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Synthesis of the racemic forms of carbon–carbon double bond locked analogues of strobilurins which are characterized by a 2-arylcyclopropane ring *cis*-substituted at C-1 by the methyl (*E*)-3-methoxypropenoate unit

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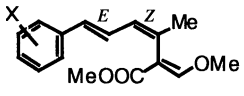
Abstract—The racemic forms of three new carbon–carbon double bond locked analogues of strobilurins, which are characterized by a 2-arylcyclopropane ring *cis*-substituted at C-1 by the methyl (*E*)-3-methoxypropenoate unit, have been synthesized according to a strategy which involves the palladium-catalyzed synthesis of methyl (*E*)-3-methoxy-2-[(*Z*)-2-(aryl)ethenyl]propenoates and their stereospecific cyclopropanation.

1. Introduction

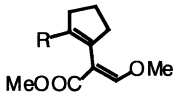
Strobilurins **1** are a group of metabolites isolated from cultures of Basidiomycetes[1] which served as leads for the design and development of photostable structural analogues able to control the major classes of fungi which affect crops.[2] These analogues, which differ from the lead structures in their pharmacophore and/or their lipophilic subunits, include agricultural fungicides of general formula **2**–**4**, which are characterized by a suitably *ortho*-substituted aromatic ring attached to the methyl (*E*)-3-methoxypropenoate unit,[3] the methyl (*E*)-*O*-methyloximinoacetate group[4] or the (*E*)-*O*-methyloximino-*N*-methylacetamide group, respectively.[2,5]



1

2: Y = MeOCH=C(E)–COOMe
3: Y = MeON=C(E)–COOMe
4: Y = MeON=C(E)–CONHMe

However, attention has also been paid to the synthesis of photostable carbon–carbon double bond locked analogues of **1** of general formula **5** in which their pharmacophore, i.e. the methyl (*E*)-3-methoxypropenoate unit, is linked to a substituted cyclopentenyl ring[3d,e] and, more recently, concise procedures[6] for the stereocontrolled preparation of compounds (1*R**,2*R**)-**6**, (1*R**,2*R**)-**7a**, (1*R**,2*R**)-**7b** and (1*R**,2*R**)-**7c**, which do not contain carbon–carbon double bond in their lipophilic subunit and are characterized by a *trans*-1,2-disubstituted cyclopropane ring, have also been reported.



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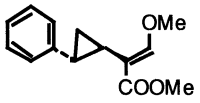
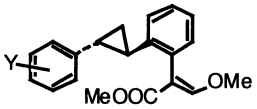


(1*R**,2*R**)-**6**



(1*R**,2*R**)-**7a**: Y = H
(1*R**,2*R**)-**7b**: Y = 4-MeO
(1*R**,2*R**)-**7c**: Y = 3-F

As regards the bioactivity of compounds **1** and their analogues, it should also be noted that naturally-occurring strobilurins D,[7] E[8] and F[7] have been found to exhibit powerful cytostatic activities in addition to antifungal properties and that, recently, we found that some analogues of **1**, which had been synthesized in our laboratory, such as compounds **2a**,[3e] **2b**,[3e] **3a**,[4] (1*R**,2*R**)-**7a**,[6] (1*R**,2*R**)-**7b**[6] and (1*R**, 2*R**)-**7c**,[6] are significantly active in the National Cancer Institute (NCI) 3-cell line, one dose primary anticancer assay at a 1.00×10^{-4} M concentration.[9] Nevertheless, these last compounds showed limited cytotoxicity against the NCI 60-cell line panel.

Keywords: strobilurin; carbon–carbon double bond; methoxy propenoate.

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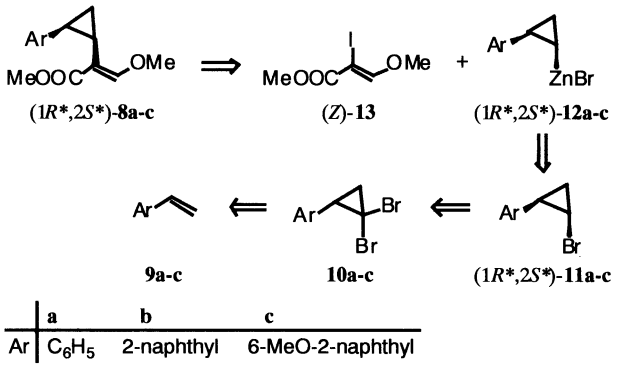
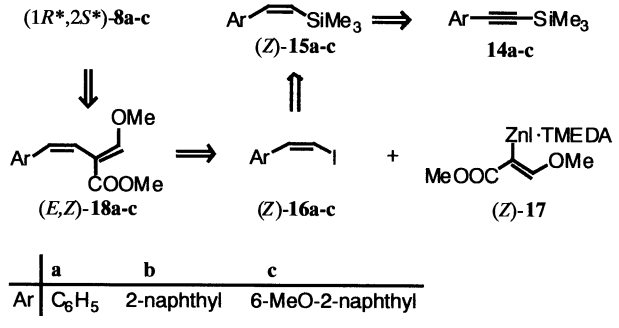


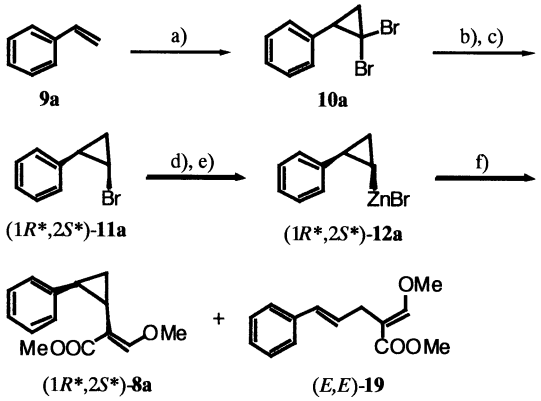
Scheme 1. Retrosynthetic analysis for compounds (1*R**,2*S**)-**8a–c**.

More recently, as part of a project aimed at developing concise and efficient protocols for the selective synthesis of analogues of natural products which are potentially cytotoxic against human tumor cell lines,[10,11] we decided to develop a general procedure for the synthesis of carbon–carbon double bond locked analogues of **1**, which are characterized by a 2-arylcyclopropane ring *cis*-substituted at C-1 by the methyl (*E*)-3-methoxypropenoate unit, and to evaluate their cytotoxic properties. To our knowledge, this type of analogue of **1** has not been described so far. Thus, we examined the possibility of accessing the racemic forms of three of these analogues, i.e. compounds (1*R**,2*S**)-**8a**, (1*R**,2*S**)-**8b** and (1*R**,2*S**)-**8c**, by a chemistry similar to that we used to prepare compounds (1*R**,2*R**)-**7a–c**.[6] In particular, we speculated that compounds (1*R**,2*S**)-**8a–c** might be prepared by a reaction sequence based on the retrosynthetic analysis depicted in Scheme 1, in which a key step is the palladium-catalyzed cross-coupling reaction between easily available methyl (*Z*)-2-iodo-3-methoxypropenoate [(*Z*)-**13**][3a,e] and the 1-[2-(aryl)cyclopropyl]zinc bromides (1*R**,2*S**)-**12a–c**.

Moreover, we considered the possibility to synthesize alternatively compounds (1*R**,2*S**)-**8a–c** by a reaction sequence based on the retrosynthetic analysis reported in Scheme 2,



Scheme 2. Alternative retrosynthetic analysis for compounds (1*R**,2*S**)-**8a–c**.



Scheme 3. (a) $CHBr_3$ (3.00 equiv.), $BnEt_3N^+Cl^-$ (1.6 mol%), NaOH (4.00 equiv.), H_2O, 60°C, 2 h; (b) Zn/Cu (7.83 equiv.), THF and H_2O, room temperature, 18 h; (c) MPLC on silica gel; (d) BuLi (1.02 equiv.), THF, hexane, −90°C, 1.5 h; (e) $ZnBr_2$ (1.20 equiv.), THF, −90°C to room temperature; (f) (*Z*)-**13** (0.83 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), THF, reflux, 8 h.

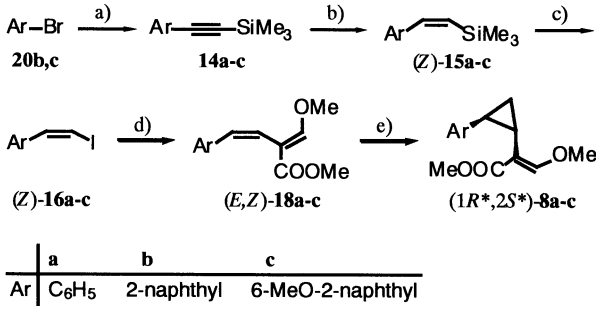
which involves the preparation and use of the methyl (*E*)-3-methoxy-2-[(*Z*)-2-(aryl)ethenyl]propenoates (*E*,*Z*)-**18a–c**.

We now wish to describe and comment on the results of these synthetic studies and to report the results of tests to evaluate the cytotoxic activities exhibited by compounds (1*R**,2*S**)-**8a–c** against the NCI 3-cell line panel.

2. Results and discussion

We began our synthetic studies by turning our attention to the synthesis of compound (1*R**,2*S**)-**8a** according to the retrosynthetic analysis depicted in Scheme 1. Thus, a possible precursor to this compound, i.e. 1,1-dibromo-2-phenylcyclopropane (**10a**), which was prepared from styrene (**9a**)[12] in 88% yield, was converted according to the literature[13] into a stereoisomeric mixture of (1*R**,2*S**)- and (1*R**,2*R**)-**11a** by treatment with a freshly prepared zinc–copper couple in THF and water at room temperature (Scheme 3).

Purification of this mixture by MPLC on silica gel allowed isolation of pure (1*R**,2*S**)-**11a** in 35% yield. This compound was then converted into the corresponding organozinc bromide (1*R**,2*S**)-**12a** by the procedure used in the literature for the stereospecific synthesis of 2-(hetero)aryl-1-phenylcyclopropanes from a stereoisomeric mixture of 1-bromo-2-phenylcyclopropane and (hetero)aryl halides.[12] In particular, (1*R**,2*S**)-**11a** was reacted with 1.02 equiv. of butyllithium in THF and hexane at −90°C for 1.5 h and the resulting mixture was added to a solution of 1.2 equiv. of $ZnBr_2$ in THF maintained at −90°C, which was then allowed to warm up to 20°C. Finally, 0.83 equiv. of iodide (*Z*)-**13** and 5 mol% $Pd(PPh_3)_4$ were added and the mixture refluxed for 8 h. Unexpectedly, this palladium-catalyzed reaction provided a mixture of the desired cross-coupled product (1*R**,2*S**)-**8a** and methyl (*E*)-3-methoxy-2-[(*E*)-3-phenyl-2-propen-1-yl]propenoate [(*E*,*E*)-**19**], where this last compound was the major component (Scheme 3). Purification of this mixture by MPLC on silica gel allowed



Scheme 4. (a) $Me_3Si–≡–MgBr$ (**21**)(1.13 equiv.), $Pd(PPh_3)_4$ (3.4 mol%), THF, C_6H_6, reflux, 4.0–5.5 h; (b) $HAl(i\text{-}Bu)_2$ (1.00–1.05 equiv.), *N*-methylpyrrolidine (1.00–1.05 equiv.), hexane, 60–64°C, 70–142 h then 0°C, H_2O; (c) NIS (2.0 equiv.), CH_3CN, room temperature, 35–50 min; (d) (*Z*)-**17** (1.50 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF, 55°C, 16.5–22 h; (e) $CF_3COOZnCH_2I$ (1.85–4.00 equiv.), CH_2Cl_2, 0–20°C, 1–4 h, then H_3O^+.

isolation of (1*R**,2*S**)-**8a** and (*E*,*E*)-**19** in 6 and 23% yield, respectively.

Taking into account this unsatisfactory result, we thought it right to drop the idea to prepare compounds (1*R**,2*S**)-**8b** and (1*R**,2*S**)-**8c** via the retrosynthetic approach indicated in Scheme 1 and to verify if the rapid synthesis of compounds (1*R**,2*S**)-**8a–c** might be conveniently and efficiently performed using the reaction sequence reported in Scheme 4, which is based on the retrosynthetic analysis depicted in Scheme 2.

Whereas one of the possible precursors to compounds (1*R**,2*S**)-**8a–c**, i.e. **14a**, was commercially available, the 2-aryl-1-trimethylsilylacetylenes **14b** and **c** were prepared in 88 and 98% yield, respectively, by reaction of aryl bromides **20b** and **c** with trimethylsilyl-ethynylmagnesium bromide (**21**) in THF/benzene in the presence of a catalytic amount of $Pd(PPh_3)_4$. Compounds **14a–c** were then converted into the corresponding (*Z*)-2-aryl-1-trimethylsilyl-ethenes (*Z*)-**15a**, (*Z*)-**15b** and (*Z*)-**15c** in 66, 79 and 65% yield, respectively, by *cis*-hydroalumination with diisobutyl-aluminum hydride (DIBAH) and *N*-methylpyrrolidine in hexane at 60–64°C followed by hydrolysis.[14] Treatment of (*Z*)-**15a** and (*Z*)-**15b** with 2.0 equiv. of *N*-iodosuccinimide (NIS) in acetonitrile at room temperature according to the method described by Kishi and co-workers[15] allowed isolation, in 89 and 86% yield, of iodides (*Z*)-**16a** and (*Z*)-**16b** having stereoisomeric purity higher than 97% (Scheme 4). However, when a similar procedure was used to prepare stereospecifically (*Z*)-**16c**, a mixture of (*Z*)- and (*E*)-**16c** in a 72:28 molar ratio, respectively, was obtained in 95% yield. It should also be noted that attempts to prepare stereoisomerically pure (*Z*)-**16c** from (*Z*)-**15c** by stereospecific iodine–silicon exchange with IPy_2BF_4/HBF_4 in acetonitrile or CH_2Cl_2[16] under various experimental conditions were fruitless. In fact, this *ipso*-substitution reaction provided mixtures of (*Z*)- and (*E*)-**16c** in 72–40:28–60 molar ratios, which were also contaminated by 1–7% of 6-methoxy-2-ethenylnaphthalene derived from protodesilylation of (*Z*)-**15c**. It should also be noted that we did not succeed in obtaining stereoisomerically pure (*Z*)-**16c** even by chromatographic purification of mixtures of (*Z*)- and (*E*)-**16c** in which (*Z*)-**16c** was the major component.

As shown in Scheme 4, compounds (*Z*)-**16a** and (*Z*)-**16b** as well as a mixture of (*Z*)- and (*E*)-**16c** in 72:28 molar ratio, respectively, were then reacted with 1.5 equiv. of TMEDA-complexed (*Z*)-2-methoxy-1-(methoxycarbonyl)ethenyl-zinc iodide [(*Z*)-**17**][3e] in THF at 55°C in the presence of 5 mol% $Pd(PPh_3)_4$. Purification by MPLC on silica gel of the resulting crude cross-coupled products allowed isolation of methyl (*E*)-3-methoxy-2-[(*Z*)-2-(phenyl)ethenyl]propenoate [(*E*,*Z*)-**18a**], methyl (*E*)-3-methoxy-2-[(*Z*)-2-(2-naphthyl)-ethenyl]propenoate [(*E*,*Z*)-**18b**] and methyl (*E*)-3-methoxy-2-[(*Z*)-2-(6-methoxy-2-naphthyl)ethenyl]-propenoate [(*E*,*Z*)-**18c**] in 41, 72 and 35% yield, respectively. Compounds (*E*,*Z*)-**18a** and (*E*,*Z*)-**18b** were stereoisomerically pure and (*E*,*Z*)-**18c** had stereoisomeric purity higher than 97%.

Finally, compounds (*E*,*Z*)-**18a–c** were stereospecifically cyclopropanated according to the general procedure which involves treatment of a CH_2Cl_2 solution of an alkene with 2.0–4.0 equiv. of the organozinc species generated by reaction of $ZnEt_2$ with equimolar amounts of trifluoroacetic acid and CH_2I_2.[17] In particular, the cyclopropanation reaction of (*E*,*Z*)-**18a** and (*E*,*Z*)-**18b** required 4.0 equiv. of $CF_3COOZnCH_2I$, occurred at room temperature in 1.5–4 h and provided pure compounds (1*R**,2*S**)-**8a** and (1*R**,2*S**)-**8b** in 71 and 75% yield, respectively. However, when a similar molar excess of $CF_3COOZnCH_2I$ was used for cyclopropanation of (*E*,*Z*)-**18c**, a complex reaction mixture, which contained (1*R**,2*S**)-**8c**, a stereoisomer of this compound as well as significant amounts of two byproducts having a molecular ion peak higher by 28 mass units than (1*R**,2*S**)-**8c**, was formed.

Nevertheless, it was found that, when the cyclopropanation

Table 1. Results of the cytotoxicity tests for compounds (1*R**,2*S**)-**8a–c** and (1*R**,2*R**)-**6** in the NCI 3-cell line, one dose primary anticancer assay

Entry	Compound	Growth percentage			Activity
		SF-269 (CNS)	MCF-7 (Breast)	NCI-H460 (Lung)	
1	(1*R**,2*S**)-**8a**	83	82	98	Inactive
2	(1*R**,2*S**)-**8b**	16	12	3	Active
3	(1*R**,2*S**)-**8c**	91	106	130	Inactive
4[a]	(1*R**,2*R**)-**6**	67	69	86	Inactive

In the protocol used, each cell line was inoculated and preincubated on a microtiter plate. Tests agents were then added at 1.00×10^{-4} M concentration in DMSO and the culture incubated for 48 h. End point determinations were made with alamar blue.

[a] See Ref. 9.

reaction of (*E*,*Z*)-**18c** was performed at 0°C for 1 h using 1.85 equiv. of $CF_3COOZnCH_2I$, the reaction went to completion and the amount either of the two above mentioned byproducts or of the stereoisomer of (1*R**,2*S**)-**8c** was minimized. Purification of the crude reaction mixture allowed us to isolate stereoisomerically pure (1*R**,2*S**)-**8c** in 70% yield.

It should also be noted that an attempt to perform alternatively the cyclopropanation reaction of (*E*,*Z*)-**18a** by the procedure involving treatment of this compound with 4.0 equiv. of diazomethane in diethyl ether at 0–5°C in the presence of a catalytic amount of $Pd(OAc)_2$[18] was unsuccessful. In fact, this reaction did not provide (1*R**,2*S**)-**8a** and compound (*E*,*Z*)-**18a** could be completely recovered from the reaction mixture.

With compounds (1*R**,2*S**)-**8a–c** now readily available, their evaluation in the NCI 3-cell line, one dose primary anticancer assay at a 1.00×10^{-4} M concentration was performed. This 3-cell line panel consisted of SF-269 (CNS), MCF-7 (Breast) and NCI-H460 (Lung). The results for each test agent are reported in Table 1 as percent of growth of the treated cells when compared to the untreated control cells. As shown from the data reported in this table, where the cytotoxicity values of compounds (1*R**,2*S**)-**8a–c** are compared to those recently found for (1*R**,2*R**)-**6**,[9] whereas compounds (1*R**,2*S**)-**8a**, (1*R**,2*R**)-**6** and (1*R**,2*S**)-**8c** were inactive, compound (1*R**,2*S**)-**8b,** which represents an analogue of strobilurin A in which the *Z* and *E* double bonds of the lipophilic subunit of this natural product are locked in a *cis*-1,2-disubstituted cyclopropane ring and in an aromatic ring of a 2-naphthyl system, respectively, was found to be significantly cytotoxic against the NCI-3-cell line panel. Thus, these data seem to indicate that: (i) the presence of a 2-naphthyl ring linked at C-2-of a cyclopropane ring *cis*-substituted at C-1 by the methyl (*E*)-3-methoxypropenoate unit is beneficial to cytotoxicity of analogues of strobilurins, which are characterized by a *cis*-1,2-disubstituted cyclopropane ring; (ii) the introduction of a 6-methoxy-2-naphthyl group in place of the 2-naphthyl group abolishes cytotoxicity.

3. Conclusions

In this study, we developed a concise procedure for the synthesis of the racemic forms of three carbon–carbon double bond locked analogues of naturally-occurring strobilurins **1**, which are characterized by a 2-arylcyclopropane ring *cis*-substituted at C-1 by the methyl (*E*)-3-methoxypropenoate unit. The strategy used to prepare these compounds, which involves the palladium-catalyzed synthesis of methyl (*E*)-3-methoxy-2-[(*Z*)-2-(aryl)ethenyl]-propenoates and their stereospecific cyclopropanation, is very flexible and appears to be suitable for the synthesis of a large variety of analogues of **1** in which the *Z* and *E* carbon–carbon double bonds present in the lipophilic subunit of these natural substances are locked in a *cis*-1,2-disubstituted cyclopropane ring and in an aromatic ring, respectively. Finally, it should be noted that one of the analogues of **1**, which was prepared in this study, i.e. compound (1*R**,2*S**)-**8b**, proved to be significantly cytotoxic in the NCI 3-cell line, one dose primary anticancer assay.

4. Experimental

4.1. General

Melting points and boiling points are uncorrected. Precoated aluminum silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech At-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC on silica gel (Merck silica gel 60, particle size 0.015–0.040 mm) were performed on a Büchi B-680 system using a Knauer K-2400 differential refractometer as detector. GLC/MS analyses were performed using a Perkin–Elmer Q-Mass 910 Mass Spectrometer (quadrupole mass spectrometer) interfaced with a Perkin–Elmer 8500 gas-chromatograph. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or on a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard. The structure of compound (*E*,*E*)-**19** was assigned on the basis of its ^1H NMR and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of NMR techniques which included ^1H–^1H COSY, NOESY (mixing time: 400 ms), Heteronuclear Multiple Quantum Coherence (HMQC) and HMBC (Heteronuclear Multiple Bond Correlation). 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. Solvents were dried and distilled before use. The following compounds were prepared by published procedures: (*Z*)-**13**,[3a,e] **10a**,[12] $Pd(PPh_3)_4$,[19] (*Z*)-**17**,[3e] and diazomethane.[20] All the other reagents are commercially available and were used as purchased.

4.1.1. (1*R,2*S**)-1-Bromo-2-phenylcyclopropane [(1*R**,2*S**)-11a].** To a stirred solution of glacial acetic acid (125 ml) and $Cu(OAc)_2$ (2.50 g, 12.5 mmol), which was heated to 110°C, was added zinc powder (25.0 g, 382.0 mmol) rapidly. The mixture was stirred for an additional 1 min and then filtered hot. The resulting couple was washed with acetic acid (30 ml) and diethyl ether (2×30 ml) and heated under vacuum (120°C, 0.05 mbar) for 3 h. After cooling to room temperature, THF (155 ml) was added to the couple and the mixture was stirred while 1,1-dibromo-2-phenylcyclopropane (**10a**) (13.47 g, 48.8 mmol) and deaerated water (12.5 ml) were added rapidly. The resulting reaction mixture was stirred overnight and then filtered through Celite. The filtrate was concentrated under reduced pressure (200 mbar) and the residue was purified by MPLC on silica gel using hexane as eluant to give (1*R**,2*S**)-**11a** (3.35 g, 35% yield) as a colorless liquid. Bp 74°C/1 mbar (lit.[21] bp 60–62°C/0.8 Torr). MS, *m*/*z* (%): 118 (10), 117 (100), 116 (11), 115 (56), 91 (23), 89 (7), 77 (3). ^1H NMR (200 MHz, $CDCl_3$): δ 7.29–7.25 (5H, m), 3.30 (1H, ddd, *J*=8.0, 7.0, 5.0 Hz), 2.30 (1H, ddd, *J*=9.5, 8.0, 7.0 Hz), 1.56 (1H, ddd, *J*=9.5, 7.0, 6.5 Hz), 1.31 ppm (1H, ddd, *J*=7.0, 6.5, 5.0 Hz).

The spectral properties of this compound were in agreement with those reported in the literature.[21]

4.1.2. Conversion of (1*R,2*S**)-11a into the corresponding organozinc bromide, (1*R**,2*S**)-12a, and palladium-catalyzed reaction between this organometallic compound and methyl (*Z*)-2-iodo-3-methoxypropenoate [(*Z*)-13].** A 1.77 M hexane solution of butyllithium (4.75 ml, 8.57 mmol) was added over 5 min to a solution of (1*R**,2*S**)-**11a** (1.65 g, 8.40 mmol) in THF (6 ml), which was stirred at −90°C. After stirring for 1.5 h, a solution of $ZnBr_2$ (2.27 g, 10.1 mmol) in THF (10 ml), which was cooled to −50°C, was added and the mixture was stirred for 1 h while the temperature was allowed to reach room temperature. A solution of compound (*Z*)-**13** (1.70 g, 7.00 mmol) in THF (10 ml) and $Pd(PPh_3)_4$ (404 mg, 0.350 mmol) were then added sequentially and the resulting mixture was stirred at room temperature for 27 h. It was then poured into a cold saturated aqueous NH_4Cl solution (100 ml) and extracted with benzene (4×30 ml). A GLC analysis of the organic extract, which was washed with H_2O (2×10 ml) and dried with Na_2SO_4, showed the presence of two new compounds in a ca. 1:3.7 molar ratio. The organic extract was concentrated under reduced pressure and the residue was purified by MPLC on silica gel using benzene as eluant. Concentration of the first eluted chromatographic fractions allowed us to obtain methyl (*E*)-3-methoxy-2-[(*E*)-(3-phenyl-2-propen-1-yl]propenoate [(*E*,*E*)-**19**] (0.40 g, 23% yield) as a pale yellow liquid. MS, *m*/*z* (%): 232 (1), 201 (11), 200 (55), 141 (87), 128 (68), 115 (100), 91 (58). IR (film): ν 1708, 1646, 1195, 1247, 1107 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.35, (1H, s), 7.32 (2H, d, *J*=7.5 Hz), 7.25 (2H, t, *J*=7.5 Hz), 7.16 (1H, t, *J*=7.5 Hz), 6.40 (1H, dt, *J*=16.0, 2.0 Hz), 6.21 (1H, dt, *J*=16.0, 6.5 Hz), 3.82 (3H, s), 3.71 (3H, s), 3.13 ppm (2H, dd, *J*=6.5, 2.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.5, 159.2, 137.8, 130.0, 128.3 (2C), 127.7, 126.8, 126.0 (2C), 108.8, 61.4, 51.2, 27.3 ppm. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.15; H, 6.77.

On the other hand, concentration of the last eluted chromatographic fraction allowed isolation of methyl (*E*) (1*R**,2*S**)-3-methoxy-2-[2-(phenyl)cyclopropyl]propenoate [(1*R**,2*S**)-**8a**] (0.11 g, 6% yield) as a pale yellow liquid. MS, *m*/*z* (%): 200 (63), 141 (100), 129 (60), 128 (82), 115 (83), 91 (43), 75 (41). IR (film): ν 1712, 1640, 1245, 1113, 1078 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35 (1H, s), 7.22–6.98 (5H, br m), 3.64 (3H, s), 3.48 (3H, s), 2.30 (1H, *pseudo*-dt, *J*=8.5, 6.0 Hz), 1.83 (1H, *pseudo*-ddt, *J*=8.5, 6.0, 1.5 Hz), 1.51 (1H, *pseudo*-q, *J*=6.0 Hz), 1.31 ppm (1H, *pseudo*-dt, *J*=8.5, 6.0 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 168.9, 161.2, 139.3, 127.5 (2C), 127.3 (2C), 125.2, 106.6, 61.4, 50.9, 22.4, 16.7, 11.1 ppm. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.21; H, 7.06.

4.1.3. 1-(2-Naphthyl)-2-trimethylsilylacetylene (14b). Trimethylsilylacetylene (6.71 g, 68.3 mmol) was slowly added to a 1.30 M THF solution of ethylmagnesium bromide (52.5 ml, 68.3 mmol) and the resulting mixture was maintained for 1 h under gentle reflux. It was then cooled to room temperature and added to a solution of 2-bromonaphthalene (**20b**) (12.52 g, 60.46 mmol) and $Pd(PPh_3)_4$ (2.40 g, 2.10 mmol) in benzene (70 ml). The resulting mixture was refluxed for 5.5 h, then cooled to room temperature, poured into a cold saturated aqueous NH_4Cl solution (250 ml) and extracted with diethyl ether (4×70 ml). The organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using hexane as eluant, to give **14b** (11.58 g, 88% yield) as a colorless solid. Mp 45–47°C (lit.[22] mp 44–44.5°C). MS, *m*/*z* (%): 224 (25), 210 (21), 209 (100), 179 (12), 155 (13), 104 (29), 90 (13). ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (1H, br s), 7.83–7.72 (3H, m), 7.53–7.42 (3H, m), 0.28 ppm (9H, s).

4.1.4. 1-(6-Methoxy-2-naphthyl)-2-trimethylsilylacetylene (14c). This compound was prepared in 98% yield starting from 2-bromo-6-methoxynaphthalene (**20c**) according to the same procedure used for the synthesis of **14b** from **20b**. Compound **14c** was a colorless solid. Mp 99–102°C. MS, *m*/*z* (%): 254 (54), 239 (100), 224 (5), 196 (14), 166 (5), 119 (8), 98 (5). IR (KBr): ν 2154, 1247, 1031, 857, 839 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (1H, d, *J*=2.0 Hz), 7.68 (1H, d, *J*=8.5 Hz), 7.64 (1H, d, *J*=8.0 Hz), 7.46 (1H, dd, *J*=8.5, 2.0 Hz), 7.14 (1H, dd, *J*=8.0, 2.0 Hz), 7.09 (1H, d, *J*=2.0 Hz), 3.91 (3H, s), 0.20 ppm (9H, s). Anal. calcd for $C_{16}H_{18}OSi$: C, 75.54; H, 7.13. Found: C, 75.73; H, 7.21.

4.1.5. (*Z*)-1-Phenyl-2-trimethylsilylethene [(*Z*)-15a]. A 1 M hexane solution of diisobutylaluminum hydride (DIBAH) (57.5 ml, 57.5 mmol) was added dropwise to *N*-methylpyrrolidine (4.89 g, 57.5 mmol). The resulting solution was then added dropwise to a stirred solution of 1-phenyl-2-trimethylsilylacetylene (**14a**) (10.02 g, 57.5 mmol) in hexane (40 ml) and the mixture was heated for 142 h at 60–64°C. After cooling to room temperature, water (25 ml) was cautiously added. Potassium sodium tartrate tetrahydrate (10.0 g) and hexane (100 ml) were then added to the suspension and the mixture was stirred for 0.5 h and then filtered. The filtrate was extracted with hexane (2×40 ml) and the organic extract was dried over Na_2SO_4 and concentrated under reduced pressure (260 mbar). The residue was fractionally distilled to give a mixture of (*Z*)-**15a** and **14a** (8.80 g) in a ca. 73:27 molar ratio, respectively. This mixture was dissolved in methanol (30 ml), treated with a 1 M KOH solution (20.0 ml, 20.0 mmol) and the resulting solution was stirred for 3 h at room temperature. It was then extracted with pentane (5×30 ml) and the organic extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure (260 mbar). The residue was fractionally distilled to give pure (*Z*)-**15a** (6.63 g, 66% yield) as a colorless liquid. Bp 63°C/2 mbar (lit.[14] bp 43–44°C/0.2 Torr). MS, *m*/*z* (%): 176 (18), 161 (100), 146 (13), 145 (85), 135 (42), 115 (12), 77 (11). IR (film): ν 1604, 1469, 1252, 851, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.36 (1H, d, *J*=15.0 Hz), 7.22 (5H, s), 5.83 (1H, d, *J*=15.0 Hz), 0.03 ppm (9H, s). The spectral properties of this compound were in agreement with those previously reported.[23]

4.1.6. (*Z*)-1-(2-Naphthyl)-2-trimethylsilylethene [(*Z*)-15b]. Compound **14b** (11.58 g, 51.61 mmol) was reacted with a 1 M hexane solution of DIBAH (54.2 ml, 54.2 mmol) and *N*-methylpyrrolidine (4.62 g, 54.2 mmol) for 70 h at 60–64°C according to the same procedure for

cis-hydroalumination of **14a**. The crude reaction product, which was obtained after hydrolysis of the reaction mixture followed by extraction with hexane (5×70 ml) and concentration of the organic extract under reduced pressure, was purified by MPLC on silica gel, using hexane as eluant, to give (*Z*)-**15b** (9.18 g, 79% yield) as a colorless liquid. MS, *m/z* (%): 226 (39), 211(100), 195 (74), 155 (14), 152 (32), 127 (8), 99 (7). IR (film): ν 1603, 1588, 1247, 857, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.87–7.68 (4H, m), 7.55–7.34 (4H, m), 5.92 (1H, d, J=15.0 Hz), 0.09 ppm (9H, s). Anal. calcd for $C_{15}H_{18}Si$: C, 79.57; H, 8.01. Found: C, 79.67; H, 7.89. GLC/MS analysis showed that (*Z*)-**15b** was chemically pure and had 96% stereoisomeric purity.

4.1.7. (*Z*)-1-(6-Methoxy-2-naphthyl)-2-trimethylsilylethene [(*Z*)-15c]. Compound **14c** (12.00 g, 47.17 mmol) was reacted with a 1 M hexane solution of DIBAH (49.5 ml, 49.5 mmol) and *N*-methylpyrrolidine (4.20 g, 49.5 mmol) for 137 h at 60–64°C according to the same procedure used for *cis*-hydroalumination of **14a**. The crude reaction product, which was obtained by hydrolysis of the reaction mixture followed by extraction with diethyl ether (5×70 ml) and concentration of the dried organic extract, was purified by MPLC on silica gel, using a mixture of petroleum ether and benzene (95:5) as eluant, to give 98% chemically pure (*Z*)-**15c** (7.83 g, 65% yield) as a colorless solid. Mp 64–67°C. MS, *m/z* (%): 256 (83), 242 (22), 241 (100), 225 (44), 215 (26), 152 (12), 139 (19). IR (KBr): ν 1626, 1605, 1586, 1251, 837 cm^{-1}. ^1H NMR (200 MHz, benzene-d_6): δ 7.68 (1H, br s), 7.53 (1H, d, J=15.0 Hz), 7.54–7.42 (2H, m), 7.22–7.12 (2H, m), 6.90 (1H, d, J=2.5 Hz), 5.93 (1H, d, J=15.0 Hz), 3.38 (3H, s), 0.15 ppm (9H, s). Anal. calcd for $C_{16}H_{20}OSi$: C, 74.94; H, 7.87. Found: C, 75.09; H, 7.76. GLC/MS and ^1H NMR analyses showed that (*Z*)-**15c** was stereoisomerically pure. It should be noted that, when the ^1H NMR spectrum of (*Z*)-**15c** was recorded in $CDCl_3$, this compound underwent stereomutation after few minutes at room temperature.

4.1.8. (*Z*)-1-Iodo-2-phenylethene [(*Z*)-16a]. *N*-iodosuccinimide (NIS) (15.29 g, 67.94 mmol) was added to a solution of (*Z*)-**15a** (5.99 g, 34.0 mmol) in acetonitrile (35 ml) and the resulting mixture was stirred for 40 min at room temperature. It was then poured into a cold saturated aqueous $Na_2S_2O_3$ solution (50 ml) and the mixture was stirred for 10 min and then extracted with a 1:1 mixture of hexane and AcOEt (4×40 ml). The organic extract was washed with 1N aqueous NaOH and brine, dried over Na_2SO_4 and concentrated under reduced pressure (100 mbar). The residue was fractionally distilled to give chemically pure (*Z*)-**16a** (6.91 g, 89% yield) as a yellow liquid. Bp 57°C/0.5 mbar (lit.[24] 60.5°C/0.5 Torr). MS, *m/z* (%): 230 (54), 128 (10), 127 (72), 103 (100), 102 (25), 77 (53), 76 (12). IR (film): ν 1599, 1493, 1298, 1262, 817 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.67–7.59 (2H, m), 7.38–7.32 (3H, m), 7.31 (1H, d, J=8.5 Hz), 6.56 (1H, d, J=8.5 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 138.8, 136.9, 128.6 (2C), 128.5, 128.3 (2C), 79.3 ppm. GLC/MS and ^1H NMR analyses showed that (*Z*)-**16a** had stereoisomeric purity higher than 97%. The spectral properties of this compound were in agreement with those reported in the literature.[25]

4.1.9. (*Z*)-1-Iodo-2-(2-naphthyl)ethene [(*Z*)-16b]. This compound, having stereoisomeric purity higher than 97%, was prepared in 86% yield from (*Z*)-**15b** according to the same procedure used for the synthesis of (*Z*)-**16a** from (*Z*)-**15a**. Compound (*Z*)-**16b** was a yellow solid. Mp 66–68°C. MS, *m/z* (%): 280 (1), 153 (4), 152 (76), 151 (100), 126 (44), 125 (15), 75 (54). IR (KBr): ν 1587, 1354, 1310, 862, 822 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.10 (1H, br s), 7.91–7.69 (3H, m), 7.57–7.40 (4H, m), 6.65 ppm (1H, d, J=8.5 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.8, 138.5, 134.1, 128.4, 128.2, 127.8, 127.7 (2C), 126.4, 126.3, 125.8, 79.7 ppm. Anal. calcd for $C_{12}H_9I$: C, 51.45; H, 3.24. Found: C, 51.57; H, 3.44.

4.1.10. (*Z*)-1-Iodo-2-(6-methoxy-2-naphthyl)ethene [(*Z*)-16c]. Some attempts were made to prepare (*Z*)-**16c** having high stereoisomeric purity by reaction of (*Z*)-**15c** with NIS in acetonitrile at room temperature or at 0°C using a NIS:(*Z*)-**15c** molar ratio of 2 or 5. The best result was obtained using the following modification of the procedure used to prepare (*Z*)-**16a** and (*Z*)-**16b**. A solution of (*Z*)-**15c** (1.50 g, 5.85 mmol) in acetonitrile (13.5 ml) was added in 30 min to a solution of NIS (2.63 g, 11.7 mmol) in acetonitrile (15 ml) and the resulting mixture was stirred at room temperature for 35 min. It was then poured into a saturated aqueous $Na_2S_2O_3$ solution (50 ml) and the mixture was stirred for 10 min and then extracted with a 1:1 mixture of hexane and AcOEt (5×40 ml). The organic extract was washed with 0.5N aqueous NaOH and brine, dried over Na_2SO_4 and concentrated under reduced pressure. GLC/MS analysis of the residue showed the presence of two compounds in a ca. 28:72 molar ratio, which were subsequently identified as (*E*)- and (*Z*)-**16c**, respectively. The residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (85:15) as eluant, to give (*Z*)-**16c** contaminated by ca. 28% of the corresponding (*E*)-stereoisomer (1.72 g, 95% yield) as a pale yellow solid. Mp 88–95°C. Some MS data for (*Z*)-**16c** are as follows. MS, *m/z* (%): 310 (100), 183 (24), 168 (19), 152 (13), 140 (32), 139 (48), 114 (11). Some MS data for (*E*)-**16c** are as follows. MS, *m/z* (%): 310 (100), 183 (21), 168 (18), 152 (12), 140 (30), 139 (46), 114 (10). The ^1H NMR data for (*Z*)-**16c** contaminated by (*E*)-**16c** are as follows. ^1H NMR (200 MHz, $CDCl_3$): δ 8.04 (0.72H, br s), 7.77 (0.28H, br s), 7.75–7.55 (3H, m), 7.53 (0.28H, d, J=15.0 Hz), 7.43 (0.72H, d, J=8.5 Hz), 7.18–7.06 (2H, m), 6.86 (0.28H, d, J=15.0 Hz), 6.56 (0.72H, d, J=8.5 Hz), 3.92 (2.16H, s), 3.91 ppm (0.84H, s). The ^{13}C NMR data for (*E*)-**16c** are as follows. ^{13}C NMR (50.3 MHz, $CDCl_3$):δ 158.1, 144.9, 134.2, 132.9, 129.6, 128.5, 127.1, 126.4, 125.9, 119.2, 105.7, 75.5, 55.3 ppm. The ^{13}C NMR data for (*Z*)-**16c** are as follows. ^{13}C NMR (50.3 MHz, $CDCl_3$):δ 158.1, 138.4, 134.2, 131.8, 129.7, 128.3, 127.7, 126.4, 123.2, 119.1, 105.6, 78.4, 55.3 ppm. IR (KBr): ν 1480, 1311, 1242, 1166, 854 cm^{-1}. Anal. calcd for $C_{13}H_{11}IO$: C, 50.35; H, 3.58. Found: C, 50.21; H, 3.65.

4.1.11. Methyl (*E*)-3-methoxy-2-[(*Z*)-2-(phenyl)ethenyl]-propenoate [(*E,Z*)-18a]. A 0.44 M THF solution of TMEDA-complexed (*Z*)-2-methoxy-1-(methoxycarbonyl)-ethenylzinc iodide [(*Z*)-**17**][3e] (98.6 ml, 43.4 mmol) was added to a solution of (*Z*)-**16a** (6.65 g, 28.9 mmol) and $Pd(PPh_3)_4$ (1.67 g, 1.45 mmol) in THF (84 ml), which was

prepared immediately prior to use, and the resulting mixture was stirred for 20 h at 55°C. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using benzene as eluant, to give pure (*E*,*Z*)-**18a** (2.57 g, 41% yield) as a yellow liquid. MS, *m*/*z* (%): 218 (20), 186 (17), 155 (19), 144 (18), 128 (21), 115 (100), 75 (63). IR (film): ν 1708, 1632, 1606, 1245, 1109 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.17 (6H, m), 6.56 (1H, d, *J*=12.0 Hz), 6.15 (1H, dd, *J*=12.0, 1.0 Hz), 3.66 (3H, s), 3.48 ppm (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 167.9, 159.3, 138.4, 131.7, 127.9 (2C), 127.7 (2C), 126.8, 119.6, 108.5, 61.6, 51.3 ppm. Anal. calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.49; H, 6.79.

4.1.12. Methyl (*E*)-3-methoxy-2-[(*Z*)-2-(2-naphthyl)-ethenyl]propenoate [(*E*,*Z*)-18b]. Compound (*Z*)-**16b** (4.92 g, 17.6 mmol) was reacted with a 0.44 M THF solution of (*Z*)-**17** (59.9 ml, 26.4 mmol) at 55°C for 16.5 h in the presence of $Pd(PPh_3)_4$ (1.02 g, 0.88 mmol) according to the same procedure used to prepare (*E*,*Z*)-**18a**. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using benzene as eluant, to give pure (*E*,*Z*)-**18b** (3.41 g, 72% yield) as a yellow liquid. MS, *m*/*z* (%): 268 (51), 237 (30), 209 (22), 193 (11), 178 (42), 165 (100), 75 (43). IR (film): ν 1706, 1633, 1606, 1244, 1102 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.83–7.58 (3H, m), 7.67 (1H, s), 7.50–7.34 (3H, m), 7.26 (1H, s), 6.72 (1H, d, *J*=12.0 Hz), 6.24 (1H, d, *J*=12.0 Hz), 3.61 (3H, s), 3.46 ppm (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 167.9, 159.5, 136.0, 133.1, 132.3, 131.6, 127.9, 127.4, 127.2, 127.1, 125.9, 125.8, 125.6, 119.9, 108.6, 61.6, 51.3 ppm. Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.05; H, 6.26.

4.1.13. Methyl (*E*)-3-methoxy-2-[(*Z*)-2-(6-methoxy-2-naphthyl)ethenyl]propenoate [(*E*,*Z*)-18c]. A mixture of (*Z*)- and (*E*)-**16c** (*Z*/*E*=72:28; 8.34 g, 26.9 mmol) was reacted at 55°C for 22 h with a 0.44 M THF solution of (*Z*)-**17** (91.6 ml, 40.3 mmol) in the presence of $Pd(PPh_3)_4$ (1.55 g, 1.34 mmol) according to the same procedure used to prepare (*E*,*Z*)-**18a**. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (94:6) as eluant. The chromatographic fractions which contained (*E*,*Z*)-**18c** were collected and concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (94:6) as eluant, to give 97% stereoisomerically pure (*E*,*Z*)-**18c** (2.78 g, 35% yield) as a pale yellow solid. Mp 98–100°C. MS, *m*/*z* (%): 298 (100), 267 (57), 235 (29), 208 (51), 195 (76), 152 (60), 75 (38). IR (KBr): ν 1694, 1599, 1265, 1224, 1104 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.72–7.56 (3H, m), 7.41 (1H, dd, *J*=8.5, 1.5 Hz), 7.26 (1H, d, *J*=1.0 Hz), 7.09 (1H, dd, *J*=8.5, 2.5 Hz), 7.07 (1H, s), 6.69 (1H, d, *J*=12.0 Hz), 6.19 (1H, dd, *J*=12.0, 1.0 Hz), 3.90 (3H, s), 3.65 (3H, s), 3.48 ppm (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 168.0, 159.3, 157.6, 133.8, 133.5, 131.7, 129.4, 128.6, 127.1, 126.5, 125.9, 119.0, 118.6, 108.8, 105.6, 61.6, 55.2, 51.4 ppm. Anal. calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.66; H, 6.10.

4.1.14. Methyl (*E*)(1*R,2*S**)-3-methoxy-2-[2-(phenyl)-cyclopropyl]propenoate [(1*R**,2*S**)-8a].** A solution of trifluoroacetic acid (1.96 g, 17.2 mmol) in freshly distilled CH_2Cl_2 (8 ml) was added over 20 min to a stirred mixture of a 1 M hexane solution of $ZnEt_2$ (17.2 ml, 17.2 mmol) and CH_2Cl_2 (17 ml), which was stirred at 0°C under argon. Upon stirring for 20 min at 0°C, a solution of CH_2I_2 (4.61 g, 17.2 mmol) in CH_2Cl_2 (7 ml) was added. After an additional 20 min at 0°C a solution of (*E*,*Z*)-**18a** (1.00 g, 4.30 mmol) in CH_2Cl_2 (6 ml) was added and the resulting suspension was stirred at room temperature for 4 h. It was then poured into a cold saturated aqueous NH_4Cl solution (60 ml) and extracted with benzene (3×50 ml). The organic extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using benzene as eluant, to give pure (1*R**,2*S**)-**8a** (0.75 g, 71% yield) as a pale yellow liquid. The spectral properties of this compound were in good agreement with those of (1*R**,2*S**)-**8a** prepared by palladium-catalyzed reaction between (1*R**,2*S**)-**12a** and (*Z*)-**13**.

4.1.15. Methyl (*E*)(1*R,2*S**)-3-methoxy-2-[2-(2-naphthyl)-cyclopropyl]propenoate [(1*R**,2*S**)-8b].** An ice cooled solution of $CF_3COOZnCH_2I$ was prepared from a 1 M hexane solution of $ZnEt_2$ (26.1 ml, 26.1 mmol), trifluoroacetic acid (2.97 g, 26.1 mmol), CH_2I_2 (6.99 g, 26.1 mmol) and CH_2Cl_2 (38 ml) according to the procedure employed for the preparation of (1*R**,2*S**)-**8a**. This solution was stirred under argon at 0°C for 20 min, then a solution of (*E*,*Z*)-**18b** (1.75 g, 6.52 mmol) in freshly distilled CH_2Cl_2 (9 ml) was added and the resulting mixture was stirred for 1.5 h at room temperature. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using a mixture of hexane and diethyl ether (80:20) as eluant, to give pure (1*R**,2*S**)-**8b** (1.38 g, 75% yield) as a pale yellow solid. Mp 64–66°C. MS, *m*/*z* (%): 282 (13), 250 (81), 191 (100), 178 (59), 165 (63), 141 (27), 89 (30). IR (KBr): ν 1707, 1632, 1243, 1111, 1080 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.82–7.64 (3H, m), 7.48–7.36 (3H, m), 7.26 (1H, dd, *J*=8.5, 1.5 Hz), 7.17 (1H, d, *J*=1.0 Hz), 3.65 (3H, s), 3.49 (3H, s), 2.50 (1H, *pseudo*-dt, *J*=8.5, 6.5 Hz), 1.96 (1H, *pseudo*-ddt, *J*=9.0, 6.5 1.0 Hz), 1.75 (1H, *pseudo*-q, *J*=6.5 Hz), 1.42 ppm (1H, *pseudo*-dt, *J*=8.5, 6.0 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 168.9, 161.2, 137.1, 133.1, 131.8, 127.3 (2C), 127.2, 126.6, 125.5, 125.4, 124.7, 106.5, 61.5, 51.0, 22.7, 17.2, 11.0 ppm. Anal. calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.40; H, 6.38.

4.1.16. Methyl (*E*)(1*R,2*S**)-3-methoxy-2-[2-(6-methoxy-2-naphthyl)-cyclopropyl]propenoate [(1*R**,2*S**)-8c].** An ice cooled solution of $CF_3COOZnCH_2I$ was prepared from a 1 M hexane solution of $ZnEt_2$ (7.0 ml, 7.0 mmol), trifluoroacetic acid (0.52 ml, 7.0 mmol), CH_2I_2 (1.87 g, 7.0 mmol) and CH_2Cl_2 (13 ml) according to the procedure employed for the preparation of (1*R**,2*S**)-**8a**. This solution was stirred under argon at 0°C for 20 min, then a solution of (*E*,*Z*)-**18c** (1.13 g, 3.80 mmol) in freshly distilled CH_2Cl_2 (5 ml) was added and the resulting mixture was stirred for 1 h at 0°C. The crude reaction product, which was obtained after usual workup, was purified by MPLC on silica gel, using a mixture of toluene and AcOEt (96:4) as eluant, to give pure (1*R**,2*S**)-**8c** (0.827 g, 70% yield) as a pale yellow solid. Mp 81–82.5°C. MS, *m*/*z* (%): 312 (54), 280 (68), 221 (100), 195 (34), 178 (26), 165 (49), 141 (25). IR (KBr): ν

1702, 1630, 1250, 1112, 1082 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.64–7.52 (2H, m), 7.35 (1H, br s), 7.19 (1H, dd, J=8.5, 1.5 Hz), 7.13 (1H, d, J=1.5 Hz), 7.10–7.04 (1H, m), 7.05 (1H, s), 3.88 (3H, s), 3.61 (3H, s), 3.46 (3H, s), 2.43 (1H, *pseudo*-dt, J=8.5, 6.5 Hz), 1.89 (1H, *pseudo*-ddt, J=9.0, 6.5, 1.0 Hz), 1.68 (1H, *pseudo*-dt, J=6.5, 5.5 Hz), 1.36 ppm (1H, *pseudo*-dt, J=8.5, 5.5 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 168.9, 161.0, 156.8, 134.6, 132.7, 128.8, 128.5, 127.7, 125.5, 125.3, 118.2, 106.6, 105.4, 61.4, 55.2, 50.9, 22.5, 16.8, 10.8 ppm. Anal. calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.36; H, 6.48.

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