93 (t, *J* = 7.0 Hz, 3 H, 5f-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.89, 159.24, 144.08, 131.62, 130.18, 127.97, 127.58, 123.11, 100.54, 95.85, 75.55, 30.30, 21.96, 19.25, 16.20, 13.52. $C_{18}H_{18}O_2$ (266.34): calcd. C 45.10, H 6.81; found C 45.24, H 6.89.

General Procedure for the Synthesis of 6-Substituted 3-Bromo-2(2*H*)-pyranones 12: A mixture of zinc dust (Aldrich, 325 mesh, 1.25 g, 19.1 mmol) and THF (30 mL) containing 1,2-dibromoethane (35 μL, 0.4 mmol) was stirred under argon at 65 °C for 1 min and was then allowed to cool to 20 °C. Chlorotrimethylsilane (44 μL, 0.34 mmol) was added, and after this had stirred at 20 °C for 20 min, a solution of a compound **11** (3.81 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at 20 °C until GLC analysis of a sample of the reaction mixture, hydrolysed with diluted H_2SO_4, showed that compound **11** had been completely consumed (2.5−13.5 h). The reaction mixture was then allowed to

settle. The clear solution of the obtained organozinc compound was transferred by syringe to a new reaction flask, hydrolysed at 0 °C with 10% H_2SO_4 and extracted with diethyl ether (4 × 15 mL). The dried organic extract was concentrated under reduced pressure and the residue, which was analysed by GLC or ^{1}H NMR spectroscopy, was purified by MPLC on silica gel. This procedure was used to prepare a stereoisomeric mixture of **12a** and **12b** as well as compound **12c**.

3-Bromo-6-[(*Z*/*E*)-2-butenyl]-2(2*H*)-pyranone (12a+b): ^{1}H NMR analysis of the crude reaction product obtained from **11a** by the general procedure described above showed that it consisted of **10a** and a mixture of two compounds, which were subsequently identified as **12a** and **12b**. Compound **10a** was the major component. Purification of this crude reaction product by MPLC on silica gel, with benzene as eluent, allowed a mixture of **12a** and **12b** (0.31 g, 36%) to be isolated as a colourless solid. GLC analysis showed that **12b** and **12a** were in a ca. 83:17 molar ratio. The configurations of these compounds were established on the basis of those of compounds **7b** and **7a**, subsequently obtained through a stereospecific Pd-catalysed reaction between a stereoisomeric mixture of **12a** and **12b** and tetramethyltin. M.p. 75−90 °C. IR (film): $\tilde{\nu}$ = 1714 cm^{-1}, 1637, 1603, 1524, 1341, 1112, 961, 809, 751. The MS and ^{1}H NMR parameters of **12a** were as follows. MS: *m*/*z* (%) = 230 (64) [M$^+$], 228 (65) [M$^+$], 202 (35), 200 (36), 121 (38), 93 (100), 77 (56). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.3 Hz, 1 H, 4-H), 6.05 (d, *J* = 7.3 Hz, 1 H, 5-H), 5.99−5.86 (m, 1 H, 6b-H), 1.99−1.81 (m, 6 H, 6a′-H and 6c-H). The MS and ^{1}H NMR parameters of **12b** were as follows. MS: *m*/*z* (%) =230 (68) [M$^+$], 228 (70) [M$^+$], 202 (35), 200 (36), 121 (36), 93 (100), 77 (50). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.3 Hz, 1 H, 4-H), 6.71 (q, *J* = 6.7 Hz, 1 H, 6b-H), 6.05 (d, *J* = 7.3 Hz, 1 H, 5-H), 1.99−1.81 (m, 6 H, 6a′-H and 6c-H). $C_9H_9BrO_2$ (229.07): calcd. C 47.19, H 3.96; found C 47.38, H 4.05.

3-Bromo-6-butyl-2(2*H*)-pyranone (12c): GLC analysis of the crude reaction product obtained from **11c** according to the general procedure described above showed the presence of a major product together with very small amounts of unidentified compounds. Purification of this crude product by MPLC on silica gel, with benzene as eluent, allowed pure **12c** (0.65 g, 74%) to be isolated as a colourless solid. M.p. 30 °C. MS: *m*/*z* (%) = 232 (77) [M$^+$], 230 (80), 187 (100), 176 (79), 174 (82), 132 (71), 123 (78). IR (film): $\tilde{\nu}$ = 1729 cm^{-1}, 1635, 1542, 1340, 1090, 985, 957, 922, 753. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 6.9 Hz, 1 H, 4-H), 5.91 (d, *J* = 6.9 Hz, 1 H, 5-H), 2.48 (t, *J* = 7.5 Hz, 2 H, 6a-H), 1.64 (quint, *J* = 7.5 Hz, 2 H, 6b-H), 1.36 (sext, *J* = 7.3 Hz, 2 H, 6c-H), 0.93 (t, *J* = 7.3 Hz, 3 H, 6d-H). $C_9H_{11}BrO_2$ (231.09): calcd. C 46.78, H 4.80; found C 47.01, H 5.01.

Palladium-Catalysed Triethylammonium Formate Reduction of 11a: Formic acid (99%, 80 μL, 2.1 mmol) was added to a mixture of **11a** (0.50 g, 1.4 mmol), triethylamine (0.59 mL, 4.2 mmol), $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) and triphenylphosphane (14.7 mg, 0.05 mmol) in dry DMF (10 mL), and the mixture was stirred at 60 °C for 5 h under argon. It was then cooled to 20 °C, diluted with water (60 mL), and extracted with diethyl ether (4 × 20 mL). GLC/MS analysis of the organic extract, which was washed with brine (30 mL) and dried, showed the presence of three major compounds in a ca. 25:20:55 molar ratio. The first two of these, on the basis of their MS spectra, presumably corresponded to 6-[(*Z*)-2-butenyl]-2(2*H*)-pyranone (**27**) and 6-[(*Z*)-2-butenyl]-5-iodo-2(2*H*)-pyranone (**28**), respectively. The last compound was subsequently identified as **12a**. However, all these compounds were contaminated with minor amounts of the corresponding stereoisomers. In particular, crude **12a** proved to be contaminated with ca. 7% of **12b**. The dried organic extract was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, with benzene as eluent, to give a mixture of **12a** and **12b** (0.11 g, 34%) as a colourless solid. M.p. 75−90 °C. GLC analysis showed that **12a** and **12b** were in a 38:62 molar ratio. The spectral properties of this stereoisomeric mixture were in agreement with those of the mixture of **12a** and **12b** prepared by insertion of activated zinc metal into the carbon−iodine bond of **11a**, followed by acidic hydrolysis.

6-Butyl-3-methyl-2(2*H*)-pyranone (7c): Compound **12c** (0.85 g, 3.7 mmol) was treated with tetramethyltin (1.97 g, 11.0 mmol) in the presence of $PdCl_2[P(o\text{-tolyl})_3]_2$ (0.144 g, 0.2 mmol) and CuI (70 mg, 0.4 mmol) in NMP (10 mL) at 80 °C for 22 h, by the same procedure as employed to prepare **22a** from **9a**. After the usual workup, the crude reaction product was purified by MPLC on silica gel, with benzene as eluent, to give **7c** (0.56 g, 91%) as a pale yellow liquid. MS: *m*/*z* (%) = 166 (50) [M$^+$], 138 (30), 124 (12), 109 (22), 95 (100), 82 (20), 53 (41). IR (film): $\tilde{\nu}$ = 1719 cm^{-1}, 1645, 1585, 1433, 1114, 1090, 1044, 815, 762. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.06 (dq, *J* = 6.6, 1.6 Hz, 1 H, 4-H), 5.90 (d, *J* = 6.6 Hz, 1 H, 5-H), 2.47 (t, *J* = 7.5 Hz, 3 H, 6a-H), 2.07 (s, 3 H, 3a-H), 1.72−1.56 (m, 2 H, 6b-H), 1.46−1.26 (m, 2 H, 6c-H), 0.93 (t, *J* = 7.2 Hz, 3 H, 6d-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.24, 163.61, 139.72, 122.29, 102.62, 33.18, 29.06, 22.08, 16.56, 13.73. $C_{10}H_{14}O_2$ (166.22): calcd. C 72.26, H 8.49; found C 72.45, H 8.61.

Palladium-Catalysed Methylation of 3-Bromo-6-[(*E*/*Z*)-2-butenyl]-2(2*H*)-pyranone (12a+b): A mixture of **12a** and **12b** (0.50 g, 2.2 mmol; **12a**/**12b** = 46:54) was treated with tetramethyltin (1.17 g, 6.6 mmol) in the presence of $PdCl_2[P(o\text{-tolyl})_3]_2$ (86 mg, 0.1 mmol) and CuI (41 mg, 0.22 mmol) in NMP (10 mL) at 80 °C for 20 h. GLC analysis of the crude reaction product obtained after the usual workup showed the presence of two compounds in a ca. 46:54 molar ratio. These were subsequently identified as gibepyrone A (**7b**) and fusalanipyrone (**7a**), respectively. This crude product was purified by MPLC analysis on silica gel, with a mixture of petroleum ether and diethyl ether (75:25) as eluent. Concentration of the first eluted chromatographic fractions allowed 85% stereoisomerically pure **7a** (0.17 g, 48%) to be isolated as a colourless liquid. IR (film): $\tilde{\nu}$ = 1713 cm^{-1}, 1643, 1557, 1381, 1122, 1101, 1040, 831, 759. The MS and ^{1}H NMR parameters of stereoisomerically pure **7a** were as follows. MS: *m*/*z* (%) = 164 (89) [M$^+$], 136 (61), 121 (100), 109 (21), 93 (31), 91 (23), 53 (52). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.13 (dq, *J* = 6.9, 1.2 Hz, 1 H, 4-H), 6.03 (d, *J* = 6.9 Hz, 1 H, 5-H), 5.79 (qq, *J* = 7.1, 1.4 Hz, 1 H, 6b-H), 2.10 (d, *J* = 1.2 Hz, 3 H, 3a-H), 1.95 (m, 3 H, 6a′-H), 1.93 (m, 3 H, 6c-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.54, 159.87, 139.55, 130.26, 127.63, 123.21, 104.36, 21.50, 16.50, 15.70. The ^{1}H NMR parameters of **7a**, except for the chemical shift of the olefinic proton 6b-H were in agreement with those reported for the natural product.[3a] In fact, a chemical shift of δ = 6.62 was reported for the aberrant proton,[3a] whereas our assignment indicated that it should be δ = 5.79. Concentration of the last eluted chromatographic fractions allowed 85% stereoisomerically pure **7b** (0.19 g, 52%) to be obtained as a colourless liquid. IR (film): $\tilde{\nu}$ = 1712 cm^{-1}, 1644, 1561, 1378, 1128, 1108, 1052, 820, 759. The MS and ^{1}H NMR parameters of stereoisomerically pure **7b** were as follows. MS: *m*/*z* (%) = 164 (80) [M$^+$], 136 (56), 121 (100), 109 (21), 93 (29), 91 (23), 53 (49). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.11 (dd, *J* = 7.0, 1.1 Hz, 1 H, 4-H), 6.61 (q, *J* = 7.1 Hz, 1 H, 6b-H), 6.04 (d, *J* = 7.0 Hz, 1 H, 5-H), 2.09 (d, *J* = 1.1 Hz, 3 H, 3a-H), 1.85 (s, 3 H, 6a′-H), 1.82 (d, *J* = 7.1 Hz, 3 H, 6c-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.49, 159.89, 140.05, 128.22, 126.84, 122.99, 100.49, 16.59, 14.10,

12.05. The spectral properties of **7b** were in good agreement with those reported for naturally occurring gibepyrone A.[3b]

Synthesis of Fusalanipyrone (7a) by Palladium-Catalysed Triethylammonium Formate Reduction of 17a: Formic acid (99%, 327 μL, 8.7 mmol) was added to a mixture of compound **17a** (1.26 g, 4.3 mmol), triethylamine (1.8 mL, 13.0 mmol), $Pd(OAc)_2$ (19.4 mg, 0.09 mmol) and triphenylphosphane (45 mg, 0.17 mmol) in dry DMF (30 mL), and the mixture was stirred under argon at 60 °C for 2 h. The crude reaction product obtained after the usual workup was purified by MPLC on silica gel, with toluene as eluent, to give pure **7a** (0.62 g, 87%) as a colourless liquid. The spectral properties of this compound were in agreement with those of **7a** prepared by Pd-catalysed methylation of a mixture of **12a** and **12b**.

Synthesis of Gibepyrone A (7b) by Palladium-Catalysed Triethylammonium Formate Reduction of 17b: Formic acid (99%, 227 μL, 6.0 mmol) was added to a mixture of compound **17b** (0.87 g, 3.0 mmol), triethylamine (1.26 mL, 9.0 mmol), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol), and triphenylphosphane (31.6 mg, 0.12 mmol) in dry DMF (30 mL), and the mixture was stirred under argon at 55 °C for 3 h. The crude reaction product obtained after the usual workup was purified by MPLC on silica gel, with a mixture of toluene and EtOAc (90:10) as eluent, to give chemically and stereoisomerically pure **7b** (0.40 g, 81%) as a colourless solid. M.p. 39−41 °C. The spectral properties of this compound were in agreement with those of **7a** prepared by palladium-catalysed methylation of a stereoisomeric mixture of **12a** and **12b**.

Acknowledgments

We wish to thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) and the University of Pisa for financial support. We also grateful to Prof. Annalaura Segre for the use of NMR facilities of the Servizio NMR dell'Area della Ricerca di Roma (CNR) and to Mr. Piergiorgio Vergamini for recording IR spectra. Finally, we wish to thank Prof. Jean-Luc Parrain (Laboratoire de Synthèse Organique, Marseille, France) for useful comments.

[1] [1a] M. S. R. Nair, S. T. Carey, *Phytochemistry* **1977**, *16*, 1613. [1b] E. L. Ghisalberti, K. Sivasithamparam, *Soil Biol. Biochem.* **1991**, *23*, 1011−1020. [1c] A. Simon, R. W. Dunlop, E. L. Ghisalberti, K. Sivasithamparam, *Soil Biol. Biochem.* **1988**, *20*, 263−264. [1d] M. O. Moss, R. M. Jackson, D. Rogers, *Phytochemistry* **1975**, *14*, 2706−2708. [1e] K. K. Chen, A. Kovarikova, *J. Pharm. Sci.* **1967**, *56*, 1535−1541. [1f] A. Gehrt, G. Erkel, T. Anke, O. Sterner, *Z. Naturforsch., Teil C* **1988**, *53*, 89−92. [1g] F. Bohlmann, H.-C. Hummel, J. Laser, *Chem. Ber.* **1968**, *101*, 3562−3566. [1h] F. M. Dean, *Naturally Occurring Oxygen Ring Compounds*, Butterworths, London, **1963**, pp. 82−134.

[2] R. E. Charlton, F. X. Webster, A. Zhang, C. Schal, D. Liang, I. Sreng, W. L. Roelofs, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10202−10205.

[3] [3a] W. R. Abraham, H.-A. Arfmann, *Phytochemistry* **1988**, *27*, 3310−3311. [3b] A. F. Barrero, J. E. Oltra, M. M. Herrador, E. Cabrera, J. F. Sanchez, J. F. Quilez, F. J. Rojas, J. F. Reyes, *Tetrahedron* **1993**, *49*, 141−150. [3c] T. Lindel, P. R. Jensen, W. Fenical, *Tetrahedron Lett.* **1996**, *36*, 1327−1330. [3d] H. Tazaki, T. Hayashida, F. Ishikawa, D. Taguchi, T. Takasawa, K. Nabeta, *Tetrahedron Lett.* **1999**, *40*, 101−104. [3e] T. McCabe, J. Clardy, L. Minale, C. Pizza, F. Zollo, R. Riccio, *Tetrahedron Lett.* **1982**, *23*, 3307−3310.

[4] [4a] R. Haensel, L. Klaproth, *Arch. Pharm. (Weinheim, Ger.)* **1966**, *299*, 503−506. [4b] R. L. Edwards, D. G. Lewis, D. V. Wilson, *J. Chem. Soc.* **1961**, 4995−5002.

[5] [5a] L. Camarda, L. Merlini, G. Nasini, *Phytochemistry* **1976**, *15*, 537−539. [5b] G. Schlingmann, L. Milne, G. T. Carter, *Tetrahedron* **1998**, *54*, 13013−13022.[5c] E. Huipe-Nava, V. G. Mendoza, E. G. Garcia, M. Soriano-Garcia, *Anal. Sci.* **1999**, *15*, 605−606.

[6] [6a] M. S. R. Nair, S. T. Carey, *Tetrahedron Lett.* **1975**, 1655−1658. [6b] Y. Kimura, T. Hamasaki, A. Isogai, H. Nakajima, *Agric. Biol. Chem.* **1982**, *46*, 1963−1966. [6c] R. Jansen, H. Irschik, H. Reichenbach, G. Hoefle, *Liebigs Ann. Chem.* **1985**, 822−836. [6d] K. M. Jenkins, S. G. Toske, P. R. Jensen, W. Fenical, *Phytochemistry* **1998**, *49*, 2299−2304.

[7] H. Sato, K. Konoma, A. Sakamura, T. Furusaki, T. Matsumoto, T. Matsusaki, *Agric. Biol. Chem.* **1981**, *45*, 795−797. [7b] B. Franck, H.-P. Gehrken, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 461−462. [7c] L. J. Mulheirn, R. B. Beechey, D. P. Leworthy, M. D. Osselton, *J. Chem. Soc., Chem. Commun.* **1974**, 874−876. [7d] G. J. Kruger, P. S. Steyn, R. Vleggaar, C. J. Rabie, *J. Chem. Soc., Chem. Commun.* **1979**, 441−442. [7e] C. Brassy, B. Bachet, C. Guidi-Morosini, S. Rebuffat, D. Molho, *Acta Crystallogr., Sect. B* **1982**, *38*, 1624−1626. [7f] S. Shimizu, I. Sakurai, Y. Yamamoto, *Chem. Pharm. Bull.* **1983**, *31*, 3781−3784.

[8] [8a] M. S. R. Nair, S. T. Carey, *Tetrahedron Lett.* **1975**, 3517−3518. [8b] J. R. Pfister, *Tetrahedron Lett.* **1980**, *21*, 1281−1284.

[9] [9a] N. Claydon, M. Allan, J. R. Hanson, A. G. Avent, *Trans. Br. Mycol. Soc.* **1987**, *88*, 503−513. [9b] ref. 1c. [9c] H. G. Cutler, R. H. Cox, F. G. Crumley, P. O. Cole, D. Patsy, *Agric. Biol. Chem.* **1986**, *50*, 2943−2948.

[10] H. Sato, K. Konoma, S. Sakamura, *Agric. Biol. Chem.* **1981**, *54*, 1675−1680.

[11] [11a] C.-H. Chen, C.-C. Liao, *Org. Lett.* **2000**, *2*, 2049−2052. [11b] R. P. Hsung, H. C. Shen, C. J. Douglas, C. D. Morgan, S. J. Degen, L. J. Yao, *J. Org. Chem.* **1999**, *64*, 690−691. [11c] B. Danieli, G. Lesma, M. Martinelli, D. Passarella, I. Peretto, A. Silvani, *Tetrahedron* **1998**, *54*, 14081−14088. [11d] V. Jram, A. Goel, *J. Chem. Res. (S)* **1997**, 460−461. [11e] Z. Liu, J. Meinwald, *J. Org. Chem.* **1996**, *61*, 6693−6699. [11f] K. Afarinkia, J. Berna-Canovas, *Tetrahedron Lett.* **2000**, *41*, 4955−4958 − [11g] K. D. Stigers, R. Mar-Tang, P. A. Bartlett, *J. Org. Chem.* **1999**, *64*, 8409−8410. [11h] A. Cobas, M. T. Diaz, S. Escudero, D. Pérez, E. Guitián, L. Castedo, in: *Current Trends in Organic Synthesis* (Eds.: C. Scolastico, F. Nicotra), Kluwer Academic/Plenum Publishers, New York, **1999**, pp. 307−314. [11i] V. J. Ram, P. Srivastava, A. S. Saxena, *J. Org. Chem.* **2001**, *66*, 5333−5337.

[12] [12a] R. Hua, M. Tanaka, *New J. Chem.* **2001**, *25*, 179−184. [12b] S. Rousset, M. Abarbri, J. Thibonnet, A. Duchêne, J.-L. Parrain, *Chem. Commun.* **2000**, 1987−1988. [12c] S. I. Kotretsou, M. P. Georgiadis, *Org. Prep. Proced. Int.* **2000**, *32*, 161−167. [12d] R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem.* **1999**, *64*, 8770−8879. [12e] B. Stanovnik, *J. Heterocycl. Chem.* **1999**, *36*, 1581−1593. [12f] V. Kepe, S. Polanc, M. Kocevar, *Heterocycles* **1998**, *48*, 671−678. [12g] T. Dubuffet, B. Cimetiere, G. Lavielle, *Synth. Commun.* **1997**, *27*, 1123−1131. [12h] V. N. Kalinin, O. S. Shilova, D. S. Okladnoy, H. Schmidhammer, *Mendeleev Commun.* **1996**, 244−245. [12i] L. S. Liebeskind, J. Wang, *Tetrahedron* **1993**, *49*, 5461−5470. [12j] S. Cerezo, M. Moreno-Mañas, R. Pleixats, *Tetrahedron* **1998**, *54*, 7813−7818. [12k] V. Kvita, W. Fischer, *Chimia* **1992**, *46*, 457−468 and references cited therein. [12l] M. Kotora, M. Ishikawa, F.-Y. Tsai, T. Takahashi, *Tetrahedron* **1999**, *55*, 4969−4978. [12m] H. Hagiwara, K. Kobayashi, T. Hoshi, T. Suzuki, M. Ando, *Tetrahedron* **2001**, *57*, 5039−5043. [12n] N. Rosas, M. Salmon, P. Sharma, C. Alvarez, R. Ramirez, J.-L. Garcia, H. Arzoumanian, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1493−1494. [12o] W. Cao, W. Ding, L. Wang, L. Song, Q. Zhang, *J. Fluorine Chem.* **2001**, *109*, 201−204.

[13] [13a] F. Bellina, C. Anselmi, R. Rossi, *Tetrahedron Lett.* **2001**, *42*, 3851−3854. [13b] R. Rossi, F. Bellina, A. Catanese, L. Mannina, D. Valensin, *Tetrahedron* **2000**, *56*, 479−487. [13c] F. Bellina, D. Ciucci, P. Vergamini, R. Rossi, *Tetrahedron* **2000**, *56*, 2533−2545. [13d] R. Rossi, F. Bellina, M. Biagetti, A. Catanese, L. Mannina, *Tetrahedron Lett.* **2000**, *41*, 5281−5286. [13e] R. Rossi, F. Bellina, E. Raugei, *Synlett* **2000**, 1749−1752. [13f] R. Rossi, F. Bellina, M. Biagetti, L. Mannina, *Tetrahedron: Asymmetry* **1999**, *10*, 1163−1172. [13g] R. Rossi, F. Bellina, M. Biagetti, L. Mannina, *Tetrahedron Lett.* **1998**, *39*, 7799−7802. [13h] R. Rossi, F. Bellina, M. Biagetti, *Synth. Commun.* **1999**, *29*, 3415−3420. [13i] R. Rossi, F. Bellina, M. Biagetti, L. Mannina, *Tetrahedron Lett.* **1998**, *39*, 7599−7602. [13j] R. Rossi, F. Bellina, L. Mannina, *Tetrahedron Lett.* **1998**, *39*, 3017−3020. [13k] R. Rossi, F. Bellina, C. Bechini, L. Mannina, P. Vergamini, *Tetrahedron* **1998**, *54*, 135−156.

[14] F. Bellina, M. Biagetti, A. Carpita, R. Rossi, *Tetrahedron* **2001**, *57*, 2857−2870.

[15] F. Bellina, M. Biagetti, A. Carpita, R. Rossi, *Tetrahedron Lett.* **2001**, *42*, 2859−2863.

[16] [16a] R. Rossi, F. Bellina, A. Carpita, R. Gori, *Gazz. Chim. Ital.* **1995**, *125*, 381−392. [16b] R. Rossi, F. Bellina, A. Carpita, R. Gori, *Synlett* **1995**, 344−346. [16c] R. Rossi, F. Bellina, A. Carpita, *Recent Dev. Synth. Org. Chem.* **1998**, *1*, 47−75 and references cited therein.

[17] A. G. Myers, M. M. Alauddin, M. A. M. Fury, P. S. Dragovich, N. S. Finney, P. M. Harrington, *Tetrahedron Lett.* **1989**, *30*, 6977−6980.

[18] G. T. Crisp, A. I. O'Donoghue, *Synth. Commun.* **1989**, *19*, 1745−1758.

[19] B. P. Warner, S. L. Buchwald, *J. Org. Chem.* **1994**, *59*, 5922−5823.

[20] For Stille-type reactions performed using catalyst precursors containing CuI, see: [20a] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9385−9395. [20b] F. Bellina, A. Carpita, D. Ciucci, M. De Santis, R. Rossi, *Tetrahedron* **1993**, *49*, 4677−4698. [20c] D. M. Hodgson, J. Witherington, B. A. Moloney, I. C. Richards, J.-L. Brayer, *Synlett* **1995**, 32−34. [20d] G. Shi, Z. Cao, X. Zhang, *J. Org. Chem.* **1995**, *60*, 6608−6611. [20e] Ref.[13e]

[21] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2392−2394.

[22] A similar reductive cleavage has been reported to occur when iodolactones derived from *endo*-bicyclo[3.2.1]oct-6-ene-3-carboxylic acid derivatives are treated with zinc in ethanol or with zinc and acetic acid: [22a] P. J. Garratt, J. F. White, *J. Org. Chem.* **1977**, *42*, 1733−1736. [22b] C. S. Rondestvedt, Jr., C. D. Ver Nooy, *J. Am. Chem. Soc.* **1955**, *77*, 4878−4883.

[23] S. Cacchi, P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1986**, *27*, 5541−5544.

[24] D. R. Coulson, *Inorg. Synth.* **1972**, *13*, 121−124.

[25] J. R. Doyle, P. E. Slade, M. B. Jonassen, *Inorg. Synth.* **1960**, *6*, 216−219.

[26] R. Rossi, F. Bellina, A. Carpita, D. Mazzarella, *Tetrahedron* **1996**, *52*, 4095−4110.

[27] G. Ohanessian, Y. Six, J.-Y. Lallemand, *Bull. Soc. Chim. Fr.* **1996**, *133*, 1143−1148.

Received September 28, 2001
[O01468]