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New Stereoselective Syntheses of Stereodefined 2-Substituted Alkyl 2-Alkenoates and Their Applications

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Abstract: Stereoisomerically pure alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**8**, which are easily prepared by palladium-catalyzed reaction between tributylstannane and alkyl 2-alkynoates, **15**, have been employed as precursors to stereodefined 2-(hetero)aryl substituted alkyl 2-alkenoates of general formula **9** as well as alkyl (*E*)-2-methyl-2-alkenoates, (*E*)-**10**, having very high stereoisomeric purity. One of these esters, *i.e.* ethyl (*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-phenyl-2-butenoate, (*Z*)-**9d**, has been employed in a very simple and efficient synthesis of 3-phenyl-5(H)-2-furanone, **12**, a metabolite of an hypnotic drug. On the other hand, the procedure employed to prepare esters (*E*)-**10**, which involves a configurational inversion, has been used to prepare the (*S*)-enantiomer of (*E*)-2,4-dimethyl-2-hexenoic acid, (*E*)-**13**, a caste-specific substance of male carpenter ants in the genus *Camponotus*, as well as 98% optically pure (*S*)(*E*)-4,6-dimethyl-4-octen-3-one, (*S*)(*E*)-**14**, an alarm pheromone component of ants in the genus *Manica*.

Recently we showed that stereodefined 2-alkyl and 2-(hetero)aryl substituted 1-silyl-1-stannylethenes of general formula (*Z*)-**1**, (*Z*)-**2** and (*E*)-**2**, which are easily synthesized in high stereoisomeric purity from easily available starting materials[1], represent a new class of stable and synthetically useful organometallic reagents[1-3]. In particular, it was found that compounds (*Z*)-**1** (R = alkyl), (*Z*)-**2** (R = Ph, 5-methyl-2-thienyl) or (*E*)-**2** (R = Ph) are effective precursors to 1,2-disubstituted (*E*)-ethenylsilanes of general formula (*E*)-**3**[2].

(*Z*)-**1** (R = alkyl; R^1 = Me, *n*-Bu; R^2 = CH_3, Ph)

(*Z*)-**2** (R = (hetero)aryl; R^1 = Me, *n*-Bu; R^2 = CH_3, Ph)

(*E*)-**1** (R = alkyl)

(*E*)-**2** (R = aryl)

(*E*)-**3**

(R = *n*-alkyl, Ph, 5-methyl-2-thienyl; R^1 = *n*-alkyl, COOEt, COPh, -CH=$\overset{E}{C}$H-COOEt; R^2 = Me)

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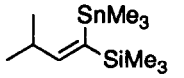
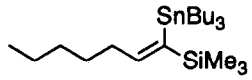
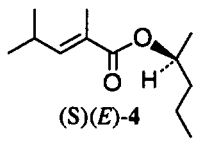
On the other hand, two compounds of general formula (*Z*)-**1**, *i.e.* (*Z*)-1-trimethylsilyl-1-trimethylstannyl-3-methyl-1-butene, (*Z*)-**1a**, and (*Z*)-1-trimethylstannyl-1-tributylstannyl-1-heptene, (*Z*)-**1b**, have been used as key intermediates in the efficient and stereocontrolled synthesis of (*S*)-1-methylbutyl (*E*)-2,4-dimethyl-2-pentenoate, (*S*)(*E*)-**4**, and (*E*)-2-butyl-2-octenal, (*E*)-**5**, which represent an aggregation pheromone component of *Rhyzopertha dominica* and an alarm pheromone component of *Oecophylla longinoda*, respectively[3].



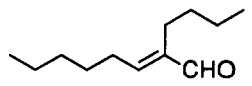
(*Z*)-**1a**



(*Z*)-**1b**

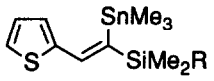


(S)(*E*)-**4**

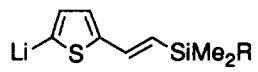


(*E*)-**5**

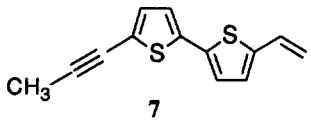
Moreover, we also showed that the (*E*)-1-silylethenyllithiums derived from (*Z*)-1-trimethylsilyl- or (*Z*)-dimethylphenylsilyl-2-(2-thienyl)1-trimethylstannylethene, (*Z*)-**2a** and (*Z*)-**2b**, respectively, rearrange at -78 °C to give the corresponding (*E*)-2-(5-lithium-2-thienyl)ethenylsilanes, (*E*)-**6a,b**[2,3] and we employed compound (*E*)-**6b** as a precursor in an efficient synthesis of 5-ethenyl-5'-(1-propynyl)-2,2'-bithiophene, **7**, a naturally-occurring phototoxin[4].



(*Z*)-**2a** (R = CH_3)
(*Z*)-**2b** (R = Ph)



(*E*)-**6a** (R = CH_3)
(*E*)-**6b** (R = Ph)



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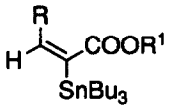
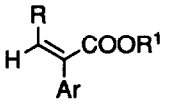
More recently, in continuation of our studies on the synthetic utilities of stereodefined 1-alkenyltin compounds bearing a functional substituent in the 1-position, we developed efficient procedures for the synthesis of stereodefined 2-(hetero)aryl substituted alkyl 2-alkenoates of general formula **9** as well as alkyl (*E*)-2-methyl-2-alkenoates, (*E*)-**10**, having very high stereoisomeric purity. These new procedures, which involve the use of stereoisomerically pure alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**8**, as precursors appear of particular interest since *i)* esters **9** and (*E*)-**10** are valuable synthetic intermediates and *ii)* compounds **9** cannot be synthesized using classical olefination methods such as the Horner-Emmons reaction or its modifications[5]. In fact, like the related reaction of stabilized ylides with aldehydes, the Horner-Emmons reaction shows a preference for formation of α,β-unsaturated esters having configuration opposite of that of compounds **9**. On the other hand, compounds (*E*)-**10** synthesized using this last reaction often contain significant amounts of the corresponding (*Z*)-stereoisomers[5].



(*E*)-**8**



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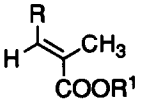
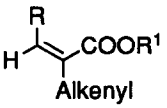
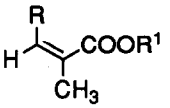


(*E*)-**10**

In this paper we will describe these new syntheses of esters **9** and (*E*)-**10** as well as the results obtained when a procedure similar to that employed to prepare compounds **9** was used for the synthesis of alkyl (*Z*)-2-alkenyl-2-alkenoates, (*Z*)-**11**, or alkyl (*Z*)-2-methyl-2-alkenoates, (*Z*)-**10**[6].

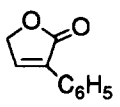


(*Z*)-**11**



(*Z*)-**10**

Furthermore, in the last part of this paper, which will be devoted to illustrate the synthetic utility of the procedures developed for the synthesis of esters **9** and (*E*)-**10**, efficient syntheses of 3-phenyl-5(H)-2-furanone, **12**, a metabolite of the hypnotic drug *glutethimide*, which causes central nervous system depression when administered in large doses[7], of the (*S*)-enantiomer of (*E*)-2,4-dimethyl-2-hexenoic acid, (*E*)-**13**, a caste-specific substance of male carpenter ants in the genus *Camponotus*[8], as well as of 98% optically pure (*S*)(*E*)-4,6-dimethyl-4-octen-3-one (manicone), (*S*)(*E*)-**14**, an alarm pheromone component of ants in the genus *Manica*[9,10] will be described.



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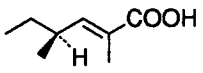
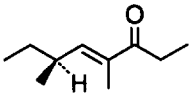


(*S*)(*E*)-**13**

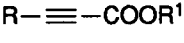


(*S*)(*E*)-**14**

RESULTS AND DISCUSSION

A) Preparation of alkyl (E)-2-tributylstannyl-2-alkenoates, (E)-8

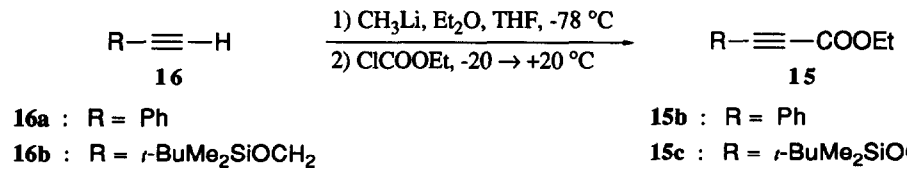
Alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**8a-d**, used for the present study were synthesized starting from the corresponding alkyl 2-alkynoates, **15a-d**. Of these esters methyl-2-octynoate, **15a**, was commercially available.



15

15a : R = *n*-C_5H_{11}; R^1 = CH_3
15b : R = C_6H_5; R^1 = C_2H_5
15c : R = *t*-$BuMe_2SiOCH_2$; R^1 = C_2H_5
15d : R = (*S*)-C_2H_5-$CH(CH_3)$; R^1 = C_2H_5

Ethyl 3-phenylpropynoate, **15b**, and ethyl 4-(*tert*-butyldimethylsilyloxy)-2-butynoate, **15c**, were prepared in 65 and 48% yields, respectively, by treatment of the corresponding 1-alkynes, **16a** and **16b**, respectively, with methyllithium in THF-Et_2O at -78 °C, followed by treatment with ethyl chloroformate [eq. (1)].



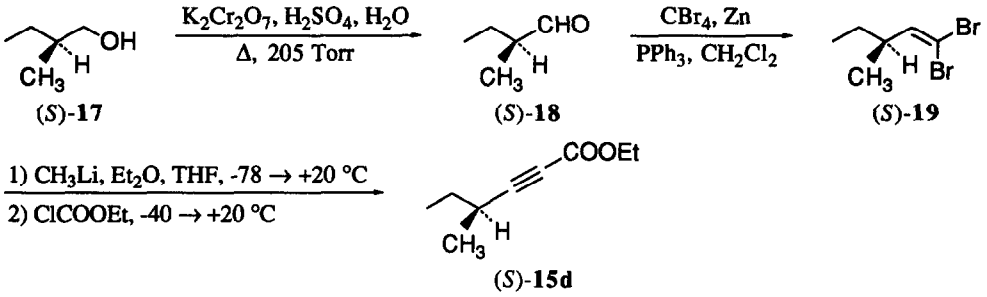
(1)

16a : R = Ph
16b : R = *t*-BuMe$_2$SiOCH$_2$

15b : R = Ph
15c : R = *t*-BuMe$_2$SiOCH$_2$

On the other hand, ethyl (*S*)-4-methyl-2-hexynoate, (*S*)-**15d**, was synthesized starting from (*S*)-2-methyl-1-butanol, (*S*)-**17**, according to the reaction sequence reported in Scheme 1.

Scheme 1



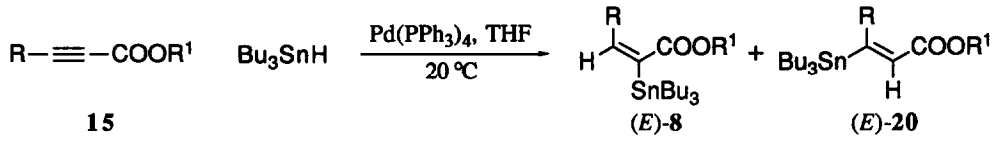
In particular, compound (*S*)-**17** having optical purity higher than 99% was oxidized to the corresponding aldehyde, (*S*)-**18**, using a procedure which involved addition of a mixture of $K_2Cr_2O_7$, sulfuric acid and water to (*S*)-**17** heated at 70 °C at 205 Torr and distillation of the azeotropic mixture of water and (*S*)-**18** so formed[11]. This aldehyde was then reacted with $Ph_3P{=}CBr_2$ in dry CH_2Cl_2[12] to provide (*S*)-1,1-dibromo-3-methyl-1-pentene, (*S*)-**19**, in 81% yield. Finally, compound (*S*)-**19**, upon treatment with 3.45 equiv of methyllithium in THF-Et_2O, followed by addition of 2.5 equiv of ethyl chloroformate, gave the desired ester, (*S*)-**15d**, in 51 % yield.

Compounds **15a-d** were then converted to the corresponding alkyl (*E*)-2-tributylstannyl-2-alkenoates, (*E*)-**8a-d**, according to a procedure very similar to that recently reported for the synthesis of some alkyl 2-trimethylstannyl-2-alkenoates[13-15] (Table 1).

In particular, compounds **15a-d** were reacted with 1 equiv of tributylstannane in THF solution at 20 °C, in the presence of 2 mol % of $Pd(PPh_3)_4$, to give reaction mixtures which contained compounds (*E*)-**8a-d** together with small amounts (2 - 9 %) of the corresponding alkyl (*E*)-3-tributylstannyl-2-alkenoates, (*E*)-**20a-d**. Purification by MPLC on silica gel allowed to obtain compounds (*E*)-**8a-d** in 71 - 93 % isolated yield (Table 1).

Interestingly, these stannyl esters underwent partial stereomutation during distillation under reduced pressure.

Table 1. Palladium-Catalyzed Reaction between α,β-Acetylenic Esters **15** and Bu_3SnH



15 (*E*)-**8** (*E*)-**20**

Entry	Starting material	R	R^1	Products (ratio)[a]	Yield (%)[b]	Stereoisomeric purity (%)[c]
1	**15a**	*n*-C_5H_{11}	CH_3	**8a**, **20a** (92:8)	85	> 98
2	**15b**	C_6H_5	C_2H_5	**8b**, **20b** (90:10)	71	99
3	**15c**	*t*-$BuMe_2SiOCH_2$	C_2H_5	**8c**, **20c** (91:9)	84	99
4	**15d**	(*S*)-$C_2H_5CH(CH_3)$	C_2H_5	**8d**, **20d** (98:2)	93[d]	> 99

a) Product ratios were determined by GLC analyses.

b) Yields refer to isolated compounds **8** having regioisomeric purity higher than 98.5%.

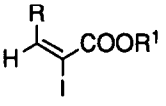
c) The stereoisomeric purity of compounds **8** were evaluated by ^1H NMR and GLC analyses.

d) $[\alpha]_D^{25}$ +23.63 (c = 2.535, heptane).

B) Preparation of stereodefined 2-substituted alkyl 2-alkenoates

Initially, it was attempted to prepare alkyl 2-(hetero)aryl-2-alkenoates of general formula **9** by reaction between compounds (*E*)-**8** and 1.1 equiv of (hetero)aryl iodides in refluxing THF, in the presence of catalytic amounts of palladium catalysts such as $(PPh_3)_2PdCl_2$ or $Pd(PPh_3)_4$. However, GLC analyses carried out after long reaction times (72 - 100 h) showed that no cross-coupling reactions had taken place.

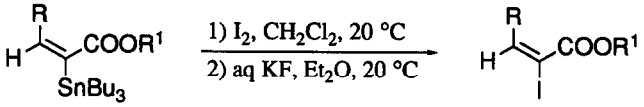
Therefore, a different strategy for preparing compounds **9** starting from compounds (*E*)-**8** was devised. It involved the stereospecific conversion of these stannyl esters to the corresponding alkyl (*E*)-2-iodo-2-alkenoates (*E*)-**21**, followed by a transition metal-catalyzed (hetero)arylation of these iodo derivatives.



(*E*)-**21**

Thus, compounds (*E*)-**8a-d** were treated with an equimolar amount of iodine in CH_2Cl_2 at 20 °C and the resulting reaction mixtures, which contained compounds (*E*)-**21a-d** and Bu_3SnI, were concentrated, diluted with Et_2O and, in order to eliminate Bu_3SnI, treated with a large excess of a semisaturated aqueous KF solution. The resulting reaction mixtures, after stirring for 2 h at room temperature, were filtered, concentrated, extracted with Et_2O and the organic extracts were purified by MPLC on silica gel to give stereoisomerically pure compounds (*E*)-**21a-d** in 73 - 95 % yield (Table 2).

Table 2. Preparation of Compounds (*E*)-**21**



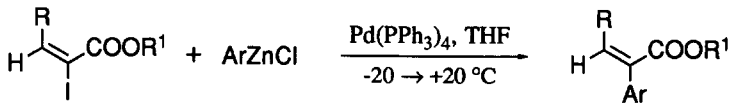
(*E*)-**8** (*E*)-**21**

Entry	Starting material	R	R^1	Products	Yield (%)	Stereoisomeric purity (%)
1	**8a**	*n*-C_5H_{11}	CH_3	**21a**	73	≥ 99
2	**8b**	C_6H_5	C_2H_5	**21b**	89	> 99
3	**8c**	*t*-$BuMe_2SiOCH_2$	C_2H_5	**21c**	95	> 99
4	**8d**	(*S*)-$C_2H_5CH(CH_3)$	C_2H_5	**21d**	90 *a)*	> 99

a) $[\alpha]_D^{25}$ +41.31 (c = 2.520, hexane).

Finally, the iodo derivatives (*E*)-**21** were converted efficiently and stereospecifically to the desired compounds **9** by reaction with THF solutions of 1.2 equiv of (hetero)arylzinc chlorides, in the presence of *ca.* 8 mol % of $Pd(PPh_3)_4$. Table 3 summarizes the results obtained in the preparation of methyl (*Z*)-2-phenyl-2-octenoate, (*Z*)-**9a**, ethyl (*Z*)-2,3-diphenyl-2-propenoate, (*Z*)-**9b**, ethyl (*E*)-3-phenyl-2-(2-thienyl)-2-propenoate, (*E*)-**9c**, and ethyl (*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-phenyl-2-butenoate, (*Z*)-**9d**.

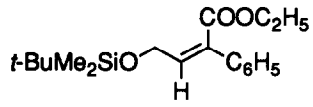
Table 3. Palladium-Catalyzed Reaction between Compounds (*E*)-**19** and (Hetero)Arylzinc Chlorides

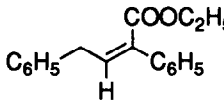


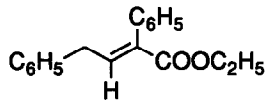
(*E*)-**21** **9**

Entry	Starting material	R	R^1	Ar	Products	Yield (%)	Stereoisomeric purity (%)
1	**21a**	*n*-C_5H_{11}	CH_3	C_6H_5	(*Z*)-**9a**	76	> 99
2	**21b**	C_6H_5	C_2H_5	C_6H_5	(*Z*)-**9b**	82	> 99
3	**21b**	C_6H_5	C_2H_5	2-thienyl	(*E*)-**9c**	73	> 98
4	**21c**	*t*-$BuMe_2SiOCH_2$	C_2H_5	C_6H_5	(*Z*)-**9d**	56	> 99

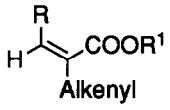
Interestingly, the reaction which gave compound (*Z*)-**9d** produced also, although in a very low yield, a stereoisomeric mixture of ethyl 2,4-diphenyl-2-propenoate, (*Z*)/(*E*)-**22**. However, purification of the crude reaction mixture by MPLC on silica gel allowed to isolate only compounds (*Z*)-**9d** and (*Z*)-**22** in *ca.* 56 and 3% yields, respectively.

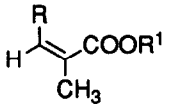

(*Z*)-**9d**


(*Z*)-**22**

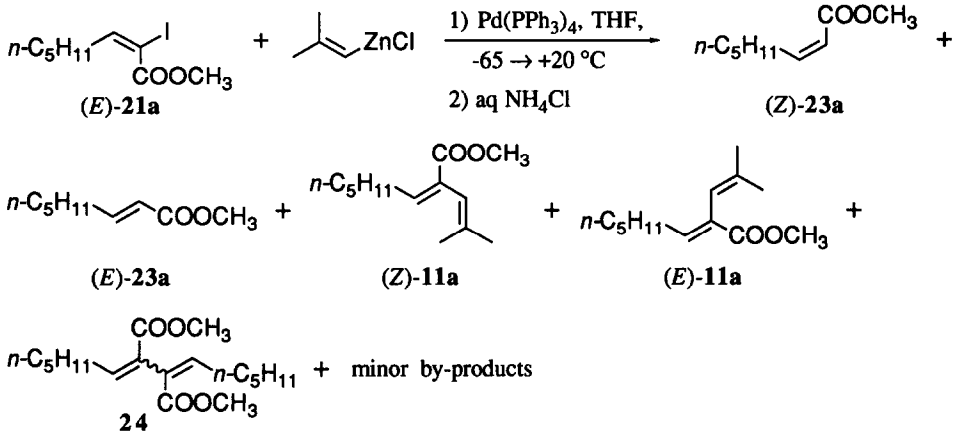

(*E*)-**22**

On the basis of the successful results obtained in the synthesis of compounds **9**, it was attempted to use a similar procedure for the preparation of alkyl (*Z*)-2-alkenyl-2-alkenoates, (*Z*)-**11**, as well as alkyl (*Z*)-2-methyl-2-alkenoates, (*Z*)-**10**, starting from compounds (*E*)-**21**.


(*Z*)-**11**

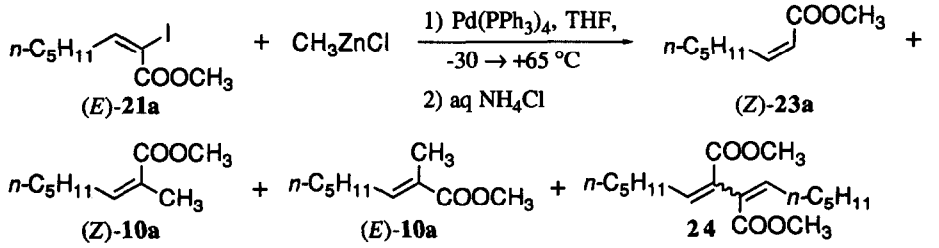

(*Z*)-**10**

Thus, in a preliminary test compound (*E*)-**21a** was reacted with 1.28 equiv of 2-methyl-1-propenylzinc chloride in THF solution, in the presence of a catalytic amount of $Pd(PPh_3)_4$. GLC/MS analysis showed that the reaction mixture was constituted of five main components, subsequently identified as methyl (*Z*)- and (*E*)-2-octenoate, (*Z*)-**23a** and (*E*)-**23a**, respectively, (*Z*)- and (*E*)-2-(2-methyl-1-propenyl)-2-octenoate, (*Z*)-**11a** and (*E*)-**11a**, respectively, and 7,8-di(carbomethoxy)-6,8-tetradecadiene, **24** [eq. (2)]. Purification by MPLC on silica gel allowed to isolate compounds (*Z*)-**11a** and **24** in 29 and 16% yields, respectively. GLC analysis showed that (*Z*)-**11a** had 96% stereoisomeric purity.



(*E*)-**21a** (*Z*)-**23a** (*E*)-**23a** (*Z*)-**11a** (*E*)-**11a** **24** (2)

On the other hand, it was found that when compound (*E*)-**21a** was reacted with a THF solution of 1.1 equiv of methylzinc chloride, in the presence of 10 mol % of $Pd(PPh_3)_4$, a complex reaction mixture containing compound (*Z*)-**23a**, methyl (*E*)- and (*Z*)-2-methyl-2-octenoate, (*E*)-**10a** and (*Z*)-**10a**, respectively, as well as compound **24** was produced [eq. (3)]. Purification by MPLC on silica gel allowed to isolate compounds (*Z*)-**10a** and **24** in 43 and 19% yields, respectively. GLC analysis showed that (*Z*)-**10a** had 81% stereoisomeric purity.



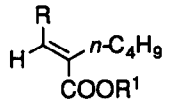
(3)

A worse result as regards either the yield or the stereoisomeric purity of compound (*Z*)-**10a** was obtained when $PdCl_2$(dppf) was used as catalyst.

Taking into account these last unsatisfactory results, it was thought it right to attempt to convert compounds (*E*)-**21** to the corresponding (*Z*)-2-methyl substituted 2-alkenoates, (*Z*)-**10**, by a procedure similar to that previously employed to prepare stereospecifically (*E*)-3-ethyl or (*E*)-3-propyl-2-alken-1-ols from the corresponding (*Z*)-3-iodo-2-alken-1-ols[16,17]. Thus, in a preliminary test compound (*E*)-**21a** was reacted with a fourfold excess of $(CH_3)_2CuLi$ in Et_2O at -78 °C for 4 h. Surprisingly, hydrolysis of the reaction mixture afforded in high yield methyl (*E*)-2-octenoate, (*E*)-**23a**, together with a small amount of a compound subsequently identified as methyl (*E*)-2-methyl-2-octenoate, (*E*)-**10a**. This result suggested that the reaction between (*E*)-**21a** and $(CH_3)_2CuLi$, which involved a configurational inversion, gave rise to the corresponding (*Z*)-(α-carbalkoxyvinyl)cuprate reagent, (*Z*)-**25**, an organometallic compound which belongs to a class of substances for which some reactivity studies with various electrophiles has been already performed[18] and which, according to the literature[18b], is able to equilibrate with the corresponding allenylcuprate, **26**.

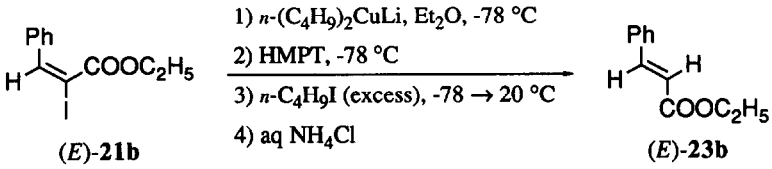
On this basis, an efficient procedure for preparing alkyl (*E*)-2-methyl-2-alkenoates, (*E*)-**10**, starting from compounds (*E*)-**21** was developed. Such procedure, which involved treatment of the iodo derivatives (*E*)-**21** with 3.5 equiv of $(CH_3)_2CuLi$ in Et_2O at -78 °C for 4 h, followed by addition of HMPA and a molar excess of methyl iodide, allowed to prepare ca. 99% stereoisomerically pure methyl (*E*)-2-methyl-2-octenoate, (*E*)-**10a**, ethyl (*E*)-2-methyl-3-phenylpropenoate, (*E*)-**10b**, and ethyl (*S*)(*E*)-2,4-dimethyl-2-hexenoate, (*S*)(*E*)-**10c**, having $[\alpha]_D^{25}$ +41.09 (c = 3.395, methanol), in 96, 87 and 81% yields, respectively (Table 4).

It is worthy of mention that it was also attempted to use a similar procedure for the preparation of alkyl (*E*)-2-butyl-2-alkenoates, (*E*)-**27**, starting from compounds (*E*)-**21**. Thus, compound (*E*)-**21b** was reacted with 3.5 equiv of $(n\text{-}C_4H_9)_2CuLi$ in Et_2O at -78 °C for 4.5 h and the reaction mixture was treated sequentially with HMPA and a molar excess of 1-iodobutane [eq. (4)]. However, GLC/MS analysis of the crude reaction mixture after hydrolysis showed that it did not contain the expected ester (*E*)-**27** (R = Ph, $R^1 = C_2H_5$).



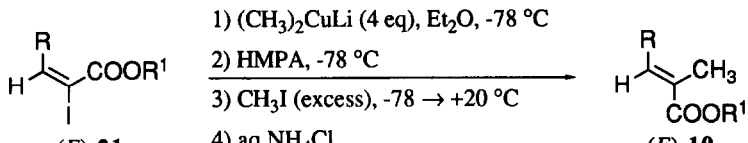
(*E*)-**27**

On the other hand, purification of the crude reaction product allowed to isolate stereoisomerically pure ethyl (*E*)-3-phenyl-2-propenoate, (*E*)-**23b**, in 64% yield [eq. (4)].



(*E*)-**21b** (*E*)-**23b** (4)

Table 4. Synthesis of Alkyl (E)-2-Methyl-2-alkenoates, (*E*)-**10**, Starting from Compounds (*E*)-**21**



(*E*)-**21** (*E*)-**10**

Entry	Starting material	R	R^1	Products	Yield (%)	Stereoisomeric purity (%)
1	**21a**	n-C_5H_{11}	CH_3	(*E*)-**10a**	96	> 98
2	**21b**	C_6H_5	C_2H_5	(*E*)-**10b**	87	> 99
3	**21d**	(*S*)-$C_2H_5CH(CH_3)$	C_2H_5	(*S*)(*E*)-**10c**	81	> 99

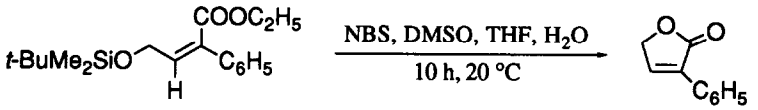
C) Synthesis of 3-phenyl-5(H)-2-furanone, 12

To demonstrate the synthetic utility of stereodefined alkyl 2-(hetero)aryl-2-alkenoates, **9**, we used one of these compounds, *i.e.* ethyl (Z)-4-(*tert*-butyldimethylsilyloxy)-2-phenyl-2-butenoate, (Z)-**9d**, in a very simple and efficient synthesis of 3-phenyl-5(H)-2-furanone, **12**, a metabolite of the hypnotic drug *glutethimide*, which can cause central nervous system depression when administered in large doses and might contribute to the toxicity of severely intoxicated patients overdosed with this drug[7].

In particular, it was found that treatment of compound (Z)-**9d** with 1.1 equiv of N-bromosuccinimide (NBS) in a mixture of DMSO, THF and water for 10 h at room temperature gave compound **12** in a 98% isolated yield [eq. (5)].

It is interesting to note that the overall procedure for the synthesis of compound **12**, which involves the use of ethyl (*E*)-2-iodo-4-(*tert*-butyldimethylsilyloxy)-2-butenoate, (*E*)-**21c**, appears much better as regard

either the selectivity or the overall yield than those previously reported[19]. Moreover, a similar procedure could be used to prepare many other 3-(hetero)aryl-5(H)-2-furanones starting from compound (*E*)-**21c**.

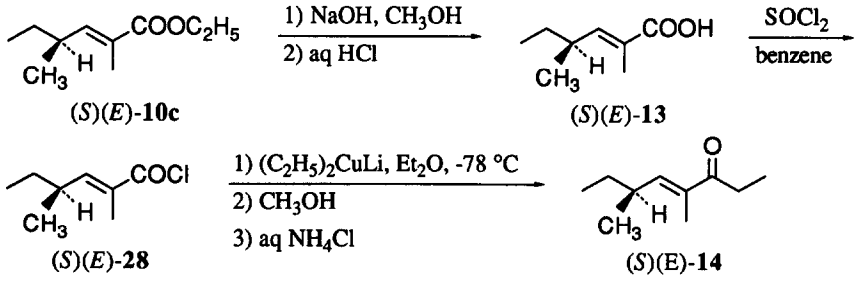


(Z)-**9d** **12** (5)

D) Synthesis of (S)(E)-4,6-dimethyl-4-octen-3-one, (S)(E)-14

Finally, to demonstrate the synthetic utility of the procedure developed for the preparation of esters (*E*)-**10**, we applied it to the synthesis of (*S*)(*E*)-4,6-dimethyl-4-octen-3-one (manicone), (*S*)(*E*)-**14**[20], an alarm pheromone component of ants in the genus *Manica*[9,10]. In particular, according to a reaction sequence very similar to that previously employed to prepare racemic **14**[21] starting from (*R*)(*S*)-2,4-dimethyl-2-hexenoic acid, (*R*)(*S*)(*E*)-**13**[16f], ethyl (*S*)(*E*)-2,4-dimethyl-2-hexenoate, (*S*)(*E*)-**10c**, was quantitatively hydrolyzed to the corresponding carboxylic acid, (*S*)(*E*)-**13** (Scheme 2).

Scheme 2



(*S*)(*E*)-**10c** (*S*)(*E*)-**13** (*S*)(*E*)-**28** (*S*)(E)-**14**

This compound, having $[\alpha]_D^{24}$ +35.84 (c = 2.715, benzene), which is present in a form of unknown configuration in the mandibular glands of male carpenter ants in the genus *Camponotus* and represents a caste-specific substance[8], was converted to the corresponding acid chloride, (*S*)(*E*)-**28**, with thionyl chloride. This was then treated with lithium diethylcuprate in Et_2O solution at -78 °C to give the desired compound (*S*)(*E*)-**14** in *ca.* 85% isolated yield (Scheme 2).

Since recently it has been reported[20c] that (*S*)(*E*)-4,6-dimethyl-4-octen-3-one having $[\alpha]_D^{20}$ +43.80 (c = 5, Et_2O) has 97% optical purity, compound (*S*)(*E*)-**14** synthesized according to the above reported reaction sequence and having $[\alpha]_D^{20}$ +44.27 (c = 4.82, Et_2O), had 98% optical purity.

D) Conclusions

The investigations described herein showed that the palladium-catalyzed cross-coupling reactions between (hetero)arylzinc halides and alkyl (*E*)-2-iodo-2-alkenoates (*E*)-**21**, which are easily available starting from the corresponding alkyl 2-alkynoates, **15**, provide good yields of alkyl 2-(hetero)aryl-2-alkenoates of general formula **9** having very high stereoisomeric purity. It was also shown that, although the palladium-

catalyzed reactions between compounds (*E*)-**21** and 1-alkenylzinc chlorides or methylzinc chloride are significantly less efficient as regards either the yields or the stereoisomeric purities of the desired cross-coupling products, the reaction between compounds (*E*)-**21** and a molar excess of lithium dimethylcuprate, followed by treatment with methyl iodide, in the presence of HMPA, allows to prepare 98 - 99 % stereoisomerically pure alkyl (*E*)-2-methyl-2-alkenoates, (*E*)-**10**, in high yield.

Furthermore, we demonstrated the utility of the procedure developed to prepare esters **9** and (*E*)-**10**. In fact, compound **9c** was employed in a very simple and efficient synthesis of 3-phenyl-5(H)-2-furanone, **12**, a metabolite of the hypnotic drug *glutethimide*. On the other hand, ester (*S*)(*E*)-**10c** was used to prepare two chiral insect pheromone components having very high optical purities, *i.e.* (*S*)(*E*)-2,4-dimethyl-2-hexenoic acid, (*S*)(*E*)-**13**, and (*S*)(*E*)-4,6-dimethyl-4-octen-3-one, (*S*)(*E*)-**14**.

EXPERIMENTAL

GLC analyses were performed on a Dani 6500 gas-chromatograph equipped with a Perkin Elmer LCI-100 integrator. Two types of capillary columns were used: a SRL-300 bonded FSOT column (30 m x 0.25 mm i.d.) and a SE-30 bonded FSOT column (30 m x 0.25 mm i.d.). Purifications by MPLC were performed on a Jobin-Yvon Chromatospac Prep-10 instrument using a Knauer differential refractometer as detector, or a Büchi 681 instrument, using a Bischoff 8100 differential refractometer as detector.

GLC/MS analyses were performed using a VG 70-70E spectrometer interfaced with a Dani 3800 gas-chromatograph. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz or on a Varian VXR 300 MHz spectrometer using TMS as an internal standard. Optical rotations were measured on a Perkin Elmer 142 polarimeter.

All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive solutions were transferred with hypodermic syringes or double-ended needles.

The following compounds were prepared according to the literature: $Pd(PPh_3)_4$[22], $PdCl_2(dppf)$[23], 3-(*tert*-butyldimethylsilyloxy)-1-propyne, **16b**[24] and ethyllithium in Et_2O solution[25].

Ethyl 4-(tert-butyldimethylsilyloxy)-2-butynoate, 15c

According to the literature[26] to a solution of 3-(*tert*-butyldimethylsilyloxy)-1-propyne, **16b** (25.85g, 138.9 mmol) in THF (400 ml), which was cooled to -78 °C, was added a 1.82 *M* Et_2O solution of MeLi (84 ml, 152.8 mmol) and the resulting solution was stirred at -78 °C for 1 h and at -20 °C for 1 h. Ethyl chloroformate (15.9 ml, 167.0 mmol) was slowly added and the reaction mixture was stirred at -20 °C for 1 h and at room temperature for 2 h. It was then poured into a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic extract was washed with water, dried, concentrated *in vacuo* and distilled to give compound **15c** (16.2 g, 48% yield): b.p. 81-82 °C/0.3 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 4.43 (2H, s, H-4)), 4.24 (2H, q, J = 7.1 Hz, OCH_2), 1.31 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.91 (9H, s, $(CH_3)_3C$), 0.14 ppm (6H, s, $Si(CH_3)_2$).

The spectral properties of this compound were in good agreement with those previously reported[26].

*Ethyl 3-phenylpropynoate, **15b***

This ester (32 g, 65% yield) was prepared starting from phenylacetylene, **16a**, *via* a procedure very similar to that employed for the synthesis of compound **15c** (see above). Compound **15b** had: b.p. 98-100 °C/0.25 Torr (lit[27] b.p. 75-76 °C/0.02 Torr). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.75-7.30 (5H, m, C_6H_5), 4.31 (2H, q, J = 7.1 Hz, OCH_2), 1.36 ppm (3H, t, J = 7.1 Hz, CH_3).

(S)-2-Methylbutanal, (S)-18

A three-necked flask, which was equipped with a mechanical stirrer and a separatory funnel and was connected through a Hempel column to a receiver cooled at -40 °C, was charged with (*S*)-2-methyl-1-butanol, (*S*)-**17** (65.0 g, 0.738 mol) having $[\alpha]_D^{25}$ -5.80 (neat). To this compound which was heated under stirring to 70 °C at 205 Torr was added during 15 min a mixture of $K_2Cr_2O_7$ (67.8g, 0.232 mol), concentrated sulfuric acid (55 ml) and water (400 ml). Upon completion of addition the reaction mixture was stirred for additional 20 min at 70 °C. The product contained into the receiver was fractionally distilled under nitrogen, in the presence of a large excess of water, and the distillate having b.p. 77 °C was separated from water and dried to give (*S*)-2-methylbutanal, **18** (16.3 g, 26% yield): b.p. 91.5-92 °C, $[\alpha]_D^{25}$ +34.33 (neat) [lit[11] b.p. 91.5-92 °C, $[\alpha]_D^{25}{}_{max}$ +35.1 (neat)].

The distillate having b.p. 94.8 °C was separated from water and dried to give unreacted (*S*)-2-methyl-1-butanol, (*S*)-**17**, (38.0 g) having $[\alpha]_D^{25}$ -5.78 (neat).

(S)-1,1-Dibromo-3-methyl-1-pentene, (S)-19

A mixture of zinc dust (41.06 g, 0.628 mol), CBr_4 (172.6 g, 0.520 mol) and PPh_3 (136.4 g, 0.520 mol) in CH_2Cl_2 (1500 ml) was stirred under nitrogen at room temperature for 96 h. This mixture was cooled to 0 °C and (*S*)-2-methylbutanal, (*S*)-**18** (18.0 g, 0.209 mol) was added. The resulting mixture was stirred for 30 min at 0 °C and at room temperature for 6 h. It was then filtered and the filtrate was concentrated under reduced pressure (450 Torr). The residue was diluted with pentane and filtered. The filtrate was concentrated under reduced pressure, diluted with pentane, filtered and concentrated. The residue was fractionally distilled to give (*S*)-**19** (41.0 g, 81% yield): b.p. 85-86 °C/36 Torr; $[\alpha]_D^{25}$ +17.30 (c = 13.35, heptane) [lit[12] b.p. 43 °C/0.01 Torr; $[\alpha]_D^{25}$ + 16.85 (c = 13.17, heptane)].

Ethyl (S)-4-methyl-2-hexynoate, (S)-15d

To a cold (-78 °C) stirred solution of the dibromoalkene (*S*)-**19** (36.3 g, 0.150 mol) in THF (850 ml) was added a solution of MeLi in Et_2O (282 ml, 0.518 mol). After the solution had been stirred at -78 °C for 1 h and at room temperature for 3 h, it was cooled to -40 °C. Ethyl chloroformate (35.8 ml, 0.373 mol) was added slowly and the reaction mixture was stirred at -40 °C for 0.5 h and then allowed to warm to room temperature. After stirring for 14 h saturated aqueous $NaHCO_3$ solution and Et_2O were added and the layers separated. The organic layer was washed with aqueous $NaHCO_3$, dried, concentrated and fractionally distilled to give compound (*S*)-**15d** (11.8 g, 51% yield): b.p. 90 °C/10 Torr. MS, *m/z* (%): 139 (M^+-15, 15), 126 (17), 109 (100), 95 (10), 81 (48), 79 (21), 67 (13), 53 (27), 41 (11). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 4.21 (2H, q, J = 7.1 Hz, OCH_2), 2.51 (1H, *pseudo*-sext, J = 7.0 Hz, H-4), 1.54 (2H, *pseudo*-quint, J = 7.2 Hz, H-5), 1.31 (3H, t, J = 7.1 Hz, -O-C-CH_3), 1.22 (3H, d, J = 7.0 Hz, C-C(CH_3)-C), 1.02 ppm (3H, t, J = 7.2

Hz, H-6). $[\alpha]_D^{25}$ +36.24 (c = 5.905, heptane). Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.79; H, 9.48.

GLC analysis showed that compound (*S*)-**15d** had chemical purity higher than 99%.

*Methyl (E)-2-tributylstannyl-2-octenoate, (E)-**8a***

A degassed solution of Bu_3SnH (18.85 g, 64.86 mmol) in dry THF (55 ml) was added during 2 h to a solution of methyl 2-octynoate, **15a** (10.0 g, 64.86 mmol) and $Pd(PPh_3)_4$ (1.49 g, 1.29 mmol) in THF (55 ml), which was stirred at 20 °C under argon. After 2 h an aliquot of the reaction mixture was removed by syringe for GLC analysis. Evidence for complete reaction was the absence of compound **15a**. THF was removed under reduced pressure and the residue was diluted with hexane (800 ml). After 1 h the precipitated palladium catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was diluted with hexane (500 ml), filtered on Celite and concentrated. GLC/MS analysis of the residue showed the presence of two compounds in a *ca.* 92:8 molar ratio. This residue was purified by MPLC on silica gel using a mixture of hexane and Et_2O (99:1 *v/v*) as eluant to give compound (*E*)-**8a** (24.5 g; 85% yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.05 (1H, t, J = 7.1 Hz, H-3), 3.69 (3H, s, OCH_3), 2.41 (2H, *pseudo*-q, J = 7.1 Hz, H-4), 1.65–1.13 (18H, m, H-2', H-3', H-5, H-6 and H-7), 1.10–0.75 ppm (18H, m, H-4', H-1' and H-8). MS, *m/z* (%): 393 (16), 391 (15), 390 (16), 389 (100), 388 (40), 387 (74), 385 (40), 357 (15), 265 (9), 179 (13), 151 (20), 121 (6). Anal. Calcd. for $C_{21}H_{42}O_2Sn$: C, 56.64; H, 9.51. Found: C, 56.74; H, 9.70.

GLC and ^1H NMR analyses showed that stereoisomerically pure (*E*)-**8a** had chemical purity higher than 99%.

By comparison of the ^1H NMR spectrum of this compound with that of the above mentioned residue, it was possible to obtain the ^1H NMR parameters of the minor component of the reaction mixture. This component, which corresponded to methyl (*E*)-3-tributylstannyl-2-octenoate, (*E*)-**20a**, had ^1H NMR ($CDCl_3$, 200 MHz): δ 5.94 (1H, t, J = 1.2 Hz, H-2), 3.68 (3H, s, OCH_3), 2.87 (2H, br t, J = 6.9 Hz, H-4), 1.68-1.16 (18H, m, H-2', H-3', H-5, H-6 and H-7), 1.13-0.77 ppm (18H, m, H-4', H-1', H-8). MS, *m/z* (%): 393 (17), 391 (16), 390 (18), 389 (100), 388 (40), 387 (73), 385 (42), 333 (15), 277 (13), 177 (9), 151 (11).

It is interesting to note that, in an attempt to purify the crude reaction mixture by fractional distillation, it was observed that compound (*E*)-**8a** underwent partial stereomutation. In fact, the ^1H NMR spectrum of the main fraction of the distillation, which had b.p. 112 °C/00.3 Torr showed signals attributable to the presence of ca. 28% of compound (*Z*)-**8a**. This compound had ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.38 (1H, t, J = 7.4 Hz, H-3), 3.70 (3H, s, OCH_3), 2.16 (2H, *pseudo*-q, J = 7.4 Hz, H-4), 1.65-1.13 (18H, m, H-2', H-3', H-5, H-6 and H-7), 1.10-0.75 ppm (18H, m, H-4', H-1' and H-8).

*Ethyl (E)-3-phenyl-2-tributylstannyl-2-propenoate, (E)-**8b***

A degassed solution of Bu_3SnH (18.5 ml, 68.96 mmol) in dry THF (60 ml) was added during 2 h to a solution of ethyl 3-phenylpropynoate, **15b** (12.0 g, 68.96 mmol) and $Pd(PPh_3)_4$ (1.66 g, 1.44 mmol) in THF (60 ml), which was stirred under argon at room temperature. The reaction mixture, which was stirred for 3.5 h at room temperature, was worked up using the same procedure employed to prepare compound (*E*)-**8a**. The

crude reaction product was analyzed by GLC/MS and showed the presence of two compounds in a *ca.* 90:10 molar ratio. Purification by MPLC on silica gel using a mixture of benzene and hexane (70:30 *v/v*) as eluant, allowed to isolate the main component, (*E*)-**8b** (22.7 g, 71% yield). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.48-7.13 (5H, m, C_6H_5), 6.71 (1H, s, H-3), 4.18 (2H, q, J = 7.1 Hz, O-CH_2), 1.78-1.26 (12H, m, H-2' and H-3'), 1.22 (3H, t, J = 7.1 Hz, O-C-CH_3), 1.07 (6H, t, J = 8.1 Hz, H-1'), 0.91 ppm (9H, t, J = 7.1 Hz, H-4'). MS, *m/z* (%): 409 (M^+- C_4H_9, 100), 407 (73), 406 (33), 405 (44), 365 (17), 295 (27), 293 (20), 251 (48), 249 (40), 247 (24), 237 (26), 235 (19), 179 (93), 178 (26), 177 (91), 176 (32), 175 (62), 165 (96), 163 (73), 161 (46), 121 (66), 91 (38), 57 (29). Anal. Calcd. for $C_{23}H_{38}O_2Sn$: C, 59.40; H, 8.23. Found: C, 59.60; H, 8.36.

GLC analysis showed that compound (*E*)-**8b** had chemical purity higher than 98%.

By comparison of the ^{1}H NMR spectrum of this compound with that of the crude reaction mixture it was possible to obtain the ^{1}H NMR parameters of the minor component of the reaction mixture. This component, which corresponded to ethyl (*E*)-3-tributylstannyl-3-phenyl-2-propenoate, (*E*)-**20b**, had: ^{1}H NMR ($CDCl_3$, 200 MHz):δ 7.43-6.85 (5H, m, C_6H_5), 6.12 (1H, s, H-3), 3.98 (2H, q, J = 7.1 Hz, O-CH_2), 1.65-1.15 (12H, m, H-2' and H-3'), 1.04 (3H, t, J = 7.1 Hz, O-C-CH_3), 1.00-0.70 ppm (15H, m, H-1' and H-4'). MS, *m/z* (%): 409 (M^+ - C_4H_9, 62), 408 (27), 407 (49), 406 (17), 405 (25), 353 (6), 291 (13), 267 (16), 223 (20), 221 (15), 179 (72), 177 (90), 175 (66), 147 (46), 137 (38), 135 (29), 133 (23), 131 (23), 121 (64), 120 (54), 116 (38), 103 (100), 102 (30), 91 (26), 77 (20), 57 (15).

Ethyl (E)-4-(tert-butyldimethylsilyloxy)-2-tributylstannyl-2-butenoate, (E)-8c

A degassed solution of Bu_3SnH (16,8 ml, 62.27 mmol) in dry THF (100 ml) was added during 1.5 h to a solution of ethyl 4-(*tert*-butyldimethylsilyloxy)-2-butynoate, **15c** (16 g, 66.11 mmol) and $Pd(PPh_3)_4$ (1.59 g, 1.37 mmol) in THF (100 ml) which was stirred under argon at room temperature. After stirring for 4 h at room temperature the reaction mixture was worked up using a procedure very similar to that employed in the preparation of compound (*E*)-**8a**. The crude reaction product was purified by MPLC on silica gel, using a mixture of hexane and benzene (70:30 *v/v*) as eluant, to give compound (*E*)-**8c** (29.8 g, 85% yield). MS, *m/z* (%): 480 (18), 479 (19), 478 (28), 477 (100), 476 (75), 475 (33), 474 (41), 431 (15), 317 (9), 277 (7), 235 (8), 179 (32), 178 (32), 121 (19), 119 (15), 75 (31), 73 (76). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 6.30 (1H, t, J = 4.6 Hz, H-3), 4.63 (2H, J = 4.6 Hz, H-4), 4.14 (2H, q, J = 7.1 Hz, OCH_2), 1.60-1.20 (15H, br m, O-C-CH_3, H-2' and H-3'), 1.05-0.80 (24H, m, $(CH_3)_3C$, H-1' and H-4'), 0.08 ppm (6H, s, $Si(CH_3)_2$). Anal. Calcd. for $C_{24}H_{50}O_3SiSn$: C, 54.04; H, 9.45. Found: C, 54.39; H, 9.78.

GLC analysis showed that compound (*E*)-**8c** had stereoisomeric purity higher than 99% and regioisomeric purity higher than 98.5%.

Concentration of the first eluted chromatographic fractions allowed to isolate ethyl (*E*)-4-(*tert*-butyldimethylsilyloxy)-3-tributylstannyl-2-butenoate, (*E*)-**20c** (1.68 g, 5% yield). MS, *m/z* (%): 477 (16), 365 (27), 363 (22), 281 (20), 279 (15), 195 (22), 194 (18), 121 (12), 73 (60), 57 (100). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 5.88 (1H, t, J = 2.6 Hz, H-3), 4.88 (2H, d, J = 2.6 Hz, H-4), 4.14 (2H, q, J = 7.1 Hz, OCH_2), 1.60-1.20 (15H, br m, O-C-CH_3, H-2' and H-3'), 1.10-0.80 (24H, m, $(CH_3)_3C$, H-1' and H-4'), 0.10 ppm (6H, s, $Si(CH_3)_3$). GLC analysis showed that compound (*E*)-**20c** had chemical purity higher than 97%.

Ethyl (S)(E)-4-methyl-2-tributylstannyl-2-hexenoate, (S)(E)-8d

A degassed solution of Bu_3SnH (19.5 ml, 72.69 mmol) in dry THF (100 ml) was added during 1.5 h to a solution of ethyl (*S*)-4-methyl-2-hexynoate, (*S*)-**15d**, (11.40 g, 73.93 mmol) and $Pd(PPh_3)_4$ (1.85 g, 1.60 mmol) in THF (100 ml), which was stirred under argon for 3.5 h at room temperature. After this period the reaction mixture was worked up using a procedure very similar to that employed in the preparation of compound (*E*)-**8a**. GLC/MS analysis of the crude reaction product showed the presence of two new compounds in a *ca.* 98:2 molar ratio. Purification by MPLC on silica gel, using a mixture of hexane and benzene (75:25 *v/v*) as eluant, allowed to isolate compound (*S*)(*E*)-**8d** (30.0 g, 93% yield): $[\alpha]_D^{25}$ +23.63 (c = 2.535, heptane). ^1H NMR ($CDCl_3$, 200 MHz), δ: 5.73 (1H, d, J = 9.6 Hz, H-3), 4.14 (2H, q, J = 7.1 Hz, OCH_2), 2.94–2.74 (1H, m, H-4), 1.61–1.20 (14H, br m, H-5, H-2' and H-3'), 1.28 (3H, t, J = 7.1 Hz, O-C-CH_3), 1.02–0.73 (12H, m, H-6, C-C(CH_3)-C, and H-1), 0.89 ppm (9H, t, J = 7.1 Hz, H-4'). MS, *m/z* (%): 390 (16), 389 (M^+ - C_4H_9, 100), 388 (39), 387 (74), 386 (30), 385 (40), 345 (25), 343 (20), 235 (16), 179 (33), 177 (32), 175 (20), 165 (20), 121 (15). Anal. Calcd. for $C_{21}H_{42}O_2Sn$: C, 56.64; H, 9.51. Found: C, 56.42; H, 9.73.

GLC analysis showed that compound (*S*)(*E*)-**8d** had chemical purity higher than 99%.

Methyl (E)-2-iodo-2-octenoate, (E)-21a

A solution of iodine (10.37 g, 40.8 mmol) in dry CH_2Cl_2 (400 ml) was added during 3.5 h to a solution of compound (*E*)-**8a** (18.17 g, 40.8 mmol) in dry CH_2Cl_2 (250 ml), which was stirred at 20 °C under argon. Upon completion of addition the reaction mixture was stirred for additional 2 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 ml) and stirred with a semisaturated aqueous solution of KF (300 ml) at room temperature for 2.5 h. The reaction mixture was filtered and the filtrate was extracted with Et_2O. The organic extract was dried and concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (85:15 *v/v*) as eluant, to give stereoisomerically pure (*E*)-**21a** (8.40 g, 73% yield). ^1H NMR ($CDCl_3$, 200 MHz), δ 6.92 (1H, t, J = 7.7 Hz, H-3), 3.79 (3H, s, OCH_3), 2.46 (2H, *pseudo*-q, J = 7.7 Hz, H-4), 1.50-1.20 (6H, m, H-5, H-6 and H-7), 0.89 ppm (3H, t, J = 6.4 Hz, H-8). MS, *m/z* (%): 283 (M^+ + 1, 11), 282 (M^+, 100), 239 (67), 213 (40), 211 (20), 181 (20), 155 (15), 112 (22), 95 (78), 81 (25). Anal. Calcd. for $C_9H_{15}IO$: C, 38.32; H, 5.36. Found: C, 38.59; H, 5.56.

Ethyl (E)-2-iodo-3-phenyl-2-propenoate, (E)-21b

This stereoisomerically pure compound, which was prepared in 89% yield starting from ethyl (*E*)-2-tributylstannyl-2-propenoate, (*E*)-**8b**, *via* a procedure very similar to that employed to prepare compound (*E*)-**21a**, had : ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.49 (1H, s, H-3), 7.45–7.12 (5H, m, C_6H_5), 4.19 (2H, q, J = 7.1 Hz, OCH_2), 1.17 ppm (3H, t, J = 7.1 Hz, CH_3). MS, *m/z* (%): 303 (M^+ +1, 17), 302 (M^+, 50), 257 (21), 175 (65), 147 (93), 129 (20), 103 (33), 102 (100), 77 (20), 76 (21), 51 (20). Anal. Cacd. for $C_{11}H_{11}IO_2$: C, 43.73; H, 3.67. Found: C, 44.07; H, 3.85.

Ethyl (E)-4-(tert-butyldimethylsilyloxy)-2-iodo-2-butenoate, (E)-21c

This regio- and stereoisomerically pure compound, which was prepared in 95% yield starting from ethyl (*E*)-4-(*tert*-butyldimethylsilyloxy)-2-tributylstannyl-2-butenoate,(*E*)-**8c**, according to a procedure very

similar to that employed to prepare compound (*E*)-**21a**, had: ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.11 (1H, t, J = 4.8 Hz, H-3), 4.59 (2H, d, J = 4.8 Hz, H-4) 4.23 (2H, q, J = 7.1 Hz, OCH_2), 1.33 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.90 (9H, s, $(CH_3)_3C$), 0.07 ppm (6H, s, $(CH_3)_2Si$). MS, *m/z* (%) 355 (M^+ - 15, 2), 325 (6), 315 (6), 314 (20), 313 (95), 285 (86), 284 (12), 211 (6), 158 (10), 103 (23), 99 (10), 76 (12), 75 (100), 73 (53), 59 (15). Anal. Calcd. for $C_{12}H_{23}IO_3Si$: C, 38.93; H, 6.26. Found: C, 38.39; H, 6.53.

*Ethyl (S)(E)-2-iodo-4-methyl-2-hexenoate, (S)(E)-**21d***

This stereoisomerically pure compound, which was prepared in 90% yield starting from ethyl (*S*)(*E*)-4-methyl-2-tributylstannyl-2-hexenoate, (*S*)(*E*)-**8d**, via a procedure very similar to that employed to prepare compound (*E*)-**21a**, had: $[\alpha]_D^{25}$ +41.31 (c = 2.520, hexane). ^{1}H NMR ($CDCl_3$, 200 MHz), δ 6.62 (1H, d, J = 10.4 Hz, H-3), 4.24 (2H, q, J = 7.1 Hz, OCH_2), 3.05–2.81 (1H, m, H-4), 1.52–1.18 (2H, m, H-5), 1.33 (3H, t, J = 7.1 Hz, O-C-CH_3), 1.01 (3H, d, J = 6.6 Hz, C-C(CH_3)-C), 0.87 ppm (3H, t, J = 7.4 Hz, H-6). MS, *m/z* (%): 282 (M^+, 100), 253 (14), 228 (26), 225 (39), 199 (21), 181 (20), 127 (28), 109 (52), 98 (33), 81 (65), 56 (94), 53 (45), 43 (65). Anal. Calcd. for $C_9H_{15}IO_2$: C, 38.32; H, 5.36. Found: C, 38.02; H, 5.49.

*Methyl (Z)-2-phenyl-2-octenoate, (Z)-**9a***

A 1.1 M solution of phenylmagnesium bromide (5.9 ml, 6.5 mol) was added to a stirred mixture of $ZnCl_2$ (0.974 g, 7.15 mmol) and THF (30 ml) which was maintained at -20 °C. To this mixture which was cooled to -30 °C was added a solution of compound (*E*)-**21a** (1.67g, 5.92 mmol) and $Pd(PPh_3)_4$ (0.547g, 0.474 mmol) in THF (30 ml) and the resulting mixture was stirred for 4 h at -30 °C and for 14 h at room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed with water, filtered, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (85:15 *v/v*) as eluant, to give compound (*Z*)-**9a** (1.04 g, 76% yield). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.35–7.23 (5H, m, C_6H_5), 6.18 (1H, t, J = 7.6 Hz, H-3), 3.79 (3H, s, OCH_3), 2.44 (2H, *pseudo*-q, J = 7.6 Hz, H-4), 1.60–1.20 (6H, m, H-5, H-6, and H-7), 0.90 ppm (3H, t, J = 6.9 Hz, H-8). MS, *m/z* (%): 233 (M^+ + 1, 18), 232 (M^+, 95), 201 (11), 189 (19), 163 (18), 162 (100), 158 (58), 129 (45), 115 (70), 104 (40), 91 (32), 77 (10), 59 (8), . Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.87; H, 8.75.

GLC analysis showed that compound (*Z*)-**9a** had chemical purity higher than 99%.

*Ethyl (Z)-2,3-diphenyl-2-propenoate, (Z)-**9b***

This compound, which was prepared in 82% yield starting from ethyl (*E*)-2-iodo-3-phenyl-2-propenoate, (*E*)-**21b**, *via* a procedure very similar to that employed to prepare (*Z*)-**9a**, had: ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.55–7.15 (10H, m, $2C_6H_5$), 7.02 (1H, s, H-3), 4.26 (2H, q, J = 7.1 Hz, OCH_2), 1.17 ppm (3H, t, J = 7.1 Hz, CH_3). MS, *m/z* (%): 253 (M^+ + 1, 18), 252 (M^+, 100), 207 (14), 179 (65), 152 (8), 135 (38), 107 (18), 44 (8). Anal. Calcd. for $C_{17}H_{16}0_2$: C, 80.92; H, 6.39. Found: C, 80.85; H, 6.38.

The spectral properties of this compound, which on the basis of GLC and ^{1}H NMR analyses had stereoisomeric purity higher than 99%, were in satisfactory agreement with those previously reported[28].

Ethyl (E)-3-phenyl-2-(2-thienyl)-2-propenoate, (E)-9c

A 1.17 *M* THF solution of 2-thienylmagnesium bromide (33 ml, 38.6 mmol) was added to a stirred solution of $ZnCl_2$ (5.80 g, 42.57 mmol) in THF (50 ml) which was maintained at -25 °C. After stirring for 0.5 h, a solution of compound (*E*)-**21b** (6.50 g, 21.5 mmol) and $Pd(PPh_3)_4$ (2.08 g, 1.80 mmol) in THF (110 ml) was added and the resulting mixture was stirred at -25 °C for 3 h and at room temperature for 3.5 h. It was then poured into a large excess of a saturated aquous NH_4Cl solution and extracted with Et_2O.The organic extract was washed with water, filtered, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (55:45 *v/v*) as eluant, to give compound (*E*)-**9c** (4.06 g, 73% yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.45–7.20 (5H, m, C_6H_5), 7.20 (1H, dd, J = 5.1 and 1.1 Hz, H-5'), 7.08 (1H, dd, J = 3.7 and 1.1 Hz, H-3'), 7.05 (1H, s, H-3), 6.98 (1H, dd, J = 5.1 and 3.7 Hz, H-4'), 4.27 (2H, q, J = 7.1 Hz, OCH_2), 1.18 ppm (3H, t, J = 7.1 Hz, CH_3). MS, *m/z* (%): 259 (M^+ + 1, 18), 258 (M^+, 100), 213 (8), 185 (65), 184 (58), 152 (17), 135 (85), 107 (54), 92 (12), 79 (15), 63 (6), 51 (9). Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.74,; H, 5.46. Found: C, 69.45; H, 5.14.

GLC analysis showed that compound (*E*)-**9c** had stereoisomeric purity higher than 98%.

Ethyl (Z)-4-(tert-butyldimethylsilyloxy)-2-phenyl-2-butenoate, (Z)-9d

A 1.15 M THF solution of phenylmagnesium bromide (85.2 ml, 97.92 mmol) was added to a stirred solution of $ZnCl_2$ (14.69 g, 107.71 mmol) in THF (50 ml) which was maintained at -23 °C. After stirring for 15 minutes at this temperature, a solution of compound (*E*)-**21c** (18.29 g, 49.39 mmol) and $Pd(PPh_3)_4$ (3.89 g, 3.38 mmol) in THF (220 ml) was added and the resulting mixture was stirred for 3.5 h at -23 °C and for 16 h at room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and exctracted with Et_2O. The organic extract was washed with water, filtered, dried and concentrated *in vacuo*. A GLC/MS analysis of the residue showed the presence of a new compound together with two minor components. Two of these substances were subsequently identified as (Z)-**9d** and ethyl (Z)-2,4-diphenyl-2-propenoate, (*Z*)-**22**. The third component, which could not be isolated and fully characterized, had a MS spectrum very similar to that of compound (*Z*)-**22**, and, on this basis, it was believed to correspond to compound (*E*)-**22**.

Purification of the residue by MPLC on silica gel, using a mixture of hexane and Et_2O (97:3 *v/v*) as eluant, allowed to isolate compound (*Z*)-**9d** (8.83 g, 56% yield): ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.73 (5 H, br, C_6H_5), 6.35 (1H, t, J = 5.1 Hz, H-3), 4.67 (2H, d, J = 5.1 Hz, H-4), 4.26 (2H, q, J = 7.1 Hz, OCH_2), 1.29 (3H, t, J = 7.1 Hz, O-C-CH_3), 0.92 (9H, s, $(CH_3)_3C$), 0.10 ppm (6H, s, $(CH_3)_2Si$). MS, *m/z* (%): 320 (M^+, 1), 305 (2), 275 (7), 263 (100), 251 (41), 173 (21), 143 (8), 115 (30), 75 (67), 59 (7). Anal. Calcd. for $C_{16}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.60; H, 9.00.

Concentration of the last eluted chromatographic fractions allowed to isolate compound (*Z*)-**22** (0.33 g, 3% yield): ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.50-7.10 (10H, m, 2 C_6H_5), 6.29 (1H, t, J = 7.7 Hz, H-3), 4.34 (2H, q, J = 7.1 Hz, OCH_2), 3.77 (2H, d, J = 7.7 Hz, H-4), 1.33 ppm (3H, t, J = 7.1 Hz, O-C-CH_3). MS, *m/z* (%): 266 (M^+, 100), 220 (50), 191 (56), 165 (9), 135 (11), 115 (46), 91 (36), 77 (9), 65 (11), 39 (6). Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.90; H, 7.01.

*Palladium-catalyzed reaction between methyl (E)-2-iodo-2-octenoate, (E)-**21a**, and 2-methyl-1-propenylzinc chloride*

A 0.65 *M* THF solution of 2-methyl-1-propenylmagnesium bromide (32.2 ml, 20.0 mmol) was added to a stirred solution of $ZnCl_2$ (2.86 g, 21.0 mmol) in THF (50 ml), cooled to -25 °C. After stirring for 0.5 h, a solution of compound (*E*)-**21a** (4.40g, 15.6 mmol) and $Pd(PPh_3)_4$ (1.43 g, 1.24 mmol) in THF (50 ml) was added. The resulting mixture was stirred at -25 °C for 3.5 h, at room temperature for 16 h and under reflux for 4 h. It was then cooled to room temperature and poured into a large excess of a saturated aqueous solution of NH_4Cl solution and extracted with Et_2O. The organic extract was washed with water, dried and concentrated *in vacuo*. A GLC/MS analysis of the residue showed the presence of two new compounds, subsequently identified as (*Z*)- and (*E*)-2-(2-methyl-1-propenyl)-2-octenoate, (*Z*)- and (*E*)-**11a**, respectively, together with methyl and (*Z*)- and (*E*)-2-octenoate, (*Z*)- and (*E*)-**23a**, respectively, 7,8-di(carbomethoxy)-6,8-tetradecadiene, **24**, and minor components. Compounds (*Z*)- and (*E*)-**11**, (*Z*)- and (*E*)-**23**, and **24** were present in a *ca.* 62:3:4:11:20 molar ratio, respectively. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (70:30 *v/v*) as eluant. Concentration of the first eluted chromatographic fractions allowed to isolate compound (*Z*)-**11a** having chemical purity higher than 96% (0.95 g, 29% yield). ^1H NMR ($CDCl_3$, 200 MHz), δ 5.63 (1H, br t, J = 7.2 Hz, H-3), 5.85–5.81 (1H, m, C<u>H</u>=$C(CH_3)_2$), 3.75 (3H, s, OCH_3), 2.42 (2H, *pseudo*-q, J = 7.2 Hz, H-4), 1.79 (3H, d, J = 1.1 Hz, C=$C(CH_3)$), 1.68 (3H, d, J = 1.2 Hz, C=$C(CH_3)$), 1.54–1.23 (6H, m, H-5, H-6 and H-7), 0.89 ppm (3H, d, J = 6.5 Hz, H-8). MS, *m/z* (%): 210 (M^+, 64), 167 (8), 125 (11), 107 (21), 95 (18), 93 (44), 91 (29), 81 (24), 80 (15), 79 (55), 77 (48), 67 (24), 65 (19), 60 (16), 55 (25), 53 (31), 41 (100), 40 (52). Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74,24; H, 10.54. Found: C, 73.96; H, 10.64.

Fractional distillation of the last eluted chromatographic fractions allowed to isolate compound **24** (0.38 g, 16% yield): ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.11 (2H, t, J = 7.4 Hz, H-6 and H-9), 2.70 (6H, s, OCH_3), 2.53 (4H, *pseudo*-q, J = 7.4 Hz, H-5 and H-10), 1.60–1.15 (12H, br m, H-2, H-3, H-4, H-11, H-12 and H-13), 0.90 ppm (6H, t, J = 6.6 Hz, H-1 and H-14). Ms, *m/z* (%): 310 (M^+, 17), 279 (40), 278 (95), 251 (21), 339 (71), 236 (19), 235 (100), 221 (22), 219 (24), 175 (19), 105 (21), 93 (21), 91 (35), 79 (30), 77 (22), 59 (41), 55 (40). Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.83; H, 10.00.

*Palladium-catalyzed reaction between methyl (E)-2-iodo-2-octenoate, (E)-**21a**, and methylzinc chloride*

A 3.55 *M* Et_2O solution of methylmagnesium bromide (7.52 ml, 26.7 mmol) was added to a stirred solution of $ZnCl_2$ (4.01 g, 29.4 mmol) in THF (50 ml) which was maintained at -20 °C. After stirring for 0.5 h and cooling at -30 °C, a solution of compound (*E*)-**21a** (6.85 g, 24.3 mmol) and $Pd(PPh_3)_4$ (1.40 g, 1.21 mmol) in THF (120 ml) was added and the resulting mixture was stirred for 4 h at -30 °C and for 18 h at room temperature. After this period a GLC analysis of a small sample of the reaction mixture, which was hydrolyzed with aqueous NH_4Cl, showed that compound (*E*)-**21a** was also present. Therefore the reaction mixture was refluxed for 4 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed with water, dried, filtered and concentrated *in vacuo*. GLC/MS analysis of the residue showed the presence of four new compounds in a 8:56:13:23 molar ratio, which were subsequently identified as methyl (*Z*)-2-octenoate, (*Z*)-**23a**, methyl (*Z*)-2-methyl-2-octenoate, (*Z*)-**10a**,

methyl (*E*)-2-methyl-2-octenoate, (*E*)-**10a**, and 7,8-di(carbomethoxy)-6,8-tetradecadiene, **24**, respectively. The residue was purified by MPLC on silica gel using a mixture of hexane and benzene (85:15 *v/v*) as eluant, to give 81% stereoisomerically pure (*E*)-**10a** (1.77 g, 43% yield): ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 5.94 (1H, dq, J = 7.4 and 1.5 Hz, H-3), 3.73 (1H, s, OCH_3), 2.45 (2H, *pseudo*-q, J = 7.4 Hz, H-4), 1.89 (3H, *pseudo*-q, CH_3–C=), 1.50-1.10 (6H, m, H-5, H-6 and H-7), 0.88 ppm (3H, t, J = 6.4 Hz, H-8). MS, *m/z* (%): 170 (M^+, 48), 139 (21), 129 (13), 127 (100), 115 (11), 114 (11), 101 (63), 95 (35), 88 (48), 84 (11), 82 (14), 81 (13), 69 (35), 67 (27), 59 (17), 55 (60).

The spectral properties of this compounds were in satisfactory agreement with those previously reported[29].

From the first eluted chromatographic fractions it was possible to isolate a small amount of compound (*Z*)-**23a**. ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 6.24 (1H, dt, J = 11.6 and 7.5 Hz, H-3), 5.78 (1H, dt, J = 11.6 and 1.7 Hz, H-2), 3.71 (3H, s, OCH_3), 2.65 (2H, *pseudo*-dq, J = 7.4 and 1.7 Hz, H-4), 1.50-1.10 (6H, m, H-5, H-6 and H-7), 0.88 ppm (3H, t, J = 6.4 Hz, H-8). MS, *m/z* (%): 156 (M^+, 84), 125 (56), 114 (40), 113 (100), 100 (38), 87 (57), 82 (38), 81 (87), 74 (51), 69 (37), 59 (30), 55 (78).

Finally, from the last eluted chromatographic fractions it was recovered compound **24** (0.71 g, 19% yield) having spectral properties very similar to those of the main by-product formed in the palladium-catalyzed reaction between (*E*)-**21a** and 2-methyl-1-propenyl zinc chloride.

It must be noted that a worse result as regard either the yield or the stereoisomeric purity of compound (*Z*)-**10a**, was obtained when the reaction between compound (*E*)-**21a** and methylzinc chloride was carried out in the presence of 10 mol % of $PdCl_2$(dppf), using reaction conditions very similar to those above described.

Methyl (E)-2-methyl-2-octenoate, (E)-10a

A 1.867 *M* Et_2O solution of methyllithium in Et_2O (79.9 ml, 0.149 mol) was slowly added to a suspension of CuI (14.16 g, 74.55 mol) in Et_2O (100 ml) cooled to -78 °C. After stirring for 15 min a solution of methyl (*E*)-2-iodo-2-octenoate, (*E*)-**21a** (6.0 g, 21.27 mmol) in Et_2O (20 ml) was added and the reaction mixture was stirred for 4.5 h at -78 °C. GLC/MS analysis of a sample of this mixture, which was hydrolyzed with NH_4Cl, showed the presence of methyl (*E*)-2-octenoate, (*E*)-**23a**, together with a small amount of the a new compound, subsequently identified as methyl (*E*)-2-methyl-2-octenoate, (*E*)-**10a**. HMPA (50 ml) and methyl iodide (45.6 g, 0.32 mol) were sequentially added and the resulting mixture was stirred for 0.5 h at -78 °C and for 14 h at room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, washed with aqueous NH_4Cl, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (80:20 *v/v*) as eluant, to give compound (*E*)-**10a** (3.47 g, 96 yield). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 6.77 (1H, tq, J = 7.5 and 1.4 Hz, H-3), 3.73 (3H, s, OCH_3), 2.17 (2H, *pseudo*-q, J = 7.5 Hz, H-4), 1.83 (3H, d, J = 1.4 Hz, =C-CH_3), 1.55-1.20 (6H, m, H-5, H-6 and H-7), 0.89 ppm (3H, t, J = 5.8 Hz, H-8). MS, *m/z* (%): 170 (M^+, 32), 139 (31), 127 (54), 114 (14), 101 (100), 88 (85), 82 (25), 69 (60), 55 (90), 41 (74).

This compound had spectral properties in good agreement with those previously reported[29]. GLC analysis showed that (*E*)-**10a** had chemical and stereoisomeric purity higher than 98%.

*Ethyl (*E*)-2-methyl-3-phenyl-2-propenoate, (*E*)-**10b***

Following a procedure very similar to that employed to prepare compound (*E*)-**10a**, ethyl (*E*)-2-iodo-3-phenylpropenoate, (*E*)-**21b** (8.0 g, 26.49 mmol) was reacted at -78 °C with $(CH_3)_2CuLi$ (92.5 mmol) in Et_2O. After stirring at -78 °C for 4.5 h, HMPA (70 ml) and methyl iodide (57 g, 401 mmol) were sequentially added and the resulting mixture was stirred for 0.5 h at -78 °C and for 14 h at room temperature. It was then poured into a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed with aqueous NH_4Cl, dried and concentrated. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (55:45 *v/v*) as eluant, to give compound (*E*)-**10b** (4.38 g, 86.9%): ^1H NMR ($CDCl_3$), 200 MHz), δ: 7.69 (1H, q, J = 1.4 Hz, H-3), 7.50–7.22 (5H, m, C_6H_5), 4.27 (2H, q, J = 7.1 Hz, OCH_2), 2.12 (3H, d, J = 1.4 Hz, CH_3-C=), 1.35 ppm (3H, t, J = 7.1 Hz, CH_3-C-O). ^1H NMR (CCl_4, 200Mz): δ 7.59 (1H, q, J = 1.4 Hz, H-3), 7.48–7.15 (5H, m, C_6H_5), 4.21 (2H, q, J = 7.1 Hz, OCH_2), 2.07 (3H, d, J = 1.4 Hz, CH_3-C=), 1.33 ppm (3H, t, J = 7.1 Hz, CH_3-C-O). MS, *m/z* (%): 190 (M^+, 62), 161 (18), 145 (69), 118 (13), 117 (100), 116 (79), 115 (70), 91 (32), 77 (8), 51 (16).

The ^1H NMR data registered in CCl_4 solution were in satisfactory agrement with those previously reported[28]. GLC analysis showed that this compound had chemical and stereoisomeric purity higher than 99%.

*Ethyl (*S*)(*E*)-2,4-dimethyl-2-hexenoate, (*S*)(*E*)-**10c***

Following a procedure very similar to that employed to prepare compound (*E*)-**10a**, ethyl (*S*)(*E*)-2-iodo-4-methyl-2-hexenoate, (*S*)(*E*)-**21c** (15.30 g, 54.23 mmol) was reacted with $(CH_3)_2CuLi$ (189.3 mmol) in Et_2O solution. After stirring for 4 h at -78 °C, HMPA (140 ml) and methyl iodide (114 g, 803 mmol) were sequentially added and the resulting mixture was stirred for 0.5 h at -78 °C and for 14 h at room temperature. It was then poured into a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, washed with aqueous NH_4Cl, dried and concentrated. The residue was purified by MPLC on silica gel, using a mixture of pentane and Et_2O (97.5:2.5 *v/v*) as eluant, followed by fractional distillation to give compound (*S*)(*E*)-**10c** (7.46 g, 81% yield): b.p. 103.5 °C/26 Torr; $[\alpha]_D^{25}$ +41.09 (c = 3.395, CH_3OH). MS, *m/z* (%): 170 (M^+, 51), 141 (14), 125 (68), 113 (86), 109 (39), 97 (40), 96 (38), 95 (45), 87 (27), 69 (35), 67 (50), 56 (40), 55 (100), 43 (70), 41 (91). ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.53 (1H, dq, J = 10.1 and 1.4 Hz, H-3), 4.19 (2H, q, J = 7.1 Hz, OCH_2), 2.53–2.38 (1H, m, H-4), 1.84 (3H, d, J = 1.4 Hz, CH_3-C=), 1.36 (2H, *pseudo*-quint, H-5), 1.30 (3H, t, J = 7.1 Hz, CH_3-C-O), 1.00 (3H, d, J = 6.7 Hz, C-C(CH_3)-C), 0.86 ppm (3H, t, J = 7.5 Hz, H-6).

GLC analysis showed that this compound had chemical and stereochemical purity higher than 99%. Its physical properties were in satisfactory agreement with those previously reported for the corresponding racemic compound[21a,e].

*Reaction between ethyl (*E*)-2-iodo-3-phenyl-2-propenoate, (*E*)-**21b**, and lithium dibutylcuprate, followed by treatment with 1-iodobutane: ethyl (*E*)-3-phenyl-2-propenoate, (*E*)-**23b***

A 1.77 *M* hexane solution of butyllithium (97.7 ml, 173 mmol) was slowly added to a suspension of CuI (16.43g , 86.5 mmol) in Et_2O (250 ml) cooled to -50 °C. After stirring for 0.5 h a solution of ethyl (*E*)-2-

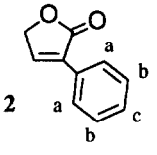
iodo-3-phenyl-2-propenoate, (*E*)-**21b** (7.5 g, 24.82 mmol) in Et_2O (40 ml) was added. After stirring for 4.5 h at -78 °C, HMPA (70 ml) and 1-iodobutane (55.2 g, 300 mmol) were sequentially added and the resulting mixture was stirred for 0.5 h at -78 °C and at room temperature for 18 h. It was then worked up according to the procedure employed for the preparation of compound (*S*)(*E*)-**10a**. The residue so obtained was purified by MPLC using a mixture of hexane and benzene (1:1 *v/v*) as eluant to give ethyl (*E*)-3-phenyl-2-propenoate, (*E*)-**23b** (2.8 g, 64% yield). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.69 (1H, d, J = 16.0 Hz, H-3), 7.57–7.44 (2H, m, H-*orto*), 7.44–7.30 (3H, m, H-*meta* and H-*para*), 6.44 (1H, d, J = 16.0 Hz, H-2), 4.26 (2H, q, J = 7.1 Hz, OCH_2), 1.33 ppm (3H, t, J = 7.1 Hz, CH_3).

GLC analysis showed that compound (*E*)-**23b** had chemical and stereochemical purity higher than 99%. The physical properties of this compound were in satisfactory agreement with those previously reported[30].

3-Phenyl-5(H)-2-furanone, 12

Ethyl (Z)-4-(*tert*-butyldimethylsilyloxy)-2-phenyl-2-butenoate, (Z)-**9d** (8.49 g, 26.49 mmol) was dissolved in a mixture of DMSO (81 ml), THF (4ml) and water (4 ml). N-Bromosuccinimide (5.19 g, 29.14 mmol) was then added and the mixture was stirred for 10 h at room temperature. The mixture was then poured into a large excces of ice-water and exctracted with Et_2O. The organic exctract was washed several times with brine and water, dried and concentrated *in vacuo*. In order to purify the residue from dimethyl-*tert*-butylsilanol, it was maintained for 16 h at 35-40 °C under reduced pressure (0.1 Torr). The new solid residue was then recrystallized from a mixture of THF and hexane to give compound **12** (4.15 g, 98% yield): m.p. 85-86 °C (lit[19b] m.p. 81-84 °C). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.90–7.80 (2H, m, Ha), 7.55-7.30 (3H, m, Hb and Hc), 4.92 ppm (2H, d, J = 2.0 Hz, H-5).

12



(S)(E)-2,4-Dimethyl-2-hexenoic acid, (S)(E)-13

A mixture of ethyl (*S*)(*E*)-2,4-dimethyl-2-hexenoate, (*S*)(*E*)-**10c** (6.5 g, 38.23 mmol), NaOH (17.4 g, 435 mmol) and methanol (175 ml) was refluxed for 5 h. It was then cooled to 0 °C and concentrated *in vacuo*. The residue was diluted with water (100 ml) and extracted with Et_2O. The aqueous layer was acidified with 10% HCl and extracted with Et_2O. The organic extract was washed with brine, dried and concentrated *in vacuo* to give compound (*S*)(*E*)-**13** (5.43 g, 100% yield): m.p. 31-32 °C; $[\alpha]_D^{24}$ + 35.84 (c = 2.715, benzene) [lit[31] $[\alpha]_D^{24}$ + 34.6 (c = 2.65, benzene)]. MS, *m/z* (%): 142 (M^+, 30), 127 (8), 113 (37), 109 (18), 97 (18), 96 (95), 95 (27), 87 (37), 81 (23), 73 (61), 69 (35), 67 (55), 55 (61), 56 (80), 53 (25), 43 (90), 41 (100). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 11.85 (1H, br s, COOH), 6.70 (1H, dq, J = 10.1 and 1.4 Hz, H-3), 2.60–2.30 (1H, m, H-4), 1.85 (3H, d, J = 1.4 Hz, CH_3-C=), 1.60–1.20 (2H, m, H-5), 1.01 (3H, d, J = 6.6 Hz, C-C(CH_3)-C), 0.86 ppm (3H, t, J = 7.4 Hz, H-6).

(S)(E)-2,4-dimethyl-2-hexenoyl chloride, (S)(E)-28

A solution of (*S*)(*E*)-2,4-dimethyl-2-hexenoic acid, (*S*)(*E*)-**13** (5.0 g, 36 mmol) in benzene (35 ml) was added to a stirred solution of $SOCl_2$ (7.0 ml, 95.6 mmol) in benzene (20 ml) and the resulting mixture was refluxed for 2 h. It was then cooled and concentrated *in vacuo* (60 Torr) to give crude (*S*)(*E*)-**28** (5.6 g, 100% yield). This compound was used in the next step without any further purification.

(S)(E)-4,6-dimethyl-4-octen-3-one, (S)(E)-14

A 1.56 *M* Et_2O solution of ethyllithium (76.8 ml, 120 mmol) was added to a stirred suspension of CuI (11.4 g, 60.0 mmol) and Et_2O (100 ml) cooled to -40 °C. After stirring for 15 min the reaction mixture was cooled to -78 °C and a solution of compound (*S*)(*E*)-**28** (5.6 g, 36 mmol) in Et_2O (40 ml) was dropwise added. After stirring for 15 min at -78 °C, methanol (10 ml) was added and the mixture was allowed to warm to room temperature. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, washed with aqueous NH_4Cl, dried and concentrated *in vacuo*. The residue was fractionally distilled to give compound (*S*)(*E*)-**14** (4.72 g, 85% yield): b.p. 106.5-107 °C/30 Torr; $[\alpha]_D^{20}$ +44.27 (c = 4.820, Et_2O) [lit[15c] b.p. 83-84 °C/20 Torr; $[\alpha]_D^{20}$ +43.80 (c = 5.0, Et_2O)]. MS, *m/z* (%): 155 (M^+ + 1, 5) 154 (M^+, 31), 139 (4), 126 (9), 125 (100), 97 (10), 69 (18), 67 (8), 57 (15), 55 (70), 53 (9), 43 (20), 41 (28). ^1H NMR ($CDCl_3$, 300 MHz), δ: 6.38 (1H, dq, J = 9.8 and 1.4 Hz, H-5), 2.69 (2H, q, J = 7.4 Hz, H-2), 2.55–2.42 (1H, m, H-6), 1.79 (3H, d, J = 1.4 Hz, CH_3-C=), 1.51–1.26 (2H, m, H-7), 1.10 (3H, t, J = 7.4 Hz, H-1), 1.02 (3H, d, J = 6.8 Hz, C-C(CH_3)-C=), 0.87 ppm (3H, t, J = 7.4 Hz, H-8). GLC analysis showed that compound (*S*)(*E*)-**14** had chemical purity higher than 99.5%.

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