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Stereocontrolled synthesis of carbon–carbon double bond locked analogues of strobilurins which are characterized by a *trans*-1,2-disubstituted cyclopropane ring

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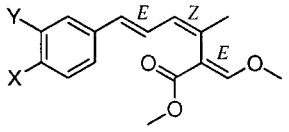
Abstract—The racemic forms of four new carbon–carbon double bond locked analogues of strobilurins, which are characterized by a *trans*-1,2-disubstituted cyclopropane ring, have been synthesized according to a strategy which involves palladium-catalyzed cross-coupling reactions between methyl (*Z*)-2-iodo-3-methoxypropenoate and organometallic derivatives such as (1*R**,2*R**)-2-phenylcyclopropylboronic acid and (1*R**,2*R*)-1-(2-bromozinciophenyl)-2-arylcyclopropanes. The boronic acid has been prepared via cyclopropanation of (*E*)-2-phenylethenyl-1,3,2-dioxaborinane and the organozinc compounds have been synthesized from easily available (*E*)-2-bromostilbenes. © 2001 Elsevier Science Ltd. All rights reserved.

Strobilurins (**1**) are metabolites isolated from basidiomycetes which inhibit mitochondrial respiration in fungi by interfering with the function of cytochrome bc_1 complex.[1] As a result, strobilurins exhibit good broad-spectrum fungicidal activity in vitro.[1] However, they can not be used directly as fungicides because of insufficient levels of activity in vivo, photolytic instability and volatility.[2]



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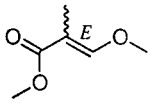

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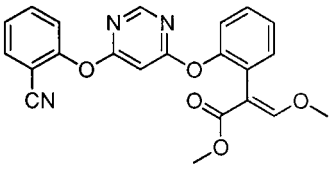
X = H, MeO, Me_2C=CH-CH_2O;
Y = H, Cl, MeO

Owing to their novel mode of action, low toxicity towards mammalian cells and favourable profiles to human safety, these natural products have been used as leads for the design and development of photostable structural analogues able to control the major classes of fungi which affect crops.[1c,2] Thus, several types of variations of the lead structures as regards their pharmacophore, i.e. the methyl (*E*)-3-methoxypropenoate unit (**2**), or their lipophilic moiety have been performed and, quite recently, the intense research activity performed in this field by more than 20 companies and research institutes allowed the development of some broad-spectrum agricultural fungicides such as *azoxystrobin* (formerly ICI A 5504) (**3**),[3] *kresoxim-methyl* (BAS 490 F) (**4**),[4] *trifloxystrobin* (CGA 279202)(**5**)[5] and *metominostrobin* (SSF 126)(**6**).[6]



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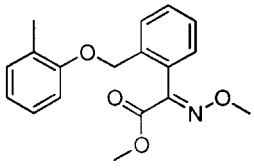

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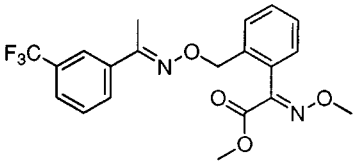

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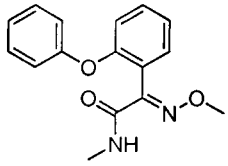

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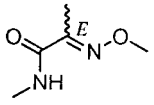

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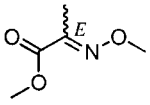

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These fungicides, similarly to several other analogues of **1**,[7,8] are characterized by direct attachment of a suitably *ortho*-substituted aromatic ring to a pharmacophore, which in the case of **3** is unit **2**, in the case of compounds **4** and **5** is the methyl (*E*)-*O*-methyloximinoacetate group (**7**), and in compound **6** is the (*E*)-*O*-methyloximino-*N*-methylacetamide group (**8**).[9]

Keywords: strobilurins; palladium; cyclopropanation; cross-coupling; organozinc derivatives.

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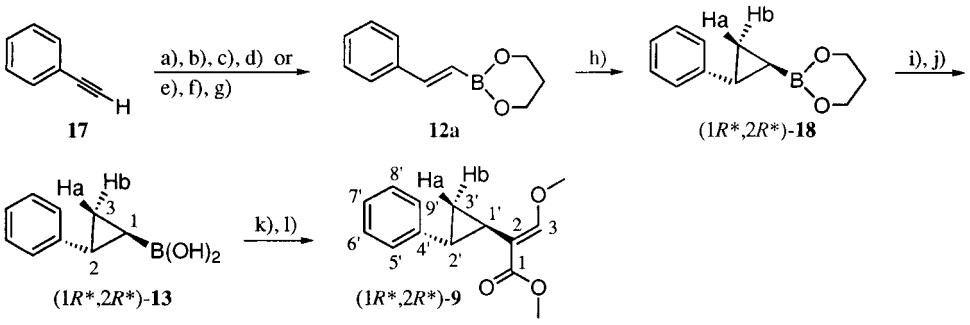
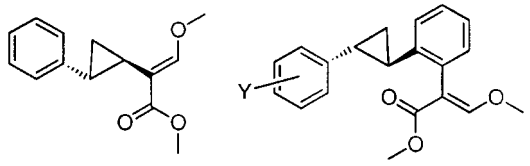


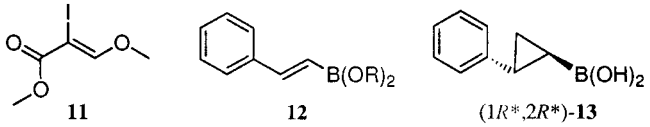
Scheme 1. (a) Catecholborane (1 equiv.), 70°C, 8 h, rt; (b) H_2O, 5 h, rt; (c) 1,3-propanediol (1.1 equiv.), pentane, 1.5 h, rt; (d) distillation (71% yield based on **17**); (e) catecholborane (1 equiv.), 70°C, 15 h; (f) 1,3-propanediol (1.1 equiv.), hexane, 20 h, rt; (g) distillation (48% yield based on **17**); (h) CH_2N_2 (5 equiv.), Et_2O, $Pd(OAc)_2$ (4 mol%), 0–5°C, 50 min (96% yield); (i) 1.5N KOH (3 equiv.), 80 min, rt; (j) 2N HCl, 0°C (93% yield based on (1*R**,2*R**)-**18**); (k) **11** (0.87 equiv.), $Pd(PPh_3)_4{\cdot}3H_2O$ (3 equiv.), toluene, 110°C, 20 h; (l) MPLC on silica gel (90% yield based on (1*R**,2*R**)-**13**).

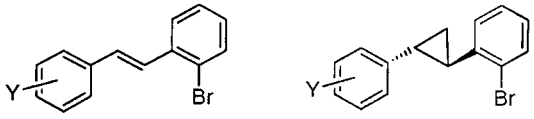
Attention has also been paid to the synthesis of photostable carbon–carbon double bond locked analogues of **1** in which unit **2** is linked to a α-substituted cyclopentenyl ring.[7d,e] However, to our knowledge, structural analogues of **1**, which do not contain olefinic carbon–carbon double bonds in their lipophilic subunit and in which the *Z* or *E* double bond present in the lipophilic subunit of naturally-occurring strobilurins is locked in a *cis*- or *trans*-1,2-disubstituted cyclopropane ring, have not been described so far. Now, we wish to report a concise synthesis of some of these analogues, i.e. compounds (1*R**,2*R**)-**9**, (1*R**,2*R**)-**10a**, (1*R**,2*R**)-**10b** and (1*R**,2*R**)-**10c**.

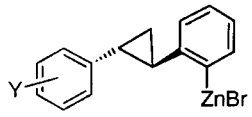


All these substances do not contain olefinic carbon–carbon double bonds in their lipophilic backbone and are characterized by a *trans*-1,2-disubstituted cyclopropane ring.[10]

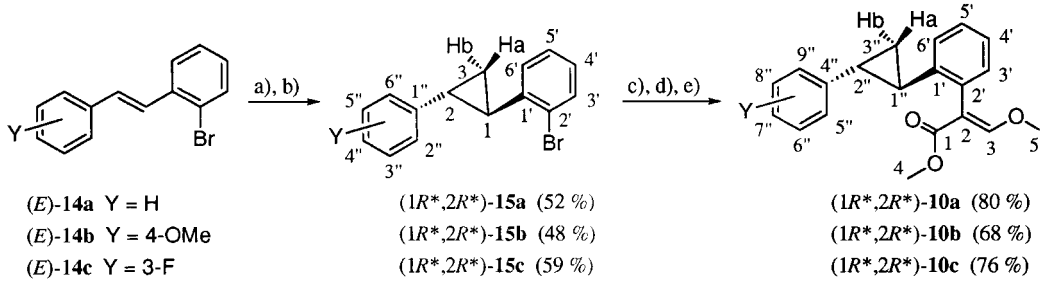
For the synthesis of compounds (1*R**,2*R**)-**9** and (1*R**,2*R**)-**10a–c**, we followed a synthetic plan in which a key step was the direct introduction of pharmacophore **2** into the lipophilic moieties of these analogues of **1** by palladium(0)-catalyzed cross-coupling reaction of easily available methyl (*Z*)-2-iodo-3-methoxypropenoate (**11**)[7a,e] with the cyclopropylboronic acid (1*R**,2*R**)-**13** and the 2-{2-[2-(aryl)-cyclopropyl]phenyl}zinc bromides (1*R**,2*R**)-**16a–c**, respectively.







This strategy was similar to that we previously employed to prepare analogues of **1** in which the key unit **2** is linked to a substituted (hetero)aromatic ring[7b] and, in the case of compound (1*R**,2*R**)-**9** involved the stereocontrolled cyclopropanation reaction of the (*E*)-β-phenylethenylboron derivative **12**. On the other hand, the synthetic plan followed to prepare the *trans*-1,2-disubstituted cyclopropane ring present in 1-(2-bromophenyl)-2-arylcyclopropanes



Scheme 2. (a) $CF_3COOZnCH_2I$ (3.5–5 equiv.), CH_2Cl_2, rt, 6–98 h; (b) H_3O^+; (c) Mg, THF, 65°C; (d) $ZnBr_2$, THF, 0°C; (e) **11** (0.83 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF, rt, 70–96 h.

(1R^*,2R^*)-**15a–c**, which we used as precursors to compounds (1R^*,2R^*)-**10a–c**, involved the stereospecific cyclopropanation reaction of (*E*)-2-bromostilbenes [(*E*)-**14a–c**].

1. Results and discussion

The synthesis of methyl (*E*)-(1R^*,2*R*)-2-[2-(phenyl)cyclopropyl]-3-methoxypropenoate [(1R^*,2R^*)-**9**] was carried out using the reaction sequence illustrated in Scheme 1.

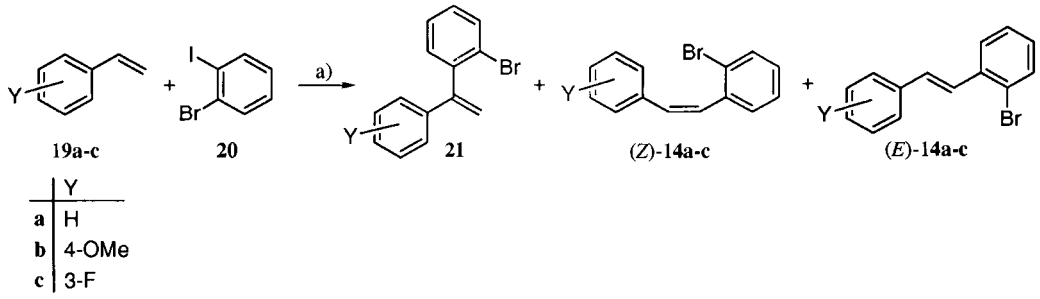
Thus, crude (*E*)-β-phenylethenylcatecholborane, which was obtained by hydroboration of phenylethyne (**17**) with catecholborane,[11] was stirred with water and the boronic acid so obtained was converted in 48% yield to 98% isomerically pure (*E*)-2-phenylethenyl-1,3,2-dioxaborinane (**12a**) by reaction with 1,3-propanediol in pentane at rt followed by distillation of the resulting hexane solution. Alternatively, 95% isomerically pure **12a** was prepared in 71% overall yield by reaction of **17** with catecholborane followed by treatment of the resulting crude (*E*)-1-alkenylcatecholborane with 1,3-propanediol in hexane and distillation of the hexane solution so obtained. Compound **12a** was then treated with a large molar excess of an ethereal solution of diazomethane at 0–5°C in the presence of a catalytic amount of $Pd(OAc)_2$[12] to give (1R^*,2R^*)-**18** in 96% yield. This boronic acid ester was saponified with 1.5N KOH at 0°C and the potassium salt so obtained was acidified with 2N HCl at 0°C to give (1R^*,2R^*)-**13** in 93% yield. Interestingly, an attempt to prepare this compound by cyclopropanation of (*E*)-2-phenylethenylboronic acid using the Simmons–Smith reaction[13] failed. Finally, the cross-coupling reaction between (1R^*,2R^*)-**13** and 0.87 equiv. of **11** in the presence of 3 equiv. of $K_3PO_4{\cdot}3H_2O$ and 4 mol% $Pd(PPh_3)_4$ in toluene at 110°C gave (1R^*,2R^*)-**9** in 90% yield.[14] The *trans*-stereochemistry of the cyclopropane moiety of this compound was confirmed by a NOESY experiment. In fact, the NOESY 2D map showed the presence of cross-peaks between the resonances of the following protons: H-3′b and H-5′; H-3′b and H-9′; H-1′ and H-5′; H-1′ and H-9′. On the other hand, cross-peaks were not observed between the resonance of the H-3′a proton and those of the aromatic protons. Therefore, it was possible to infer that either the H-3′a and the H-2′ protons or the H-3′b and H-1′ protons are close in proximity.

We then directed our attention to the synthesis of compounds (1R^*,2R^*)-**10a–c**. Their preparation was performed as shown in Scheme 2.

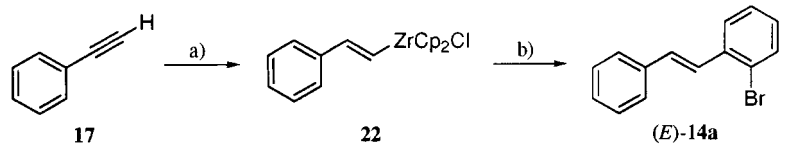
In particular, (*E*)-2-bromostilbenes (*E*)-**14a–c** were stereospecifically cyclopropanated according to a modification of the general procedure,[15] which involves treatment of a CH_2Cl_2 solution of the alkene with 2 equiv. of the organozinc species $CF_3COOZnCH_2I$ generated by reaction of $ZnEt_2$ with equimolar amounts of trifluoroacetic acid and CH_2I_2. We found that the cyclopropanation reaction of (*E*)-**14a** and (*E*)-**14c** required the use of a very large molar excess (5 equiv.) of $CF_3COOZnCH_2I$, occurred at rt in 40 and 42 h, respectively, and provided compounds (1R^*,2R^*)-**15a** and (1R^*,2R^*)-**15c** in 52 and 59% yield, respectively. However, we observed that when a similar molar excess of $CF_3COOZnCH_2I$ and a long reaction time (20 h) were used for the cyclopropanation reaction of (*E*)-**14b**, a complex reaction mixture which contained (1R^*,2R^*)-**15b** as the major product (36%) was obtained. The main byproduct (7%), which we did not succeed to isolate in pure form and to characterize, had a molecular ion peak higher for 14 mass units than that of (1R^*,2R^*)-**15b**. Purification of this reaction mixture by MPLC on silica gel allowed to isolate (1R^*,2R^*)-**15b** in 24% yield. Nevertheless, we found that when the cyclopropanation reaction of (*E*)-**14b** was carried out for 6 h at rt using 3.5 equiv. of $CF_3COOZnCH_2I$, the reaction was not complete but the amount of the above-mentioned byproduct was minimized (ca. 1%). Purification of the reaction mixture provided (1R^*,2R^*)-**15b** in 48% yield. It must also be noted that in our hands, the cyclopropanation reaction of compounds (*E*)-**14a–c** by treatment with $CF_3COOZnCH_2I$ proved to be superior to the procedure involving the reaction of these alkenes with diazomethane in the presence of $Pd(OAc)_2$.[12] In fact, the cyclopropanation of (*E*)-**14a** according to this last protocol proved to be a very sluggish reaction which provided (1R^*,2R^*)-**15a** in ca. 20% GLC yield.

Compounds (1R^*,2R^*)-**15a**, (1R^*,2R^*)-**15b** and (1R^*,2R^*)-**15c** were then converted to the corresponding Grignard reagents by the standard procedure and these organometallics were transmetallated by treatment with a molar excess of dry $ZnBr_2$ in THF at 0°C to give the (1R^*,2R^*)-**16a**, (1R^*,2R^*)-**16b** and (1R^*,2R^*)-**16c**, respectively. Finally, the cross-coupling reaction of these organozinc derivatives with 0.83 equiv. of **11** at rt for 70–96 h, in the presence of 5 mol% $Pd(PPh_3)_4$, provided compounds (1R^*,2R^*)-**10a**, (1R^*,2R^*)-**10b** and (1R^*,2R^*)-**10c** in 80, 68 and 76% yield, respectively. The *trans*-stereochemistry of the 1,2-disubstituted cyclopropane moiety of these analogues of **1** was confirmed by NOESY experiments. In fact, the NOESY 2D maps of these compounds showed cross-peaks between the resonances of the following protons: H-3″a and H-2″; H-3″a and H-3′; H-3″b and H-5″; H-3″b and H-1″. Therefore, it was possible to infer that either the H-3″a and H-2″ protons or the H-3″b and H-1″ protons are near in the space.

Finally, as regards 2-bromostilbenes (*E*)-**14a–c**, which we used as precursors to compounds (1R^*,2R^*)-**10a–c**, it must be mentioned that a variety of compounds of this class which include (*E*)-**14a** have been prepared either by Wittig–Horner–Emmons olefination of arenecarbaldehydes with diethyl 2-bromobenzylphosphonate[16] or by Wittig reaction of 2-bromobenzaldehyde with the ylides derived from substituted benzyltriphenylphosphonium bromides, followed by photoisomerization of the (*Z*)-2-bromostilbenes which were obtained as major products from this olefination reaction.[16] Nevertheless, we preferred to prepare these bromoalkenes by Heck reaction[17] between 2-bromoiodobenzene (**20**) and styrenes **19a**, **b** and **c**, respectively.[18,19] In fact, all these reagents were commercially available and we expected that their Heck reaction could afford the desired (*E*)-2-bromostilbenes chemo- and stereoselectively and in good yields. In the event, we found that, when this reaction was performed in acetonitrile at 95°C in the presence of 1.1 equiv. of Et_3N and a catalytic amount of



Scheme 3. (a) $Pd(OAc)_2$ (8 mol%), Et_3N (1.1 equiv.), CH_3CN, 95°C, 24 h.



Scheme 4. (a) Cp_2ZrHCl (1.2 equiv.), benzene, rt, 2.5 h; (b) 1,2-dibromobenzene (**23**) (1.5 equiv.), $Pd(PPh_3)_2$ (10 mol%), THF, 50°C, 34 h (48% yield based on **17**).

$Pd(OAc)_2$ and using compounds **19a–c** and **20** in a 1.16:1 molar ratio, mixtures which contained compounds (*E*)-**14a–c** as the major products besides a very small amount (ca. 1%) of their (*Z*)-stereoisomers, (*Z*)-**14a–c**, and 4–11% of the corresponding regioisomers **21a–c** were chemoselectively obtained (Scheme 3).

The amount of these regioisomers was higher (11%) for the Heck reaction between **19b** and **20** and was lower (4%) in the case of the reaction involving **19c**. Purification of the crude reaction mixtures by MPLC on silica gel allowed to obtain compounds (*E*)-**14a**,[20] (*E*)-**14b**,[21] and (*E*)-**14c** in 85, 71 and 84% yield, respectively. These 2-bromostilbenes had isomeric purity higher than 98%. On the other hand, regio- and stereoisomerically pure (*E*)-**14a** was prepared by the reaction sequence illustrated in Scheme 4.

Thus, a benzene solution of **17** was treated with 1.2 equiv. of bis(cyclopentadienyl)zirconium chloride hydride for 2.5 h in dark at rt. The resulting organozirconium derivative **22** was then cross-coupled with 1.5 equiv. of 1,2-dibromobenzene (**23**) for 34 h at 50°C in the presence of a palladium(0) catalyst (10 mol%) which was prepared in situ by reaction of a THF suspension of $PdCl_2(PPh_3)_2$ with 2 equiv. of a 1 M hexane solution of diisobutylaluminum hydride (DIBAH) at 0°C over 10 min. This cross-coupling reaction yielded pure (*E*)-**14a** in 48% isolated yield. However, the high cost of the Schwartz's reagent as well as the modest yield of the reaction sequence used to prepare (*E*)-**14a** discouraged us from using a similar protocol for the synthesis of (*E*)-**14b** and (*E*)-**14c**.

2. Conclusions

In this study, we developed concise procedures for the stereocontrolled synthesis of carbon–carbon double bond locked analogues of strobilurins (**1**), which are characterized by a *trans*-1,2-disubstituted cyclopropane ring in their lipophilic subunit. One of these racemic analogues, i.e. methyl (*E*)(1R^*,2R^*)-2-[2-(phenyl)cyclopropyl]-3-methoxypropenoate [(1R^*,2R^*)-**9**], was synthesized in 59% overall yield by a reaction sequence in which a key step was the palladium-catalyzed cross-coupling reaction between a cyclopropylboronic acid and methyl (*Z*)-2-iodo-3-methoxypropenoate (**11**). On the other hand, the synthesis of three other structural analogues of **1**, i.e. [(1R^*,2R^*)-**10a**], [(1R^*,2R^*)-**10b**] and [(1R^*,2R^*)-**10c**], was accomplished according to a strategy which involved the stereospecific cyclopropanation of (*E*)-2-bromostilbenes (*E*)-**14a–c** by treatment with the organozinc species $CF_3COOZnCH_2I$ and the conversion of the organic bromides so obtained into the corresponding organozinc bromides followed by the palladium-catalyzed cross-coupling reaction between these organometallics and **11**. This strategy is very flexible and appears to be suitable for the synthesis of a great variety of analogues of **1** in which the *Z* and *E* carbon–carbon double bonds, which are present in the lipophilic subunit of these natural products, are locked in an *ortho*-substituted benzene ring and in a *trans*-1,2-disubstituted cyclopropane ring, respectively. Finally, it must be noted that compounds (*E*)-**14a–c**, which we used as precursors to (1R^*,2R^*)-**10a–c**, were conveniently and efficiently synthesized by a chemo- and stereoselective Heck reaction between 2-bromoiodobenzene (**20**) and styrenes **19a–c**.

3. Experimental

3.1. General

Melting points and boiling points are uncorrected. Precoated plastic silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 mm×0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument using a Bischoff

8110 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas chromatograph. NMR spectra were recorded on Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as internal standard, respectively. The structure and relative stereochemistry of compounds ($1R^*,2R^*$)-**9**, ($1R^*,2R^*$)-**15b**, ($1R^*,2R^*$)-**15c** and ($1R^*,2R^*$)-**10a–c** were assigned by a combination of NMR techniques which included $^1H-^1H$ COSY, NOESY, $^1H-^{13}C$ heteronuclear shift correlation and $^1H-^{13}C$ long-range heteronuclear shift correlation. IR spectra were recorded on a Perkin–Elmer 1725 FT-IR spectrophotometer. All reactions of air and water sensitive materials were performed in flame-dried glassware under an atmosphere of nitrogen or argon using standard syringe, cannula and septa techniques. The following compounds were prepared by published procedures: $Pd(PPh_3)_4$,[22] $PdCl_2(PPh_3)_2$,[23] methyl (*Z*)-2-iodo-3-methoxypropenoate (**11**)[7a,e] and diazomethane.[24] All the other reagents are commercially available and were used as purchased. Solvents were dried and distilled before use.

3.1.1. (*E*)-2-Phenylethenyl-1,3,2-dioxaborinane (12a). Under a nitrogen atmosphere, catecholborane (7.20 g, 60.0 mmol) was added over a period of 15 min to freshly distilled phenylethyne (**17**) (6.13 g, 60.0 mmol), and the resulting mixture was stirred at 70°C for 15 h. It was then cooled to rt and diluted with deaerated hexane (54 ml). Freshly distilled 1,3-propanediol (5.02 g, 66.0 mmol) was then added dropwise and the resulting mixture was stirred at rt for 20 h. After this period of time, the hexane phase of this heterogeneous reaction mixture was separated. The residue was washed with hexane (5×20 ml), and the collected hexane solutions were concentrated under reduced pressure. The residue was fractionally distilled to give **12a** (7.98 g, 71%) as a colourless liquid. Bp 90°C/0.01 Torr. MS: *m/z*: 188 (100), 187 (28), 130 (76), 129 (74), 115 (19), 104 (34), 103 (44), 78 (56), 77 (65). IR (film): ν 1623, 1422, 1341, 1313, 1278, 1228 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.65–7.25 (5H, m, Harom), 7.29 (1H, d, J=18.2 Hz, H-2), 6.07 (1H, d, J=18.2 Hz, H-1), 4.07 (4H, t, J=5.5 Hz, OCH_2), 1.98 (2H, q, J=5.5 Hz, $C-CH_2-C$). Anal. calcd for $C_{11}H_{13}BO_2$: C, 70.26; H, 6.97. Found: C, 70.52; H, 7.14. GLC and GLC/MS analyses showed that **12a** had purity higher than 95%. This same compound was alternatively synthesized according to the following procedure. Crude (*E*)-2-phenylethenylcatecholborane, which was obtained by reaction of **17** (7.46 g, 73.0 mmol) with catecholborane (8.75 g, 73.0 mmol) for 8 h at 70°C, was stirred with deaerated water (70 ml) for 5 h at rt and the mixture was cooled to 0°C. The so obtained colourless solid was separated, maintained at 0.01 Torr for 4 h and identified as (*E*)-2-phenylethenylboronic acid on the basis of its ^1H NMR spectrum. ^1H NMR (200 MHz, DMSO-d_6): δ 7.80 (2H, s, OH), 7.55 (5H, m, Harom), 7.26 (1H, d, J=18.4 Hz, H-2), 6.13 (1H, d, J=18.4 Hz, H-1). This boronic acid (6.15 g) was treated with pentane (80 ml) and 1,3-propanediol (3.60 g, 47.3 mmol) and the resulting mixture was stirred for 1.5 h at rt. The pentane phase of this mixture was separated, concentrated under reduced pressure, and the residue was fractionally distilled to give **12a** (6.60 g, 48%). Bp 92–93°C/0.01 Torr. GLC analysis showed that this compound had isomeric purity higher than 98%.

3.1.2. ($1R^*,2R^*$)-2-Phenylcyclopropyl-1,3,2-dioxaborinane [($1R^*,2R^*$)-18]. Under a nitrogen atmosphere, an ethereal solution of diazomethane[24] (260 ml, ca. 133 mmol) was added over a period of 50 min to a stirred mixture of **12a** (5.00 g, 26.6 mmol) and $Pd(OAc)_2$ (0.12 g, 0.53 mmol) in dry diethyl ether (55 ml) which was cooled to 0–5°C. When half of the ethereal solution of diazomethane had been added, more $Pd(OAc)_2$ (0.12 g, 0.53 mmol) was added. The reaction mixture was then allowed to warm up to rt and the catalyst was removed by filtration over Celite. The filtrate was concentrated under reduced pressure and the residue was fractionally distilled to give ($1R^*,2R^*$)-**18** (5.18 g, 96%) as a colourless liquid. Bp 95°C/ 0.02 Torr. MS: *m/z* (%): 202 (26), 143 (25), 130 (33), 129 (23), 128 (9), 118 (9), 117 (44), 116 (100), 115 (74), 91 (25), 89 (11). IR (film): ν 1442, 1405, 1341, 1278, 1231, 1202 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.27–7.01 (5H, m, Harom), 3.96 (4H, t, J=5.5 Hz, $O-CH_2$), 2.00 (1H, ddd, J=8.1, 5.5 and 5.2 Hz, H-2), 1.92 (2H, q, J=5.5 Hz, $C-CH_2-C$), 1.08 (1H, ddd, J=8.1, 6.8 and 3.4 Hz, H-3a), 0.92 (1H, ddd, J=9.5, 5.2 and 3.4 Hz, H-3b), 0.14 (1H, ddd, J=9.5, 6.8 and 5.5 Hz, H-1). Anal. calcd for $C_{12}H_{15}BO_2$: C, 71.33; H, 7.48. Found: C, 71.01; H, 7.24. GLC analysis showed that ($1R^*,2R^*$)-**18** had purity higher than 97%.

3.1.3. ($1R^*,2R^*$)-2-Phenylcyclopropylboronic acid [($1R^*,2R^*$)-13]. The cyclopropyl boronic acid ester ($1R^*,2R^*$)-**18** (3.00 g, 14.8 mmol) was added dropwise to a 1.5N aqueous solution of KOH (29.6 ml, 44.3 mmol), and the mixture was stirred at rt for 1.5 h. It was then extracted with diethyl ether (4×10 ml), and the resulting solution was cooled to 0°C and acidified with 2N HCl. The so formed colourless solid was separated, washed with cold water (2×5 ml) and maintained at 0.01 Torr for 10 h to give ($1R^*,2R^*$)-**13** (2.23 g, 93%) as a colourless solid. IR (KBr): ν 3220, 1605, 1462, 1195, 698, 642 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6): δ 7.50–6.90 (5H, m, Harom), 6.69 (2H, s, OH), 2.06–1.90 (1H, m, H-2), 1.13 (1H, ddd, J=8.1, 6.9 and 3.4 Hz, H-3a), 0.94 (1H, ddd, J=9.6, 5.2 and 3.4 Hz, H-3b), 0.13 (1H, ddd, J=9.6, 6.9 and 6.6 Hz, H-1). This boronic acid was directly used in the next step without any further purification and characterization.

3.1.4. Methyl (*E*)($1R^*,2R^*$)-2-[2-(phenyl)cyclopropyl]-3-methoxypropenoate [($1R^*,2R^*$)-9]. A deaerated solution of methyl (*Z*)-2-iodo-3-methoxypropenoate (**11**) (1.56 g, 6.44 mmol) in toluene (10 ml) and a suspension of the crude cyclopropylboronic acid ($1R^*,2R^*$)-**13** (1.20 g, 7.40 mmol) in deareated toluene (10 ml) were sequentially added under argon to a deaerated mixture of K_3PO_4 (4.72 g, 22.2 mmol), water (1.20 ml, 66.6 mmol) and toluene (30 ml), and the resulting mixture was stirred at 110°C for 20 h. It was then cooled to rt and water (100 ml) was added. The mixture was extracted with diethyl ether (5×60 ml), and the organic extract was washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with the solvent used for its purification by MPLC and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel using benzene as eluant to give ($1R^*,2R^*$)-**9** (1.35 g, 90%) as a colourless solid. Mp 43–45°C. MS: *m/z* (%): 201 (23), 200 (100), 172 (34), 168 (21), 157 (36), 155 (15), 141 (57), 129 (23), 128 (42), 127

(15), 115 (42). IR (KBr): ν 1700, 1632, 1281, 1245, 1144, 1101 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.34 (1H, d, J=0.6 Hz, H-3), 7.27 (2H, m, H-6′ and H-8′), 7.15 (3H, m, H-5′, H-7′ and H-9′), 3.82 (3H, brs, H-5), 3.70 (3H, brs, H-4), 2.30 (1H, ddd, J=8.7, 5.5 and 5.3 Hz, H-2′), 1.75 (1H, dddd, J=8.9, 6.1, 5.3 and 0.6 Hz, H-1′), 1.45 (1H, ddd, J=8.7, 6.1 and 4.7 Hz, H-3′a), 1.18 (1H, ddd, J=8.9, 5.5 and 4.7 Hz, H-3′b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.56 (C-1), 159.95 (C-3), 143.74 (C-4′), 126.11 (C-5′ and C-9′), 128.22 (C-6′ and C-8′), 125.46 (C-7′), 109.94 (C-2), 61.63 (C-5), 51.19 (C-4), 23.56 (C-2′), 18.96 (C-1′), 15.42 (C-3′). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45; H, 7.03. GLC analysis showed that (1R^*,2R^*)-**9** had purity higher than 98%.

3.2. General procedure for the synthesis of 2-bromostilbenes (*E*)-14a–c starting from 2-bromoiodobenzene (20)

Compound **20** (8.15 g, 28.8 mmol), a styrene derivative **19** (33.6 mmol) and dry Et_3N (3.40 g, 33.6 mmol) were sequentially added under nitrogen to a deaerated mixture of $Pd(OAc)_2$ (485 mg, 2.16 mmol) and acetonitrile (13.5 ml), and the resulting mixture was stirred at 95°C for 24 h. After this period of time, a GLC analysis indicated that compound **20** had been completely consumed. After being cooled to rt, the reaction mixture was stirred with cold 10% aqueous HCl solution (120 ml) and extracted with diethyl ether (3×70 ml). The organic extract was washed with water (50 ml), dried with Na_2SO_4, filtered over Celite and concentrated under reduced pressure. This procedure was employed to prepare (*E*)-2-bromostilbene [(*E*)-**14a**], (*E*)-2-bromo-4′-methoxystilbene [(*E*)-**14b**] and (*E*)-2-bromo-3′-fluorostilbene [(*E*)-**14c**], starting from styrene (**19a**), 4-methoxystyrene (**19b**) and 3-fluorostyrene (**19c**), respectively.

3.2.1. (*E*)-2-Bromostilbene [(*E*)-14a]. GLC analysis of the crude reaction mixture, which was obtained from the Heck reaction between **19a** and **20**, showed the presence of three compounds in a ca. 92:7:1 molar ratio, which were subsequently identified as (*E*)-**14a**, 2-(2-bromophenyl)styrene (**21a**) and (*Z*)-**14a**, respectively. This crude reaction mixture was purified by MPLC on silica gel, using hexane as eluant to give (*E*)-**14a** (6.37 g, 85%) as a colourless liquid. MS: *m/z* (%): 260/258 (30/33), 180 (10), 179 (96), 178 (100), 177 (11), 176 (15), 152 (7), 151 (6), 89 (9), 76 (7). IR (film): ν 1466, 1025, 960, 757, 708, 690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.69–7.19 (9H, m, Harom), 7.47 (1H, d, J=16.5 Hz, =CH), 7.02 (1H, d, J=16.5 Hz, =CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.1, 137.0, 133.0, 131.3, 128.6, 128.0, 127.4, 127.3, 126.7, 126.6, 124.1. The spectral properties of this compound were in agreement with those previously reported.[16] Anal. calcd for $C_{14}H_{11}Br$: C, 64.89; H, 4.28. Found: C, 64.90; H, 4.59. Concentration of an intermediate chromatographic fraction, which contained (*E*)-**14a** and **21a** in a ca. 2:1 molar ratio, respectively, allowed to characterize in part this last compound. MS: *m/z* (%): 260/258 (6/7), 179 (100), 178 (78), 176 (15), 152 (15), 151 (10), 89 (76), 88 (25), 76 (62), 75 (21). ^1H NMR (200 MHz, $CDCl_3$): δ 7.68–7.05 (9H, m, Harom), 5.83 (1H, s, =CH), 5.26 (1H, s, =CH). On the other hand, (*Z*)-**14a** was in part characterized by analysis of the residue obtained by concentration of a first eluted chromatographic fraction, which contained 86% of (*Z*)-**14a**, 8% of **21a** together with other minor byproducts. Compound (*Z*)-**14a** had MS: *m/z* (%): 260/258 (11/11), 180 (19), 179 (100), 178 (94), 152 (18), 89 (87), 88 (30), 77 (19), 76 (55), 75 (20). ^1H NMR (200 MHz, $CDCl_3$): δ 7.62–6.98 (9H, m, Harom), 6.69 (1H, d, J=11.6 Hz, =CH), 6.61 (1H, d, J=11.6 Hz, =CH).

3.2.2. (*E*)-2-Bromo-4′-methoxystilbene [(*E*)-14b]. GLC analysis of the crude reaction mixture, which was obtained from the Heck reaction between **19b** and **20**, showed the presence of three compounds in a ca. 88:11:1 molar ratio. The first of these compounds was subsequently identified as (*E*)-**14b**. On the other hand, the second and the third compounds were tentatively identified as 2-(2-bromophenyl)-4′-methoxystyrene (**21b**) and (*Z*)-**14b**, respectively. This crude reaction mixture was purified by MPLC on silica gel, using a mixture of hexane and benzene (86/14) as eluant, to yield (*E*)-**14b** (5.94 g, 71%) as a colourless solid. Mp 67–69°C (mp 64–65°C).[21] MS: *m/z* (%): 290/288 (68/68), 289 (12), 194 (51), 178 (26), 177 (27), 166 (75), 165 (100), 164 (12), 139 (13), 82 (14). IR (KBr): ν 1602, 1509, 1255, 1175, 1025, 748 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.64 (1H, dd, J=7.8 and 1.4 Hz, Harom), 7.57 (1H, dd, J=7.8 and 1.2 Hz, Harom), 7.49 (2H, d, J=8.8 Hz, Harom), 7.33 (1H, d, J=16.6 Hz, =CH), 7.28 (1H, td, J=7.8 and 1.2 Hz, Harom), 7.08 (1H, td, J=7.8 and 1.4 Hz, Harom), 6.98 (1H, d, J=16.6 Hz, =CH), 6.91 (2H, d, J=8.8 Hz, Harom), 3.83 (3H, s, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.5, 137.3, 132.9, 130.9, 129.2, 128.3, 128.0, 127.4, 126.3, 125.2, 123.8, 114.1, 55.3. The spectral properties of this compound were in agreement with those previously reported.[16]

3.2.3. (*E*)-2-Bromo-3′-fluorostilbene [(*E*)-14c]. GLC analysis of the crude reaction mixture, which was obtained from the Heck reaction between **19c** and **20** showed the presence of three compounds in a ca. 95:4:1 molar ratio. The first two compounds were subsequently identified as (*E*)-**14c** and 2-(2-bromophenyl)-3′-fluorostyrene (**21c**), respectively. The third compound very likely corresponded to (*Z*)-**14c**. This crude reaction mixture was purified by MPLC on silica gel using hexane as eluant to yield (*E*)-**14c** (6.71 g, 84%) as a pale yellow liquid. MS: *m/z* (%): 279/277 (10/11), 278/276 (69/73), 198 (12), 197 (90), 196 (100), 195 (12), 194 (18), 177 (72), 176 (24). IR (film): ν 1609, 1582, 1488, 958, 779, 748 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.62 (1H, dd, J=8.0 and 1.4 Hz, Harom), 7.56 (1H, dd, J=7.8 and 1.4 Hz, Harom), 7.45 (1H, d, J=16.2 Hz, =CH), 7.38–7.15 (4H, m, Harom), 7.10 (1H, dt, J=7.8 and 1.4 Hz, Harom), 7.02–6.92 (1H, m, Harom), 6.95 (1H, d, J=16.2 Hz, =CH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0 ($^1J_{C-F}$=244.2 Hz), 139.2 ($^3J_{C-F}$=8.2 Hz), 136.5, 133.0, 130.1, 129.0, 128.6, 127.5, 126.7, 124.1, 122.6, 114.7 ($^2J_{C-F}$=21.3 Hz), 113.0 ($^2J_{C-F}$=21.3 Hz). Anal. calcd for $C_{14}H_{10}BrF$: C, 60.67; H, 3.64. Found: C, 60.68; H, 3.72. Concentration of a first eluted chromatographic fraction, which contained (*E*)-**14c** and **21c** in a ca. 1:1 molar ratio, allowed to characterize in part this last compound. Compound **21c** had MS: *m/z* (%): 278/276 (23/30), 198 (12), 197 (100), 196 (73), 194 (13), 178 (9), 177 (48), 176 (19). ^1H NMR (200 MHz, $CDCl_3$): δ

7.66–6.86 (8H, m, Harom), 5.83 (1H, d, J=0.8 Hz, =CH), 5.30 (1H, d, J=0.8 Hz, =CH).

3.2.4. Synthesis of (*E*)-14a via Pd-catalyzed cross-coupling reaction between (*E*)(2-phenylethenyl)-bis-(cyclopentadienyl)zirconium chloride (22) and 1,2-dibromobenzene (23). Bis(cyclopentadienyl)zirconium chloride hydride (12.38 g, 48.00 mmol) was added under argon over 20 min to a deaerated solution of **17** (4.08 g, 40.0 mmol) in benzene (150 ml), and the mixture was stirred for 2.5 h at rt under exclusion of light. A mixture of $PdCl_2(PPh_3)_2$ (2.80 g, 4.00 mmol) and THF (500 ml) was treated with a 1 M hexane solution of DIBAH (8.0 ml, 8.0 mmol) at 0°C over 10 min and the dark suspension obtained was sequentially treated at 0°C with the benzene solution of (*E*)(2-phenylethenyl)bis(cyclopentadienyl)-zirconium chloride prepared above and with a solution of **23** (14.16 g, 60.00 mmol) in THF (100 ml). After stirring for 34 h at 50°C in dark, the reaction mixture was cooled to rt, poured into cold 2N HCl (200 ml), and extracted with diethyl ether (3×100 ml). The organic extract was washed with water (100 ml), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel using hexane as eluant to give (*E*)-**14a** (4.95 g, 48%) as a colourless liquid. GLC analysis showed that this compound had chemical purity higher than 97%. Its spectral properties were in good agreement with those of (*E*)-**14a** prepared by Heck reaction between **19a** and **20**.

3.2.5. (*E*)(1*R,2*R**)-1-(2-Bromophenyl)-2-phenylcyclopropane [(1*R**,2*R**)-15a].** A solution of trifluoroacetic acid (8.80 g, 77.2 mmol) in freshly distilled CH_2Cl_2 (35 ml) was added over 30 min to a stirred mixture of a 1 M hexane solution of $ZnEt_2$ (77.2 ml, 77.2 mmol) and CH_2Cl_2 (77 ml) which was stirred under argon at 0°C. Upon stirring for 20 min at 0°C, a solution of CH_2I_2 (20.68 g, 77.20 mmol) in CH_2Cl_2 (30 ml) was added. After an additional 20 min, a solution of (*E*)-**14a** (4.00 g, 15.44 mmol) in CH_2Cl_2 (20 ml) was added and the resulting mixture was stirred at rt for 40 h. It was then poured into a saturated aqueous NH_4Cl solution (200 ml) and extracted with hexane (3×70 ml). The organic extract was washed with water, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel using hexane as eluant to give (1*R**,2*R**)-**15a** (2.18 g, 52%) as a colourless solid. Mp 33–35°C. MS: *m/z* (%): 274/272 (23/27), 193 (77), 192 (25), 191 (29), 189 (18), 179 (23), 178 (79), 165 (27), 115 (100), 91 (21). IR (film): ν 1498, 1477, 1438, 1024, 751, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.56 (1H, m, Harom), 7.36–7.16 (6H, m, Harom), 7.07 (2H, brd, J=7.2 Hz, Harom), 2.46 (1H, dt, J=7.2 and 5.2 Hz, H-1 or H-2), 2.12 (1H, dt, J=7.2 and 5.2 Hz, H-2 or H-1), 1.43 (2H, t, J=7.2 Hz, H-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 142.1, 141.3, 132.5, 128.7, 128.3, 127.4, 126.9, 126.0, 125.8, 27.9, 26.9, 17.1. Anal. calcd for $C_{15}H_{13}Br$: C, 65.95; H, 4.80. Found: C, 66.10; H, 4.59. GLC analysis showed that (1*R**,2*R**)-**15a** had 97% chemical purity.

3.2.6. (*E*)(1*R,2*R**)-1-(2-Bromophenyl)-2-(4-methoxyphenyl)cyclopropane [(1*R**,2*R**)-15b].** An ice cooled solution of $CF_3COOZnCH_2I$ was prepared starting from a 1 M hexane solution of $ZnEt_2$ (27.0 ml, 27.0 mmol), trifluoroacetic acid (3.08 g, 27.0 mmol), CH_2I_2 (7.23 g, 27.0 mmol) and CH_2Cl_2 (50 ml), according to the procedure employed for the preparation of (1*R**,2*R**)-**15a**. This solution was stirred under argon at 0°C for 20 min, then a solution of (*E*)-**14b** (2.23 g, 7.71 mmol) in freshly distilled CH_2Cl_2 (10 ml) was added and the resulting mixture was stirred for 6 h at rt. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using a mixture of hexane and benzene (86/14) as eluant, to give (1*R**,2*R**)-**15b** (1.12 g, 48%) as a colourless solid. Mp 44–47°C. MS: *m/z* (%): 304/302 (91/100), 223 (83), 208 (55), 192 (35), 191 (27), 179 (32), 178 (46), 165 (28), 121 (28), 115 (49). IR (KBr): ν 1515 cm^{-1}. 1248, 1033, 1019, 823, 815. ^1H NMR (600 MHz, $CDCl_3$): δ 7.56 (1H, dd, J=7.4 and 1.2 Hz, H-3′), 7.25 (1H, ddd, J=7.4, 7.4 and 1.2 Hz, H-5′), 7.16 (2H, d, J=8.7 Hz, H-2″ and H-6″), 7.07 (1H, dd, J=7.4 and 1.6 Hz, H-6′), 7.06 (1H, ddd, J=7.4, 7.4 and 1.6 Hz, H-4′), 6.86 (2H, d, J=8.7 Hz, H-3″ and H-5″), 3.80 (3H, s, OCH_3), 2.40 (1H, ddd, J=8.6, 6.3 and 4.9 Hz, H-1), 2.08 (1H, ddd, J=8.6, 6.3 and 4.9 Hz, H-2), 1.39 (1H, ddd, J=8.6, 6.3 and 5.0 Hz, H-3a), 1.38 (1H, ddd, J=8.6, 6.3 and 5.0 Hz, H-3b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.95 (C-4″), 141.57 (C-1′), 134.18 (C-1″), 132.51 (C-3′), 127.36 (C-5′), 127.32 (C-4′), 127.28 (C-6″ and C-2″), 126.80 (C-6′), 126.07 (C-2′), 113.88 (C-3″ and C-5″), 55.32 (OCH_3), 27.41 (C-1), 26.28 (C-2), 16.63 (C-3). Anal. calcd for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Found: C, 63.21; H, 5.08. GLC analysis showed that (1*R**,2*R**)-**15b** had chemical purity higher than 97%.

3.2.7. (*E*)(1*R,2*R**)-1-(2-Bromophenyl)-2-(3-fluorophenyl)-cyclopropane [(1*R**,2*R**)-15c].** An ice cooled solution of $CF_3COOZnCH_2I$ was prepared starting from a 1 M hexane solution of $ZnEt_2$ (87.5 ml, 87.5 mmol), trifluoroacetic acid (9.98 g, 87.5 mmol), CH_2I_2 (23.44 g, 87.50 mmol) and CH_2Cl_2 (170 ml), according to the procedure employed for the preparation of (1*R**,2*R**)-**15a**. This solution was stirred under argon at 0°C for 20 min, then a solution of (*E*)-**14c** (4.85 g, 17.5 mmol) in freshly distilled CH_2Cl_2 (22 ml) was added and the resulting mixture was stirred for 42 h at rt. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel using hexane as eluant to give (1*R**,2*R**)-**15c** (3.00 g, 59%) as a colourless solid. Mp 50–53°C. MS: *m/z* (%): 292/290 (10/10), 211 (53), 196 (35), 183 (19), 133 (73), 116 (17), 115 (100), 109 (24), 91 (19), 89 (16). IR (KBr): ν 1587, 1454, 782, 772, 746, 687 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.57 (1H, dd, J=8.2 and 1.4 Hz, H-3′), 7.26 (1H, ddd, J=7.4, 7.4 and 1.4 Hz, H-5′), 7.25 (1H, ddd, J=7.8, 7.8 and 6.0 Hz, H-5″), 7.08 (1H, dd, J=7.4 and 1.6 Hz, H-6′), 7.08 (1H, ddd, J=8.2, 7.4 and 1.6 Hz, H-4′), 7.00 (1H, ddd, J=7.8, 1.4 and 1.0 Hz, H-6″), 6.90 (1H, ddd, J=10.2, 2.5 and 1.0 Hz, H-2″), 6.89 (1H, dddd, J=8.8, 7.8, 2.5 and 1.0 Hz, H-4″), 2.45 (1H, ddd, J=8.8, 6.3 and 5.0 Hz, H-1), 2.09 (1H, ddd, J=8.8, 5.5 and 5.0 Hz, H-2), 1.48 (1H, ddd, J=8.8, 6.3 and 5.3 Hz, H-3a), 1.43 (1H, ddd, J=8.8, 5.5 and 5.3 Hz, H-3b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.07 ($^1J_{C-F}$= 245.2 Hz, C-3″), 145.02 ($^3J_{C-F}$=7.1 Hz, C-1″), 140.89 (C-1′), 132.58 (C-3′), 129.73 ($^3J_{C-F}$=9.2 Hz, C-5″), 127.65 (C-4′), 127.40 (C-5′), 127.04 (C-6′), 126.18 (C-2′), 121.84 ($^4J_{C-F}$=3.1 Hz, C-6″), 112.82 ($^2J_{C-F}$=21.4 Hz, C-2″), 112.72 ($^2J_{C-F}$=21.4 Hz, C-4″), 28.32 (C-1), 26.57 ($^4J_{C-F}$=2.0 Hz, C-2), 17.07 (C-3). Anal. calcd for

$C_{15}H_{12}BrF$: C, 61.88; H, 4.15. Found: C, 61.54; H, 4.15. GLC analysis showed that compound (1*R**,2*R**)-**15c** had chemical purity higher than 97%.

3.3. Preparation of the Grignard reagents corresponding to compounds (1*R**,2*R**)-15a–c

1,2-Dibromoethane (25.8 μl, 0.3 mmol) was added to mixture of Mg turnings (0.365 g, 15.0 mmol) and dry THF (8 ml), which was stirred under nitrogen. The resulting mixture was maintained under reflux and a solution of (1*R**,2*R**)-**15a** (2.73 g, 10.0 mmol) in dry THF (25 ml) was added dropwise. The mixture was refluxed for 4 h and then cooled to rt. GLC analysis of a sample of this mixture, which was hydrolyzed with a saturated aqueous NH_4Cl solution, showed that (1*R**,2*R**)-**15a** had been completely consumed. The solution of this Grignard reagent was standardized by the Gilman double-titration method.[25] A similar procedure was employed to prepare the Grignard reagents corresponding to bromides (1*R**,2*R**)-**15b** and (1*R**,2*R**)-**15c**.

3.3.1. Methyl (*E*)(1*R,2*R**)-2-{2-[2-(phenyl)cyclopropyl]-phenyl}-3-methoxypropenoate [(1*R**,2*R**)-10a].** A 0.30 M THF solution of the Grignard reagent derived from (1*R**,2*R**)-**15a** (20.0 ml, 6.00 mmol) was added dropwise to a slurry of dry $ZnBr_2$ (1.76 g, 7.80 mmol) in THF (14 ml) which was stirred under argon at 0°C. After stirring for 15 min at 0°C, a solution of methyl (*Z*)-2-iodo-3-methoxypropenoate (**11**) (1.21 g, 5.00 mmol) in THF (12 ml) and $Pd(PPh_3)_4$ (0.289 g, 0.250 mmol) were sequentially added and the resulting mixture, which was periodically monitored by GLC, was stirred for 70 h at rt. It was then poured into a cold saturated aqueous NH_4Cl solution (150 ml) and extracted with diethyl ether (4×50 ml). The organic extract was washed with water, dried with Na_2SO_4, filtered over Celite, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel using benzene as eluant to yield (1*R**,2*R**)-**10a** (1.23 g, 80%) as a colourless solid. Mp 67–70°C. MS: *m*/*z* (%): 308 (1), 217 (93), 216 (62), 215 (59), 204 (95), 202 (56), 189 (49), 134 (100), 121 (35), 115 (30), 91 (52). IR (KBr): ν 1705, 1638, 1254, 1136, 1043, 745 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.44 (1H, s, H-3), 7.30 (1H, dd, *J*=7.6 and 7.6 Hz, H-4′), 7.28 (1H, dd, *J*=7.6 and 7.6 Hz, H-6″), 7.26 (1H, dd, *J*=7.6 and 7.6 Hz, H-8″), 7.21 (1H, dd, *J*=7.6 and 7.6 Hz, H-5′), 7.16 (1H, m, H-7″), 7.13 (1H, d, *J*=7.6 Hz, H-6′), 7.07 (1H, m, H-3′), 7.07 (2H, d, *J*=7.6 Hz, H-5″ and H-9″), 3.72 (3H, brs, H-5), 3.40 (3H, brs, H-4), 2.13 (1H, ddd, *J*=8.9, 5.5 and 5.5 Hz, H-2″), 2.02 (1H, ddd, *J*=8.7, 5.5 and 5.5 Hz, H-1″), 1.47 (1H, ddd, *J*=8.7, 5.5 and 5.5 Hz, H-3″b), 1.30 (1H, ddd, *J*=8.9, 5.5 and 5.5 Hz, H-3″a). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.30 (C-1), 159.92 (C-3), 143.03 (C-4″), 141.12 (C-2′), 132.95 (C-1′), 130.65 (C-6′), 128.23 (C-6″ and C-8″), 128.06 (C-4′), 125.48 (C-5′), 125.39 (C-5″ and C-9″), 125.38 (C-3′), 123.88 (C-7″), 110.48 (C-2), 61.68 (C-5), 51.56 (C-4), 27.73 (C-2″), 26.01 (C-1″), 17.41 (C-3″). Anal. calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.18; H, 6.77. GLC analysis showed that (1*R**,2*R**)-**10a** had purity higher than 98.5%.

3.3.2. Methyl (*E*)(1*R,2*R**)-2-{2-[2-(4-methoxyphenyl)-cyclopropyl]phenyl}-3-methoxypropenoate [(1*R**,2*R**)-10b].** A 0.30 M solution of the Grignard reagent derived from (1*R**,2*R**)-**15b** (21.4 ml, 6.42 mmol) was added dropwise to a slurry of dry $ZnBr_2$ (1.88 g, 8.35 mmol) in THF (15 ml) which was stirred under argon at 0°C. After stirring for 15 min at 0°C, a solution of **11** (1.29 g, 5.35 mmol) in THF (13 ml) and $Pd(PPh_3)_4$ (0.309 g, 0.267 mmol) was sequentially added and the reaction mixture was stirred for 72 h at rt. It was then poured into a cold saturated aqueous NH_4Cl solution (100 ml) and extracted with diethyl ether (4×50 ml). After usual workup, the crude reaction product was diluted with the solvent which was subsequently used for its purification by MPLC and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using a mixture of petroleum ether and diethyl ether (60/40) as eluant, to give (1*R**,2*R**)-**10b** (1.23 g, 68%) as a colourless solid. Mp 86–88°C. MS: *m*/*z* (%): 338 (2), 247 (13), 215 (13), 189 (15), 165 (25), 164 (100), 151 (69), 149 (26), 121 (79), 115 (73), 91 (22). IR (KBr): ν 1702, 1616, 1515, 1247, 1127, 1101 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.46 (1H, s, H-3), 7.28 (1H, ddd, *J*=7.5, 7.5 and 1.4 Hz, H-4′), 7.19 (1H, ddd, *J*=7.5, 7.5 and 1.4 Hz, H-5′), 7.12 (1H, dd, *J*=7.5 and 1.4 Hz, H-6′), 7.04 (1H, d, *J*=7.5 Hz, H-3′), 7.01 (2H, d, *J*=8.7 Hz, H-5″ and H-9″), 6.81 (2H, d, *J*=8.7 Hz, H-6″ and H-8″), 3.79 (3H, s, H-10″), 3.59 (3H, brs, H-5), 3.56 (3H, brs, H-4), 2.06 (1H, ddd, *J*=8.7, 5.3 and 5.3 Hz, H-1″), 1.99 (1H, ddd, *J*=8.7, 5.3 and 5.3 Hz, H-2″1.39 (1H, ddd, *J*=8.7, 5.5 and 5.3 Hz, H-3″a), 1.23 (1H, ddd, *J*=8.7, 5.5 and 5.3 Hz, H-3″b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.30 (C-1), 159.82 (C-3), 157.71 (C-7″), 141.36 (C-2′), 135.09 (C-4″), 132.84 (C-1′), 130.67 (C-6′), 128.02 (C-4′), 126.63 (C-5″and C-9″), 125.45 (C-5′), 124.17 (C-3′), 113.73 (C-6″ and C-8″), 111.00 (C-2), 61.71 (C-5), 55.32 (C-10″), 51.53 (C-4), 26.64 (C-2″), 25.29 (C-1″), 17.07 (C-3″). Anal. calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.87; H, 6.35. GLC analysis showed that (1*R**,2*R**)-**10b** had purity higher than 99%.

3.3.3. Methyl (*E*)(1*R,2*R**)-2-{2-[2-(3-fluorophenyl)cyclopropyl]phenyl}-3-methoxypropenoate [(1*R**,2*R**)-10c].** A 0.30 M solution of the Grignard reagent derived from (1*R**,2*R**)-**15c** (25.0 ml, 7.50 mmol) was added dropwise to a slurry of dry $ZnBr_2$ (2.20 g, 9.77 mmol) in THF (18 ml) which was stirred under argon at 0°C. After stirring for 15 min at 0°C, a solution of **11** (1.52 g, 6.26 mmol) in THF (15 ml) and $Pd(PPh_3)_4$ (0.362 g, 0.313 mmol) was sequentially added and the reaction mixture was stirred for 96 h at rt. After usual workup the crude reaction product was diluted with the solvent, which was subsequently used for its purification by MPLC and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using benzene as eluant, to give (1*R**,2*R**)-**10c** (1.55 g, 76%) as a colourless solid. Mp 72–75°C. MS: *m*/*z* (%): 326 (1), 235 (20), 204 (53), 189 (26), 152 (100), 139 (39), 129 (15), 115 (46), 109 (60), 102 (24), 75 (35). IR (KBr): ν 1703, 1635, 1284, 1261, 1139 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.44 (1H, s, H-3), 7.29 (1H, ddd, *J*=7.5, 7.5 and 1.4 Hz, H-4′), 7.21 (1H, ddd, *J*=7.5, 7.5 and 4.0 Hz, H-5′), 7.21 (1H, ddd, *J*=8.2, 7.8 and 6.0 Hz, H-8″), 7.13 (1H, dd, *J*=7.5 and 1.4 Hz, H-6′), 7.06 (1H, d, *J*=7.5 Hz, H-3′), 6.86 (1H,

ddd, J=7.8, 1.4 and 1.0 Hz, H-9″), 6.84 (1H, dddd, J=8.6, 8.2, 2.5 and 1.0 Hz, H-7″), 6.75 (1H, ddd, J=10.4, 2.5 and 1.4 Hz, H-5″), 3.62 (3H, brs, H-5), 3.56 (3H, brs, H-4), 2.13 (1H, ddd, J=9.0, 6.0 and 5.0 Hz, H-1″), 2.00 (1H, ddd, J=8.8, 5.4 and 5.0 Hz, H-2″), 1.49 (1H, ddd, J=8.8, 6.0 and 5.3 Hz, H-3″a), 1.30 (1H, ddd, J=9.0, 5.4 and 5.3 Hz, H-3″b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.10 (C-1), 163.04 ($^1J_{C-F}$=244.1 Hz, C-6″), 159.79 (C-3), 146.00 ($^3J_{C-F}$=7.1 Hz, C-4″), 140.68 (C-2′), 133.01 (C-1′), 130.77 (C-6′), 129.61 ($^3J_{C-F}$=7.5 Hz, C-8″), 128.06 (C-4′), 125.78 (C-5′), 124.57 (C-3′), 121.27 ($^4J_{C-F}$= 3.0 Hz, C-9″), 112.31 ($^2J_{C-F}$=21.4 Hz, C-7″), 112.29 ($^2J_{C-F}$=21.4 Hz, C-5″), 111.10 (C-2), 61.70 (C-5), 51.50 (C-4), 27.07 (C-2″), 26.27 (C-1″), 17.36 (C-3″). Anal. calcd for $C_{20}H_{19}FO_3$: C, 73.60; H, 5.87. Found: C, 73.49; H, 5.86. GLC analysis showed that (1R^*,2R^*)-**10c** was 98% chemically pure.

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References

1. (a) Clough, J. M. *Nat. Prod. Rep.* **1993**, *10*, 565–574. (b) Anke, T.; Steglich, W. In *Biologically Active Molecules*; Schlunegger, U. P., Ed.; Springer: Berlin, 1989; pp. 9–25. (c) Sauter, H.; Steglich, W.; Anke, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 1328–1349.
2. (a) Beautement, K.; Clough, J. M.; de Fraine, P. J.; Godfrey, C. R. A. *Pestic. Sci.* **1991**, *31*, 499–519. (b) Sauter, H.; Ammermann, E.; Röhl, F. In *Strobilurins—From Natural Products to a New Class of Fungicides in Crop Protection Agents from Nature: Natural Products and Analogues*; Copping, L. G., Ed.; The Royal Society of Chemistry: Cambridge, 1996. (c) Clough, J. M.; Godfrey, C. R. A. In *Fungicidal Activity*; Hutson, D. H., Miyamoto, J., Eds.; Wiley: Chichester, 1998; pp. 109–148.
3. (a) Godfrey, C. R. A.; Streeting, I.; Cheethmam, R. EP-A 382375, 1989. (b) Godfrey, C. R. A.; Streeting, I.; Cheethmam, R. *Chem. Ind.* **1997**, 7.
4. Wenderoth, B.; Rentzea, C.; Ammermann, E.; Pommer, E. H.; Steglich, W.; Anke, T. EP-A 253213, 1986.
5. (a) de Fraine, P. J.; Martin, A. EP-A 370629, 1988. (b) Isenring, H. P.; Trah, S.; Weiss, B. WO-A 90/07493, 1988.
6. (a) Frednhagen, A.; Kühn, A.; Peter, H. H.; Cuomo, V.; Giuliano, U. *J. Antibiot.* **1990**, *43*, 655–660. (b) Fredenhagen, A.; Hug, P.; Peter, H. H. *J. Antibiot.* **1990**, *43*, 661–667.
7. For the synthesis of strobilurins in which the methyl (*E*)-3-methoxypropenoate unit is linked to substituted aromatic substrates, see: (a) Hodgson, D. M.; Witherington, J.; Moloney, B. A.; Richards, I. C.; Brayer, J.-L. *Synlett* **1995**, 32–34. (b) Rossi, R.; Bellina, F.; Carpita, A. *Synlett* **1996**, 356–358. (c) Clough, J. M.; Evans, A. D.; de Fraine, P. J.; Fraser, T. E. M.; Godfrey, C. R. A.; Youle, D. *ACS Symp. Ser.* **1994**, *551*, 37–53. (d) Yue, X.; Qing, F. I.; Sun, H.; Fan, J. *Tetrahedron Lett.* **1996**, *37*, 8213–8216. (e) Rossi, R.; Bellina, F.; Ciucci, D.; Carpita, A.; Fanelli, C. *Tetrahedron* **1998**, *54*, 7595–7614.
8. For the synthesis of analogues of strobilurins in which the methyl (*E*)-*O*-methyloximinoacetate group is linked to a substituted aromatic ring, see: (a) Rossi, R.; Carpita, A.; Pazzi, P.; Mannina, L.; Valensin, D. *Tetrahedron*, **1999**, *55*, 11343–11364, and references cited therein. (b) Ref 7c.
9. For a summarizing account which describes the known processes for the construction of enol ether, oxime ether and oxime ether amide pharmacophores as well as Pd-catalyzed couplings of entire pharmacophores to bridging arene ortho to preexisting side chains, see: Ref. 7c.
10. For reactivity studies and molecular orbital calculations of cyclopropanes, see: Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229–234.
11. (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255.
12. For the synthesis of cyclopropylboronic acid esters by treatment of alkenylboronic acid esters with diazomethane in the presence of catalytic quantities of $Pd(OAc)_2$, see: (a) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605–609. (b) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845–2847. (c) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287–8297.
13. (a) Takai, K.; Kakiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671–2673. (b) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988.
14. For similar Pd-catalyzed cross-coupling reactions of cyclopropylboronic acids, see: (a) Wang, X.-Z.; Deng, M.-Z. *J. Chem. Soc., Perkin Trans 1* **1996**, 2663–2664. (b) Zhou, S.-M.; Yan, Y.-L.; Deng, M.-Z. *Synlett* **1998**, 198–200. (c) Ref 12b. (d) Zhou, S.-M.; Deng, M.-Z. *Tetrahedron Lett.* **2000**, *41*, 3951–3954.
15. Yang, I.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621–8624.
16. de Meijere, A.; Song, Z. Z.; Lansky, A.; Hyuda, S.; Rauch, K.; Noltenmeyer, M.; König, B.; Knieriem, B. *Eur. J. Org. Chem.* **1998**, 2289–2299.
17. (a) Heck, R. F. *Org. React.* **1982**, *27*, 345–390. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; vol. 4, pp. 833–863.
18. For previously reported Pd-catalyzed vinylic substitutions with bromoiodoaromatics, see: (a) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078–4080. (b) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131–3132. (c) Carlström, A.-S.; Frejd, T. *J. Org. Chem.* **1991**, *56*, 1289–1293. (d) Gibson, S. E.; Jones, J.-O.; Mc Cague, R.; Tozer, M.; Whitcombe, N. J. *Synlett*, **1999**, 954–956.
19. For a review on transition metal-catalyzed selective carbon–carbon bond forming reactions which involve dihalo(hetero)-arenes and dihaloethenes, see:Rossi, R.; Bellina, F. *Org. Prep. Proced. Int.* **1997**, *29*, 137–176.
20. For previous syntheses of (*E*)-2-bromostilbenes, see: (a) Detar, D. F.; Carpino, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 475–479. (b) Darses, S.; Jeffery, T.; Brayer, J.-L.; Demoute, J.-P.; Genet, J.-P. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1095–1102.

21. For previous syntheses of (*E*)-2-bromo-4′-methylstilbene, see: Brown, C.; Sikkel, B. J.; Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1982**, 3007–3010.
22. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121–124.
23. Itatani, H.; Bailar, J. C. *J. Am. Oil Chem. Soc.* **1967**, *44*, 147–151.
24. De Boer, T. J.; Backer, J. *Org. Synth. Coll.* **1963**, *IV*, 250–253.
25. Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379–1389.