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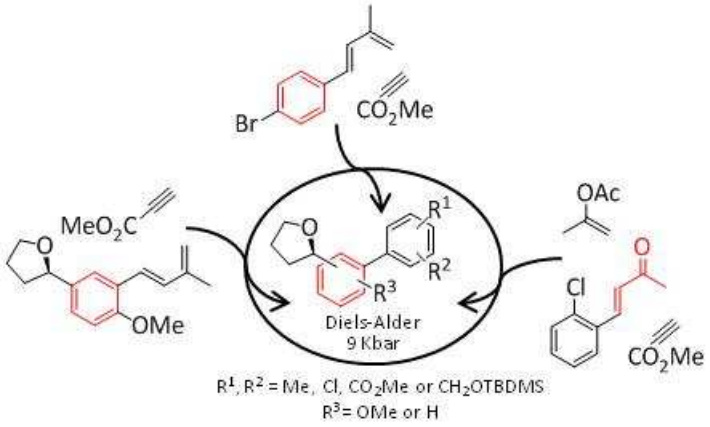

Exploration of Synthetic Strategies for the Stereoselective Preparation of Novel Tetrahydrofuran-containing Biaryls: a High-Pressure Promoted Diels-Alder approach

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Abstract

Three stereoselective synthetic approaches to tetrahydrofuran-containing biaryl scaffolds are described. All approaches involve a high-pressure promoted Diels-Alder reaction of substituted diene with methyl propiolate to give, after aromatization, the corresponding biaryl. The tetrahydrofuran moiety can be created starting from aryl-Br or aryl-CO_2Me functional groups through a γ-phenylseleno ketone intermediate.

Keywords:

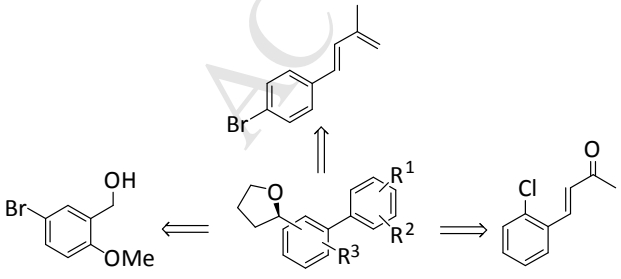
biaryls; tetrahydrofuran; high-pressure; Diels-Alder; selenones

1. Introduction

Tetrahydrofurans represent a structural motif widely present in natural compounds, such as macrolide antibiotics,[1] polyether ionophores,[2] acetogenins,[3] and oxidized lignans[4] with significant and various

biological activities. Thus, considerable efforts have been devoted to the stereoselective synthesis of such structures.[5,6] Similarly, biaryl templates are privileged structures[7] occurring in pharmaceutical agents, such as anti-infective,[8] hypocholesterolemic,[9] antipsychotic,[10] anti-inflammatory,[11] antidiabetic,[12] and antihypertensive drugs.[13] Moreover, biaryls are valuable synthetic building blocks for metal ligands[14-16] and novel organic materials,[17,18] and transition metal-catalysed cross-coupling[19,20] is the preferred method for their synthesis. The development of new chemical entities represents an important challenge in pharmaceutical science, being the use of privileged scaffolds for library design and drug discovery a valuable approach. As part of our general interest in high-pressure promoted Diels-Alder reactions[21-24] for the synthesis of 1,1–biaryls and the utility of organochalcogen intermediates in organic synthesis,[25-30] we focused our attention on the tetrahydrofuran-containing biaryl scaffold due to the ability of each motif to bind multiple targets.

Herein, we report three different and stereoselective syntheses of novel tetrahydrofuran-containing biaryls (Scheme 1) by combining a high-pressure promoted regiospecific [4+2] Diels-Alder reaction with our previously reported approach to 2-substituted tetrahydrofurans.[6] To the best of our knowledge, the synthesis of 2-biaryl substituted tetrahydrofurans has not been previously investigated except for some C-ribonucleoside and C-2'-deoxyribonucleosides.[31] Only a few examples of 2-aryl- and 2-heteroaryltetrahydrofurans[32-34] non-stereoselective synthesis, based on the activation of THF at the α-position,[35] have been reported.



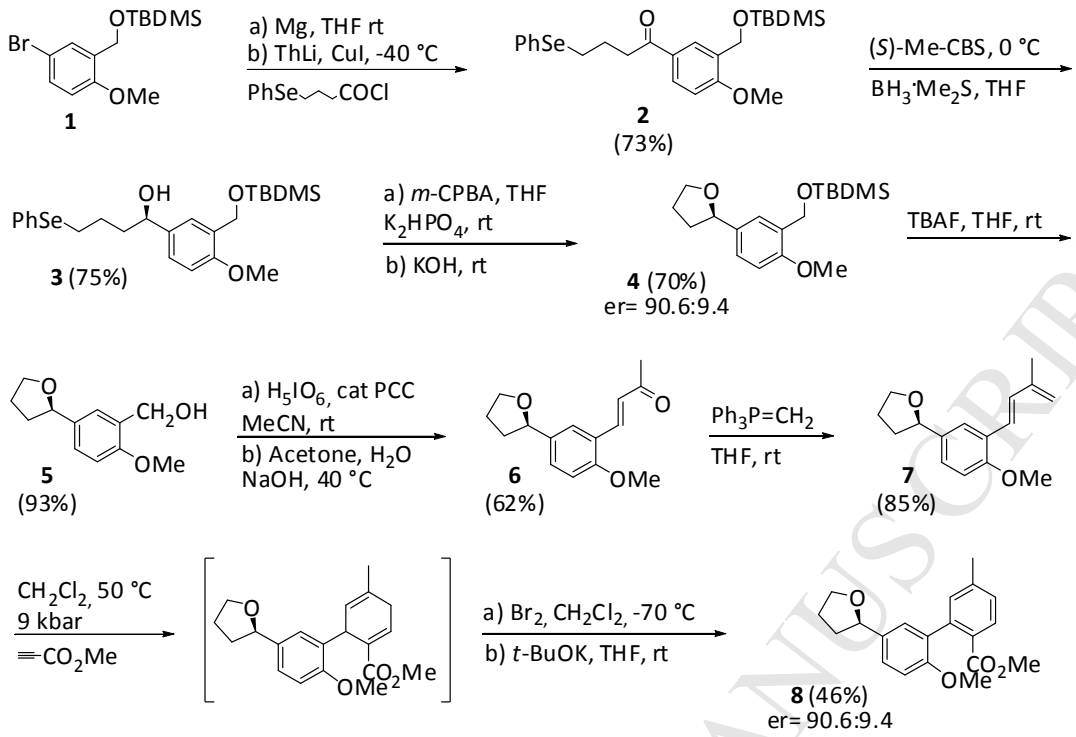
Scheme 1. Envisaged general approach for the synthesis of tetrahydrofuran-containing biaryls.

2. Results and Discussion

A retrosynthetic analysis showed three possible strategies for the assembly of the 2-tetrahydrofuran moiety on the biaryl system. The first approach (Method 1) was based on the construction of the tetrahydrofuran ring from a bromo-substituted benzene to give a 2-arylsubstituted tetrahydrofuran intermediate, which was then employed for the synthesis of the biaryl system (Scheme 2). Our second strategy (Method 2) featured a late stage installation of the tetrahydrofuran ring on a bromo-functionalized biaryl (Scheme 3). Finally (Method 3), to overcome the drawbacks of the first and the second methods, we realised that the tetrahydrofuran could be prepared starting from a carbomethoxy-functionalized biaryl. This led to a simple and short synthetic pathway (Scheme 5).

2.1. First strategy

In Method 1, the protected benzyl alcohol **1** was transformed into the corresponding mixed magnesium cuprate intermediate following the procedure reported in the literature[6] and it was then subjected to couple with 4-(phenylseleno)butanoyl chloride in THF (Scheme 2).



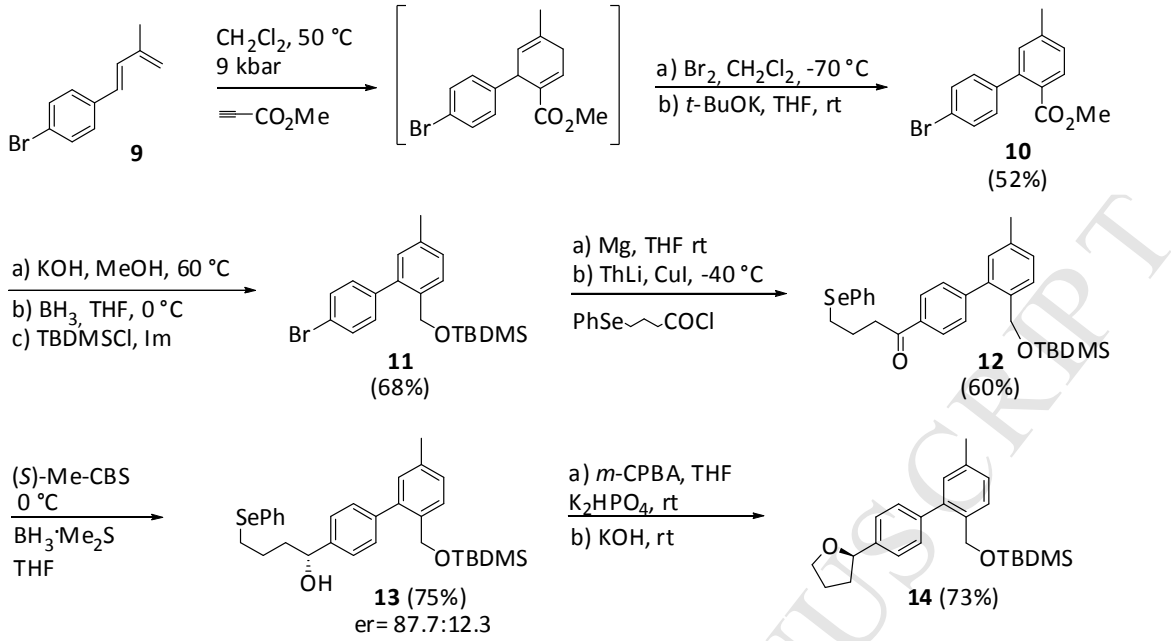
Scheme 2. Method 1: Preparation of the tetrahydrofuran-containing biaryl **8** from *O*-protected-5-bromo-2-methoxy benzyl alcohol **1**.

The resulting γ-phenylseleno ketone **2** was enantioselectively reduced by the oxazaborolidine-catalyzed Corey procedure[36] to give the optically active phenylseleno alcohol **3** in excellent yield. The configuration of the major enantiomer of compound **3** was tentatively assumed according to the mechanism proposed by Corey and others. Reaction of **3** with an excess of *m*-chloroperoxybenzoic acid in the presence of dipotassium hydrogen phosphate afforded the selenone intermediate, which was further converted into the corresponding 2-substituted tetrahydrofuran **4** by treatment with powdered potassium hydroxide.[6,29] The optically active tetrahydrofuran **4** was obtained in good yield and in 90.6:9.4 enantiomeric ratio as determined by HPLC analysis on chiral stationary phase. Deprotection of hydroxyl group in compound **4** with TBAF afforded the free alcohol **5**, which was then oxidised with periodic acid to the corresponding aldehyde intermediate. The aldehyde was immediately reacted with

acetone in the presence of sodium hydroxide to give the benzylideneacetone **6** derivative in satisfactory 62 % global yield.[21] Wittig reaction of this enone with methyltriphenylphosphonium bromide furnished the expected phenyl-butadiene **7** in excellent yield (Scheme 2). In our approach to tetrahydrofuran-containing biaryl **8** a high pressure promoted and regiospecific Diels-Alder reaction of **7** with methyl propiolate[21] was involved to give a cyclohexadiene intermediate which, after aromatization, gave the biaryl. Although the expected Diels-Alder product was easily obtained, the reaction of the cyclohexadiene intermediate with DDQ did not furnish the awaited biaryl **8**, whereas treatment with NBS and subsequent reaction with Et_3N resulted in a complex mixture and no trace of **8** was observed. To overcome this drawback, a milder and sequential bromination-elimination reaction on the activated double bond of cyclohexadienyl benzene intermediate was performed. Thus, bromination[37] of the isolated double bond with a solution of bromine in dichloromethane at -70°C afforded the brominated derivative that was readily converted into the new benzene ring of the desired biaryl **8** by simple treatment with potassium *tert*-butoxide at r.t. The novel functionalized scaffold **8** was obtained in 46% global yield from **7** (Scheme 2). To our knowledge, this aromatization protocol has not been reported before. No loss of enantiomeric purity occurred during these reactions, as demonstrated by the enantiomeric ratio of **8**, measured by HPLC analysis on chiral stationary phase.

2.2. Second strategy

Method 2 was based on the construction of the tetrahydrofuran ring in the last part of the synthetic sequence described above. This second approach to obtain a novel tetrahydrofuran-containing biaryl **14** is reported in Scheme 3.



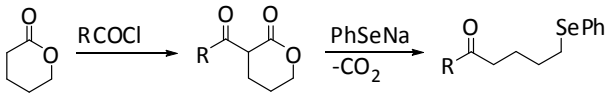
Scheme 3. Method 2: Preparation of tetrahydrofuran-containing biaryl scaffold **14** from (*E*)-3 methyl-1-(4-bromophenyl)buta-1,3-diene **9**.

The required substituted butadiene **9** was readily synthesized in high yield by Wittig reaction[22] from the commercially available (*E*)-3 methyl-1-(4-bromophenyl)but-3-ene-2-one. Then, diene **9** was used in a regiospecific Diel-Alder reaction with methyl propiolate promoted by high-pressure (9 Kbar) in dichloromethane at 50 °C. According to Scheme 3, the cycloadduct intermediate obtained was aromatised to biaryl **10** through the same procedure followed to prepare **8**. Thus, addition of bromine to cyclohexadiene intermediate resulted in the formation of a brominated derivative, which was immediately treated with potassium *tert*-butoxide to yield biaryl **10** in 52 % global yield. Through the simple synthetic steps described above for compound **1**, it appeared useful to synthesise the tetrahydrofuran ring from bromobiaryl **10**. In this case, due to the reactivity of the carboxymethyl group under Grignard reaction conditions, ester **10** was easily converted in three steps (without isolation of the intermediates) into the *O*-silyl protected benzyl alcohol **11**. It is interesting to note that the direct reaction of **10** with $LiAlH_4$ afforded the benzyl alcohol **11** with the corresponding

debrominated benzyl alcohol derivative as an equimolecular mixture. Therefore, we reasoned that **11** could be more conveniently prepared through the borane reduction of the acid intermediate (Scheme 3). The preparation of the Grignard reagent from **11** was the key step of the entire procedure because we needed it to prepare the required mixed magnesium-cuprate reagent. Following the protocol used to prepare **2**, the γ-phenylseleno ketone **12** was obtained in satisfactory 63% yield (Scheme 2). The enantioselective reduction of **12** with (*S*)-Me-CBS[36] gave the expected γ-phenylseleno alcohol **13** in 75% yield and in 87.7:12.3 enantiomeric ratio, measured by HPLC analysis on chiral stationary phase. Finally, oxidation of the selenium atom of alcohol **13** into the corresponding selenone intermediate was carried out in THF at r.t. with an excess of *m*-chloroperoxybenzoic acid in the presence of dipotassium hydrogen phosphate as above. The tetrahydrofuran-containing biaryl scaffold **14** was clearly formed in good global yield after addition of powdered potassium hydroxide as reported before.[6,29] No loss of enantiomeric purity occurred during this conversion, as demonstrated by the enantiomeric ratio of **14**, measured by HPLC analysis on chiral stationary phase.

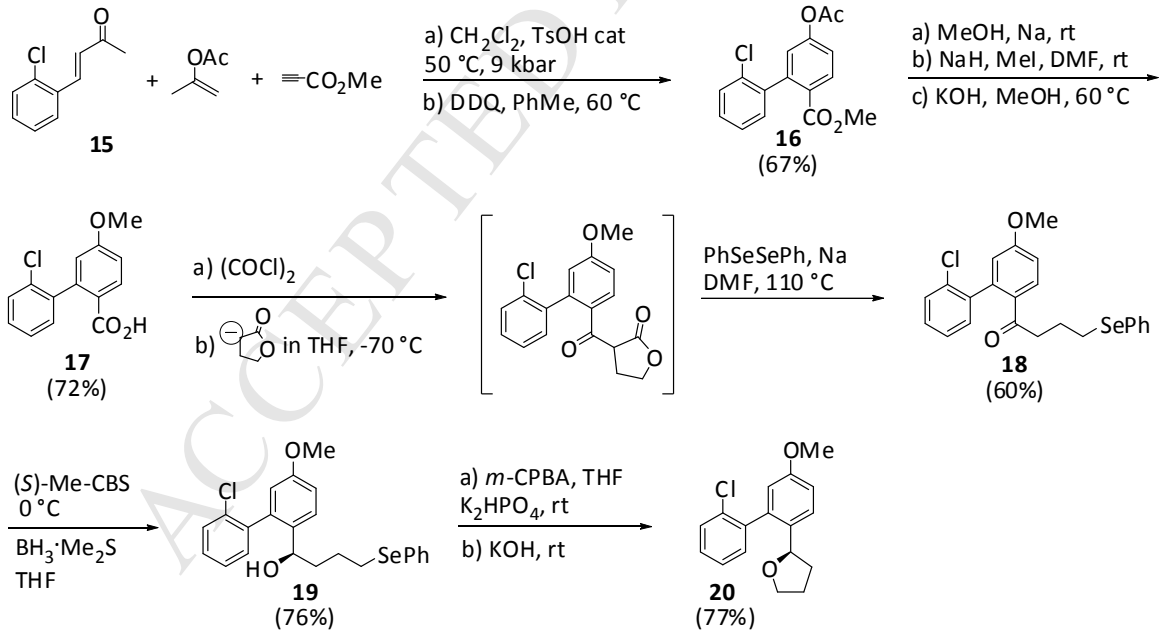
2.3. Third strategy

Methods 1 and 2 described above were unsatisfactory because of the incompatibility of some functional groups, especially the carbonyl, to Grignard reagent. Therefore, we turned our attention to an alternative approach to successfully prepare the γ-phenylseleno ketone required for the synthesis of the tetrahydrofuran moiety. Recently, it has been reported a new complementary route to δ-phenylseleno ketone[38] starting from δ-valerolactone *via* a β-ketolactone intermediate which undergoes cleavage of the alkyl carbon-oxygen bond of lactone by phenylselenolate anion (Scheme 4).



Scheme 4: Complementary route to δ-phenylseleno ketone.

Inspired by this procedure, we envisioned the possibility of using the carbomethoxy group of methyl propiolate, introduced during the biaryl synthesis by Diels-Alder reaction, as a precursor of the acyl group necessary to prepare the β-ketolactone. Thus, according the method 3, the commercially available (*E*)-4-(2-chlorophenyl)but-3-en-2-one **15** was reacted with isopropenyl acetate, methyl propiolate and catalytic *p*-toluenesulfonic acid under high-pressure (9 Kbar) at 40 °C (Scheme 5). Under these conditions a multicomponent reaction occurred where an acetoxy-1,3-diene, generated *in situ* by acid catalysed enolacetylation of the enone with isopropenyl acetate, reacted with the dienophile methyl propiolate to give a Diels-Alder cycloadduct intermediate as recently reported.[24] After a quick purification through a short silica gel column, the crude cycloadduct obtained from **15** was submitted to oxidation with DDQ and the expected biaryl **16** was isolated in 67% global yield.



Scheme 5. Method 3: Preparation of tetrahydrofuran-containing biaryl **20** from (*E*)-4-(2-chlorophenyl)but-3-en-2-one **15**.

Then biaryl **16** was easily converted in three steps (without isolation of the intermediates) into the methoxy substituted biaryl acid **17** in 72% overall yield (Scheme 4). The synthesis of γ-phenylseleno ketone **18** was the key step of the entire synthetic strategy. Thus, γ–butyrolactone was deprotonated by treatment with LDA in THF at -70 °C and the resulting enolate was reacted with the corresponding acyl chloride derived from **17** to give the β-ketolactone intermediate, which was employed in the successive reaction without purification. The crude lactone, upon treatment with sodium phenylselenolate, underwent clean nucleophilic lactone scission with concomitant loss of CO_2 to easily afford the γ-phenylseleno ketone **18** in 60% overall yield. The stereoselective reduction of **18** using Corey procedure[36,29] furnished the expected γ-phenylseleno alcohol **19** in 76% yield. Chromatographic separation of configurational isomers of **19** was attempted using different conventional chiral columns, such as Chiracel OD-H, Lux-Cellulose 2, Lux-Amilose 2, and Welk R,R-1. However, none of the above-mentioned phases was successful in determination of the enantiomeric ratio of alcohol **19**. Finally, oxidation of **19** with an excess amount of *m*-chloroperoxybenzoic acid in the presence of dipotassium hydrogen phosphate occurred smoothly at r.t. to give the corresponding phenylselenone intermediate, which cyclised in the presence of powdered KOH according to a 5-*exo*-tet ring pattern to deliver the new desired tetrahydrofuran-containing biaryl **20** in 77% yield. Unfortunately, the enantiomeric ratio determination of **20** was not achieved on available chiral stationary phase columns. Moreover, in the chromatographic run carried out on Lux-Cellulose 2 at 10°C a classical peak-plateau-peak shape, characteristic of simultaneous on-column separation and intercoversion process of unresolved atropoisomers, was observed.[39] The presence of four species was visible at 5°C but unfortunately the four peaks were not resolved. As a matter of fact, the biaryl **20**, as well as alcohol **19**, contains two different *ortho* substituents besides the presence of a chiral centre. These structural features are characteristic of a molecule with the potential for hindered rotation about the single bond connecting the aryl rings, which can lead to formation of conformational isomers (atropoisomers) as

enantiomeric pairs.[40] In general, NMR spectra recorded at r.t. for congested biaryl compounds show duplications and broadening of signals. In our case the ^{1}H NMR spectra of **20** in $CDCl_3$ at 293 K did not show any signal splitting, while it was possible to see the peaks duplication on most ^{13}CNMR signals. However, not even ^{1}HNMR in DMSO-d_6 allowed a clear signal assignment (see SI) as it presented complicated patterns, indicating *a priori* the presence of different conformers.[41] It was not possible to establish the relative conformer ratio by NMR nor HPLC profile and further studies are currently ongoing in our laboratory, given the importance of atropoisomerism in drug discovery and development.[42]

3. Conclusions

Three different and stereoselective strategies for the synthesis of new tetrahydrofuran-containing biaryls were developed. The procedures were based on the construction of functionalised biaryls by transition metal-free and high-pressure (9 Kbar) promoted Diels-Alder reactions. The use of a stereospecific intramolecular nucleophilic substitution of the phenylselenone residue by the oxygen atom of a hydroxy group allowed efficient formation of the tetrahydrofuran ring. Moreover, we also showed a mild aromatisation of cyclohexadiene by a novel bromination/dehydrohalogenation procedure and a new preparation of γ-phenylseleno ketones from butyrolactone. Our current efforts are directed toward the synthesis of tetrahydropyran-substituted biaryls and heterobiaryls.

4. Experimental section

4.1. Materials and methods

All reaction of air- and water-sensitive organometallics were carried out in flame-dried glassware under argon using standard techniques. All the compounds were purified by column chromatography. Chromatography was performed on silica gel (Merck 60, 70-230 mesh), and analytical TLC was

carried out on pre-coated silica gel plates (Merck 60 F254, 0.25 mm) using UV light and 0.5% w/v potassium permanganate aqueous solution (followed by gentle heating) for visualisation. Melting points were measured on a hot plate apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 and 400 MHz. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 50 and 100 MHz. Unless otherwise specified, $CDCl_3$ was used as solvent at 293 K and chemical shifts (δ) are reported in parts per million (ppm). The NMR spectra were calibrated using the proton or carbon signals of residual, non-deuterated solvents peak: δ_H 7.27 and δ_C 77.0 for $CDCl_3$. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broadened), number of protons, coupling constants, assignments (where possible). Coupling constant (J) are quoted in Hertz (Hz) to the nearest 0.1 Hz. Infrared (IR) spectra were recorded with a FT-IR instrument, using a diffuse reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). GC-MS analysis were obtained with a gas chromatograph (HP-5MS capillary column 29.0 m, ID 0.25, film 0.25 μm) equipped with a mass selective detector at an ionizing voltage of 70 eV. Optical rotations were measured in a 50 mm cell using the D-line of sodium at the specified temperature. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g $100mL^{-1}$. HPLC analyses were performed on an HPLC system equipped with a UV/vis detector with chiral columns and solvents specified. All chromatograms were run at 25 °C. Combustion analyses were carried out on a elemental analyzer. Hyperbaric experiments were conducted on a Unipress LV30/16 apparatus. The synthesis of **1** from the commercially available alcohol has been previously reported.[43] The Grignard reagents for the preparation of ketones **2** and **12** were synthesized in large preparation by standard method from the corresponding halide and analyzed by the method of Knochel[44] prior to use. Freshly opened bottle of cuprous iodide was found to be satisfactory. The well-known diene (**9**)[45] was prepared by Wittig reaction from the commercially available enone.[22] The remaining enone **15** is commercially available.

4.2. Synthesis of tetrahydrofuran-containing biaryl 8 from *O*-protected-5-bromo-2-methoxy benzyl alcohol 1

4.2.1. Preparation of γ-phenylseleno ketone 2

4-Phenylselenobutanoic acid (1.46 g, 6.00 mmol) was reacted with oxalyl chloride (2.54 mL, 30.00 mmol) at r.t. for 15 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (5 mL), the solvent was removed and the crude acyl chloride obtained was immediately used for the next reaction.[6] In a 100 mL three-necked round-bottom flask , a suspension of cuprous iodide (1.59 g, 8.40 mmol) in dry THF (20 mL) was cooled down to -30 °C. A 1M 2-thienyllithium solution in THF (7.2 mL) was added by syringe and the resulting suspension was stirred for 30 min at the same temperature. After cooling the mixture to -40 °C, a solution of the Grignard reagent from **1** (7.2 mmol) was added with a syringe. The resulting suspension was stirred for 20 min and then a solution of 4-phenylselenobutanoic chloride (6.00 mmol) in dry THF (6 mL) was slowly added. The reaction mixture was allowed to slowly warm to r.t. After 4 h the reaction was quenched with 10 mL of saturated aqueous ammonium chloride solution and 50 mL of ethyl acetate. Stirring for 2 h dissolved the copper salts. The organic phase was then separated and the aqueous portion was washed with two 20 mL portions of ethyl acetate. The combined organic fractions were washed once with 10 mL of 0.1M aqueous sodium thiosulfate and brine. The organic phase was dried and concentrated *in vacuo*. Purification of the crude product by chromatography (SiO_2, dietyl ether/petroleum ether 5:95) afforded 2.05 g (73% yield) of *1-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-methoxy-phenyl]-4-phenylselanyl-butan-1-one* (**2**); Light yellow oil; FTIR: ν_{max}/cm^{-1} 2931, 1676, 1603, 1257, 1087, 839, 777, 736. ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 8.12 (d, 1H, *J* = 2.3 Hz, *H*-Ar), 7.90 (dd, 1H, *J* = 8.6, 2.3 Hz, *H*-Ar), 7.57-7.46 (m, 2H, *H*-Ar), 7.30-7.20 (m, 3H, *H*-Ar), 6.87 (d, 1H, *J* = 8.6 Hz, *H*-Ar),4.75 (s, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 3.11 (t, 2H, *J* = 7.1 Hz, CH_2), 3.02 (t, 2H, *J* =

7.1 Hz, C*H*$_2$), 2.14 (quint, 2H, *J* = 7.1 Hz, C*H*$_2$), 0.99 (s, 9H, C*H*$_3$), 0.13 (s, 6H, *Si*-CH$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 198.2, 159.7, 132.5 (2C), 130.0, 129.8, 129.0 (2C), 128.5, 127.0, 126.7, 109.1, 59.8, 55.3, 37.7, 27.4, 25.9 (3C), 24.5, 18.4, -5.3, -5.4. EIMS (70 eV) m/z $[M - 57]^+$ 421 (52), 321 (100), 263 (49), 249 (48), 207 (31), 120 (17), 105 (12), 77 (22). Anal. Calc. for $C_{24}H_{34}N_2O_3SeSi$: C, 60.36; H, 7.18. Found: C, 60.62; H, 7.40.

4.2.2. Asymmetric reduction of ketone 2

To a solution of (*S*)-Me-CBS (1.0 M in toluene, 0.25 mL, 0.25 mmol) in dry THF (10 mL) at 0 °C 2.0 M borane-dimethyl sulfide complex (0.50 ml, 1.00 mmol) was added under inert atmosphere. A solution of ketone **2** (0.48 g, 1.00 mmol) in dry THF (10 mL) was added slowly along the side of the reaction flask by using a syringe pump over 2 h under vigorous stirring and allowing the solution to warm to r.t. The mixture was stirred at r.t. until the ketone disappeared on TLC monitoring (4 h). The mixture was quenched with methanol and saturated ammonium chloride solution (5 mL). The mixture was extracted with ethyl acetate (2 x 20 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified on a silica gel column with a mixture of petroleum ether and diethyl ether (70:30) as eluent to give *(1R)-1-[3-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-4-methoxyphenyl]-4-(phenylseleno)butan-1-ol* **3** (0.36 g, 75% yield) as colorless oil. FTIR: ν_{max}/cm^{-1} 3403, 2928, 1499, 1251, 1084, 838, 777. ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.55-7.38 (m, 3H, *H*-Ar), 7.32-7.10 (m, 4H, *H*-Ar), 7.15 (d, 1H, *J* = 8.3 Hz, *H*-Ar), 4.75 (s, 2H, OC*H*$_2$), 4.70-4.56 (m, 1H, OC*H*), 3.80 (s, 3H, OC*H*$_3$), 2.89 (t, 2H, *J* = 7.2Hz, C*H*$_2$), 2.02-1.53 (m, 5H, O*H* and C*H*$_2$), 0.98 (s, 9H, C*H*$_3$), 0.11 (s, 6H, *Si*-CH$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 155.5, 136.2, 132.4 (2C), 130.3, 129.8, 128.9 (2C), 126.6, 125.0, 124.5, 109.4, 73.9, 60.1, 55.1, 38.6, 27.7, 26.4, 25.9 (3C), 18.4, -5.3, -5.4. EIMS (70 eV) m/z $[M - 57]^+$ 423 (80), 405 (51), 233 (77), 173 (70), 91 (100), 75 (66). $[\alpha]^{25}$ D -3,14 (c 1.075, $CHCl_3$); Anal. Calc. for $C_{24}H_{36}O_3SeSi$: C, 60.11; H, 7.57. Found: C, 60.35; H, 7.83.

4.2.3. Oxidative-cyclisation of phenylseleno alcohol 3

To a solution of phenylseleno alcohol **3** (1.45 g, 3.02 mmol) in THF (60 mL) at r.t. powdered dipotassium hydrogen phosphate (2.63 g, 15.10 mmol) and *m*-chloroperoxybenzoic acid (2.08 g, 12.08 mmol) were added.[6,29] The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2 h). Then powdered potassium hydroxide was added (1.27 g, 22.65 mmol). The consumption of the selenone was monitored by TLC (14 h). The mixture was then poured into 10% aqueous sodium carbonate (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with 10% aqueous sodium carbonate (20 mL), brine, dried over sodium sulphate, and concentrated *in vacuo*. The reaction product was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (30:70) as eluent. *tert-Butyl({2-methoxy-5-[(2R)-tetrahydrofuran-2-yl]benzyl}oxy)dimethylsilane* (**4**) was obtained as colorless oil (0.68 g, 70 % yield). FTIR: ν_{max}/cm^{-1} 2954, 1613, 1500, 1462, 1250, 1082, 840, 777. ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.45 (d, 1H, *J* = 2.3 Hz, *H*-Ar), 7.22 (dd, 1H, *J* = 8.4, 2.3 Hz, *H*-Ar), 6.80 (d, 1H, *J* = 8.4 Hz, *H*-Ar), 4.88 (t, 1H, *J* = 7.1 Hz, O-C*H*), 4.77 (s, 2H, OCH_2), 4.19-3.85 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 2.40-2.20 (m, 1H, CH_2), 2.12-1.70 (m, 3H, CH_2), 0.96 (s, 9H, CH_3), 0.12 (s, 6H, *Si*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 155.2, 135.1, 129.6, 124.8, 124.5, 109.3, 80.7, 68.5, 60.2, 55.2, 34.5, 26.1, 26.0 (3C), 18.5, -5.2, -5.4. EIMS (70 eV) m/z [M − 57]$^+$ 265 (100), 235 (55), 173 (449, 105 (40), 91 8299, 75 (59). $[\alpha]^{22}$ D 12.89 (c 1.530, $CHCl_3$); Anal. Calc. for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.89; H, 9.62. Phenomenex® Lux Cellulose-2, 1 mL/min hexane/i-PrOH/EtOH 94/5/1, (obs: 254 nm): retention times: 4.9 min (S-enantiomer), 5.1 min (R-enantiomer, major), er = 90.6:9.4.

4.2.4. Preparation of alcohol 5

TBAF (0.32 g, 1.00 mmol) was added to a stirred solution of protected alcohol **4** (0.32 g, 1.00 mmol) in THF (10 mL) at r.t. The reaction mixture was stirred for 16 h, poured into saturated aqueous sodium

hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (30:70) as eluent to obtain *{2-methoxy-5-[(2R)-tetrahydrofuran-2-yl]phenyl}methanol* (**5**) as colorless oil (0.19 g, 93 % yield). FTIR: ν_{max}/cm^{-1} 3335, 2930, 1613, 1506, 1249, 1043, 815. ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.45-7.20(m, 2H, *H*-Ar), 6.86 (d, 1H, *J* = 8.8 Hz, *H*-Ar), 4.83 (t, 1H, *J* = 7.3 Hz, O-C*H*), 4.69 (s, 2H, OCH_2), 4.18-4.03 (m, 1H, OCH_2), 4.01-3.88 (m, 1H, OCH_2), 3.87 (s, 3H, OCH_3), 2.65 (br s, 1H, O*H*), 2.40-2.18 (m, 1H, CH_2), 2.10-1.91 (m, 2H, CH_2), 1.90-1.80 (m, 1H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 156.5, 135.2, 129.0, 126.1, 126.0, 109.9, 80.4, 68.4, 61.8, 55.3, 34.4, 26.0. EIMS (70 eV) m/z $[M - 1]^+$ 207 (61), 177 (100), 165 (50), 135 (33), 99 (22), 77 (26). $[\alpha]^{22}$ D 29.01 (c 1.050, $CHCl_3$); Anal. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.03; H, 7.99.

4.2.5. Synthesis of enone 6

Alcohol **5** (0.42 g, 2.00 mmol) was dissolved in acetonitrile (16 mL) and periodic acid (0.54 g, 2.26 mmol) and pyridinium chlorochromate (8 mg, 0.04 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and then diluted with ethyl acetate (100 mL) and washed once with 10 mL of 0.1M aqueous sodium sulphite and then brine, dried over sodium sulphate, and concentrated *in vacuo* giving the crude aldehyde which was employed in the next step. To a stirred solution of the crude aldehyde in absolute ethanol (12 mL) at 40 °C, acetone (1.3 mL, 20.00 mmol) and NaOH (10% w/v aq., 0.5 mL) were added. The resulting mixture was stirred for 17 h, ethanol was evaporated under reduced pressure and HCl (2N, 10 mL) was added. The resulting mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with brine, dried over sodium sulphate, and concentrated *in vacuo*. *(3E)-4-{2-Methoxy-5-[(2R)-tetrahydrofuran-2-yl]phenyl}but-3-en-2-one* (**6**) (0.15 g) was isolated after column chromatography on SiO_2 (ethyl acetate/petroleum ether 30:70) in a 62% global yield from **5**. Colorless oil; FTIR: ν_{max}/cm^{-1} 2958, 1670, 1496, 1250, 1063, 820; ^{1}H NMR (200 MHz,

$CDCl_3$) δ/ppm 7.88 (d, 1H, *J* = 16.5 Hz, C*H*), 7.53 (d, 1H, *J* = 2.1 Hz, *H*-Ar), 7.34 (dd, 1H, *J* = 8.6, 2.1 Hz, *H*-Ar), 6.90 (d, 1H, *J* = 8.6 Hz, *H*-Ar), 6.89 (d, 1H, *J* = 16.5 Hz, C*H*), 4.84 (t, 1H, *J* = 7.1 Hz, O-C*H*), 4.20-4.01 (m, 1H, OCH_2), 3.99-3.80 (m, 1H, OCH_2), 3.90 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 2.39-2.20 (m, 1H, CH_2), 2.15-1.91 (m, 2H, CH_2), 1.89-1.69 (m, 1H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 199.0, 157.5, 138.7, 135.6, 129.2, 127.8, 125.7, 123.1, 11.0, 80.0, 68.5, 55.6, 34.5, 27.1, 26.0. EIMS (70 eV) m/z $[M]^+$ 246 (14), 215 (100), 203 (23), 173 (24), 145 (13), 115 (11). $[\alpha]^{24}$ D 6.33 (c 1.370, $CHCl_3$); Anal. Calc. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.63.

4.2.6. Synthesis of diene 7

To a suspension of methyltriphenylphosphonium bromide (1.78 g, 5.00 mmol) in dry THF (25 mL) at -16 °C (NaCl-ice bath) was added dropwise n-butyllithium (1.6 M in hexane, 3.2 mL, 5.00 mmol). The reaction mixture was stirred for 30 min and the enone **6** (0.62 g, 2.50 mmol) was added as a solution in THF (4 mL) at 0 °C. After 1 h the solution was warmed to r.t. and stirred for additional 2 h. A saturated solution of NH_4Cl (10 mL) was added and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic phases were washed with brine, dried over MgSo4, and the solvent was removed under reduced pressure. The residue was purified on a silica gel column with a mixture of petroleum ether and ethyl ether (70:30) as eluent to give the corresponding *(2R)-2-{4-Methoxy-3-[(1E)-3-methylbuta-1,3-dien-1-yl]phenyl}tetrahydrofuran* (**7**); (0.52 g, 85% yield). Colorless oil; FTIR: ν_{max}/cm^{-1} 2970, 1604, 1495, 1246, 1065, 885, 811; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.50 (d, 1H, *J* = 2.1 Hz, *H*-Ar), 7.19 (dd, 1H, *J* = 8.5, 2.1 Hz, *H*-Ar), 6.93-6-80 (m, 3H, *H*-Ar and C*H*), 6.84 (d, 1H, *J* = 8.5 Hz, *H*-Ar), 5.22 (s, 1H, CH_2), 5.06 (s, 1H, CH_2), 4.84 (t, 1H, *J* = 7.2 Hz, O-C*H*), 4.20-4.05 (m, 1H, OCH_2), 4.00-3.79 (m, 1H, OCH_2), 3.85 (s, 3H, OCH_3), 2.38-2.20 (m, 1H, CH_2), 2.14-1.90 (m, 2H, CH_2), 2.01 8s, 3H, CH_3), 1.89-1.70 (m, 1H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 156.0, 142.7, 135.3, 132.2, 126.2, 125.8, 123.8, 123.3, 116.8, 110.8, 80.5, 66.5, 55.6, 34.5, 26.1, 18.7. EIMS (70 eV)

m/z $[M]^+$ 244 (44), 185 (36), 173 (100), 158 (60), 128 (21), 115 (20), 71 (51). $[\alpha]^{25}$ D 5.54 (c 1.020, $CHCl_3$); Anal. Calc. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.47; H, 8.51.

4.2.7. Transformation of 1-arylbuta-1,3-diene 7 into biaryl 8

A solution of arylbutadiene **7** (0.12 g, 0.5 mmol) in 3 ml of CH_2Cl_2 was placed in a 5 mL Teflon vial. Methyl propiolate (0.42 mL, 1.5 mmol) and a few crystals of hydroquinone were added, and the vial was filled with the solvent. The vial was closed and kept at 9 Kbar at 45°C for 60 h. After depressurizing, the mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated under vacuum and the residue filtered through a plug of silica and eluted with a mixture of ethyl acetate/petroleum ether 30:70. After evaporation, the crude cycloadduct intermediate was dissolved in dichloromethane (10 mL) and a 0.1 M bromine solution in chloroform (5 mL) was slowly added at - 70 °C. The addition was stopped when a further drop gave a persistent red colour. The mixture was poured into saturated aqueous NaCl and extracted twice with 10 mL of chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated under *vacuum.* The crude residue was dissolved in THF (10 mL) and potassium *tert*-butoxide (0.45 g, 4.00 mmol) was added at r.t. When the elimination/aromatization reaction ceased (3 h), the mixture was poured into saturated aqueous NH_4Cl and extracted twice with 10 mL of ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under *vacuum*. Purification of the residue by silica gel column chromatography with a mixture of petroleum ether and diethyl ether 80:20 as eluent gave 75 mg of *Methyl 2'-methoxy-5-methyl-5'-[(2R)-tetrahydrofuran-2-yl]biphenyl-2-carboxylate* (**8**) in 46% global yield. Colorless oil; FTIR: ν_{max}/cm^{-1} 2951, 1729, 1608, 1501, 1290, 1097, 783; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.80 (d, 1H, *J* = 7.8 Hz, *H*-Ar), 7.47-7.11 (m, 4H, *H*-Ar), 6.86 (d, 1H, *J* = 8.4 Hz, *H*-Ar), 4.89 (t, 1H, *J* = 7.3 Hz, O-C*H*), 4.21-4.08 (m, 1H, OCH_2), 4.00-3.86 (m, 1H, OCH_2), 3.72 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 2.41-2.22 (m, 1H, CH_2), 2.11-1.87 (m, 3H, CH_2). ^{13}C

NMR (50 MHz, $CDCl_3$) δ/ppm 168.5, 155.3, 141.9, 138.8, 135.2, 132.1, 130.6, 129.5, 128.7, 127.8, 127.4, 126.0, 109.8, 80.4, 68.4, 56.3, 51.5, 34.4, 26.0, 21.4. EIMS (70 eV) m/z $[M]^+$ 326 (100), 295 (4), 265 (55), 253 (77), 225 (49), 165 (43), 152 (37). $[\alpha]^{26}$ D 23.48 (c 0.800, $CHCl_3$); Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.78; H, 7.05. Phenomenex® Lux Cellulose-2, 1 mL/min hexane/*i*-PrOH 96/4, (obs: 254 nm): retention times: 17.29 min (R-enantiomer, majour), 27.6 min (S-enantiomer, minor), er = 90.6:9.4.

4.3. Synthesis of tetrahydrofuran-containing biaryl scaffold 14 from (*E*)-3 methyl-1-(4-bromophenyl)buta-1,3-diene 9

4.3.1. Synthesis of biaryl 10

A solution of arylbutadiene **9** (0.11 g, 0.5 mmol) in 3 ml of CH_2Cl_2 was placed in a 5 mL Teflon vial. Methyl propiolate (0.42 mL, 1.5 mmol) and a few crystals of hydroquinone were added and the vial was filled with the solvent. The vial was closed and kept at 9 Kbar and 45°C for 60 h. After depressurizing, the mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated under vacuum and the residue was filtered through a plug of silica and eluted with a mixture of ethyl acetate/petroleum ether 30:70. After evaporation, the crude cycloadduct intermediate was dissolved in dichloromethane (10 mL) and a 0.1 M bromine solution in chloroform (5 mL) was slowly added at -70 °C.[46] The addition was stopped when a further drop gave a persistent red colour. The mixture was poured into saturated aqueous NaCl and extracted twice with 10 mL of chloroform. The combined organic layers were dried over Na_2SO_4 and concentrated under *vacuum.* The crude residue was dissolved in THF (10 mL) and potassium *tert*-butoxide (0.45 g, 4.00 mmol) was added at r.t. When the elimination/aromatization reaction ceased (3 h), the mixture was poured into saturated aqueous NH_4Cl and extracted twice with 10 mL of ethyl acetate. The combined organic layers were washed with brine,

dried over Na_2SO_4, and concentrated under *vacuum*. Purification of the residue by silica gel column chromatography with a mixture of petroleum ether and diethyl ether 90:10 as eluent gave 79 mg of *Methyl 4'-bromo-5-methylbiphenyl-2-carboxylate* (**10**) as pale yellow oil in 52% global yield. FTIR: ν_{max}/cm^{-1} 2926, 1734, 1653, 1559, 1457, 1009, 828; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.81 (d, 1H, *J* = 7.9 Hz, *H*-Ar), 7.52 (d, 2H, *J* = 8.4 Hz, *H*-Ar), 7.28-7.18 (m, 4H, *H*-Ar), 3.65 (s, 3H, OC*H*$_3$), 2.43 (s, 3H, C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 168.4, 142.0, 141.6, 140.5, 131.4, 130.9 (2C), 130.3, 129.9 (2C), 128.2, 127.3, 121.3, 51.8, 21.4. EIMS (70 eV) m/z $[M]^+$ 304 (52), 273 (40), 194 (100), 165 (80); Anal. Calc. for $C_{15}H_{13}BrO$: C, 59.04; H, 4.29. Found: C, 58.89; H, 4.53.

4.3.2. Preparation of protected biaryl alcohol 11

To a solution of **10** (0.46 g, 1.50 mmol) in 1:1 mixture of methanol and water (8 mL), solid potassium hydroxide (84 mg, 1.5 mmol) was added and the resulting mixture was kept at 60°C until complete consumption of the starting material (10 h) and then allowed to cool to r.t. After addition of 10% hydrochloric acid (5 mL) the acidic mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude acid, which was dissolved in THF (2 mL). The flask was immersed in an ice bath and cooled to 0°C. Then 1.95 mL (1.95 mmol) of borane-THF solution was slowly added over a period of 15 min and the solution was vigorously stirred for an additional period of 2 h.[47] Excess hydride was carefully destroyed with 5 mL of a 1:1 mixture of THF and water and the aqueous phase was saturated with potassium carbonate. The mixture was extracted three times with 10 mL portions of ethyl acetate. The combined organic extracts were dried over magnesium sulfate. Removal of the solvent gave the crude alcohol. The alcohol, *tert*-butyldimethylsilyl chloride (0.25 g, 1.65 mmol), and imidazole (13.82 g, 3.30 mmol) were stirred in DMF (8 mL) for 18 h. The solution was poured into water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The organic phase was washed with HCl (1N, 5 mL), water, then brine,

and dried over $MgSO_4$ to give, after evaporation of solvent, the crude product. Purification on a silica gel column with a mixture of petroleum ether and ethyl ether (80:20) as eluent gave *[(4'-Bromo-5-methylbiphenyl-2-yl)methoxy](tert-butyl)dimethylsilane* (**11**) in 68% yield (0.399 g) as a colorless oil. FTIR: ν_{max}/cm^{-1} 2955, 1472, 1252, 1074, 836, 776; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.58-7.38 (m, 3H, *H*-Ar), 7.31-7.11 (m, 3H, *H*-Ar), 7.04 (s, 1H, *H*-Ar), 4.54 (s, 2H, O*CH*$_2$), 2.38 (s, 3H, C*H*$_3$), 0.88 (s, 9H, C*H*$_3$), 0.02 (s, 6H, *Si*-CH_3).. ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 140.6, 139.5, 136.5, 135.3, 130.9 (2C), 130.4, 128.5 (2C), 128.0, 127.0, 62.9, 26.0, 25.9 (2C), 21.1, 18.3, -5.2, -5.3. EIMS (70 eV) m/z $[M-57]^+$ 333 (100), 259 (31), 180 (99), 165 (53), 75 (28); Anal. Calc. for $C_{20}H_{27}BrOSi$: C, 61.37; H, 6.95. Found: C, 61.59; H, 7.10

4.3.3. Preparation of γ-phenylseleno ketone 12

4-Phenylselenobutanoic acid (0.49 g, 2.00 mmol) was reacted with oxalyl chloride (0.85 mL, 10.00 mmol) at r.t. for 15 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (5 mL), the solvent was removed, and the crude phenylselenobutanoic chloride obtained was immediately used for the next reaction. In a 100 mL three-necked round-bottom flask, a suspension of cuprous iodide (0.53 g, 2.80 mmol) in dry THF (10 mL) was cooled down to -30 °C. A 1M 2-thienyllithium solution in THF (2.4 mL) was added by syringe and the resulting suspension was stirred for 30 min at the same temperature. After cooling the mixture to -40°C, a solution of the Grignard reagent from **12** (2.4 mmol) was added with a syringe. The resulting suspension was stirred for 20 min and then a solution of 4-phenylselenobutanoic chloride in dry THF (4 mL) was slowly added. The reaction mixture was allowed to slowly warm to r.t. After 4 h the reaction was quenched with 5 mL of saturated aqueous ammonium chloride solution and 20 mL of ethyl acetate. Stirring for 2 h dissolved the copper salts. The organic phase was then separated and the aqueous portion was washed with two 10 mL portion of ethyl acetate. The combined organic fractions were washed once with 5 mL of 0.1M aqueous sodium thiosulfate and brine. The organic phase was dried and concentrated *in vacuo*.

Purification of the crude product by chromatography (SiO_2, diethyl ether/petroleum ether 20:80) afforded 0.64 g (60% yield) of *1-[2'-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-5'-methylbiphenyl-4-yl]-4-(phenylseleno)butan-1-one* (**12**) as pale yellow oil. FTIR: ν_{max}/cm^{-1} 2927, 1683, 1604, 1477, 1222, 1073, 839, 738; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.97 (d, 2H, *J* = 8.6 Hz, *H*-Ar), 7.59-7.42 (m, 5H, *H*-Ar), 7.34-7.18 (m, 4H, *H*-Ar), 7.06 (s, 1H, *H*-Ar), 4.56 (s, 2H, OC*H*$_2$), 3.19 (t, 2H, *J* = 7.1 Hz, C*H*$_2$), 3.07 (t, 2H, *J* = 7.1 Hz, C*H*$_2$), 2.40 (s, 3H, C*H*$_3$), 2.20 (quint, 2H, *J* = 7.1 Hz, C*H*$_2$), 0.89 (s, 9H, C*H*$_3$), 0.10 (s, 6H, *Si*-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 199.1, 146.0, 139.5, 136.9, 135.4, 135.3, 132.6 (2C), 130.1, 129.4 (3C), 129.1 (2C), 128.8, 128.4, 127.8 (2C), 126.8, 62.8, 38.1, 27.4, 25.9, 25.8 (2C), 24.5, 21.0, 18.3, -5.3 (2C). EIMS (70 eV) m/z $[M-157]^+$ 380 (6), 249 (64), 231 (19), 216 (15), 178 (20), 75 (43). Anal. Calc. for $C_{30}H_{38}O_2SeSi$: C, 67.02; H, 7.12. Found: C, 67.18; H, 7.27

4.3.4. Asymmetric reduction of ketone 12

To a solution of (*S*)-Me-CBS (1.0 M in toluene, 0.25 mL, 0.25mmol) in dry THF (10 mL) at 0°C a 2.0 M borane-dimethyl sulfide complex (0.50 ml, 1.00 mmol) was added under inert atmosphere.. A solution of ketone **2** (0.54 g, 1.00 mmol) in dry THF (10 mL) was added slowly along the side of the reaction flask by using a syringe pump over 2 h with vigorous stirring and the solution was allowed to warm to r.t. The mixture was stirred at r.t. until the ketone disappeared on TLC monitoring (6 h). The mixture was quenched with methanol and saturated ammonium chloride solution (5 mL). The mixture was extracted with ethyl acetate (2 x 20 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified on a silica gel column with a mixture of petroleum ether and ethyl acetate (70:30) as eluent to give the corresponding *(1R)-1-[2'-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-5'-methylbiphenyl-4-yl]-4-(phenylseleno)butan-1-ol* (**13**) in 79% yield (0.42 g) as pale yellow oil. FTIR: ν_{max}/cm^{-1} 3028, 2920, 1611,1457, 1338, 1011, 850, 737; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.57-7.42 (m, 3H, *H*-Ar), 7.35 (s, 4H, *H*-Ar), 7.30-7.13 (m, 4H, *H*-Ar), 7.08 (s, 1H, *H*-Ar), 4.82-4.68 (m, 1H, OC*H*), 4.58 (s, 2H, OC*H*$_2$), 3.03-2.88 (m, 2H, C*H*$_2$), 2.40 (s,

3H, C*H*$_3$), 2.09-1.71 (m, 5H, C*H*$_2$), 0.92 (s, 9H, C*H*$_3$), 0.30 (s, 6H, *Si*-CH$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 143.0, 140.4, 140.2, 136.6, 135.3, 132.6 (2C), 130.4, 129.7, 129.3 (2C), 128.9, 128.2 (2C), 126.7, 125.5 (2C), 73.8, 62.9, 38.9, 27.7, 26.4, 25.9, 25.8 (2C), 21.0, 18.3, -5.3 (2C). EIMS (70 eV) m/z [M- 214]$^+$ 325 (14), 233 (100), 218 (30), 205 (19), 178 (15), 165 (22), 75 (16). $[\alpha]^{21}$ D 6.66 (c 2.750, $CHCl_3$); Anal. Calc. for $C_{30}H_{40}O_2SeSi$: C, 66.77; H, 7.47. Found: C, 66.89; H, 7.73. Phenomenex® Lux Cellulose-2, 1 mL/min hexane/i-PrOH 97:3, (obs: 254 nm): retention times: 7.1 min (S-enantiomer, minor), 8.0 min (R-enantiomer, major), er= 87.7:12.3.

4.3.5. Synthesis of biaryl 14 by oxidative-cyclization of phenylseleno alcohol 13

To a solution of phenylseleno alcohol **13** (0.32 g, 0.59 mmol) in THF (20 mL) at r.t. powdered dipotassium hydrogenphosphate (0.51 g, 2.95 mmol) and m-chloroperoxybenzoic acid (0.41 g, 2.36 mmol) were added. The reaction mixture was stirred until TLC analysis showed that the starting selenide had been completely converted into the corresponding selenone (2 h). Then powdered potassium hydroxide was added (0.25 g, 4.42 mmol). The consumption of the selenone was monitored by TLC (16 h). The mixture was then poured into 10% aqueous sodium carbonate (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with 10% aqueous sodium carbonate (10 mL), then brine, dried over sodium sulphate, and concentrated *in vacuo*. The reaction product was purified by column chromatography on silica gel using a mixture of diethyl ether and petroleum ether (20:80) as eluent. *tert-Butyl(dimethyl)({5-methyl-4'-[(2R)-tetrahydrofuran-2-yl]biphenyl-2-yl}methoxy)silane* (**14**) was isolated in 73% yield (0.17 g) as colourless oil. FTIR: νmax/cm-1 2856, 1610, 1462, 1254, 1069, 834, 775. 1H NMR (400 MHz, $CDCl_3$) δ/ppm 7.51 (d, 1H, J = 8.0 Hz, H-Ar), 7.42 (d, 2H, J = 8.4 Hz, H-Ar), 7.37 (d, 2H, J = 8.4 Hz, H-Ar), 7.23 (d, 1H, J = 8.0 Hz, H-Ar), 7.10 (s, 1H, H-Ar), 4.98 (t, 1H, J = 7.2 Hz, O-CH), 4.62 (s, 2H, OCH_2), 4.23-4.14 (m, 1H, OCH_2), 4.05-3.97 (m, 1H, OCH_2), 2.50-2.34 (m, 1H, CH_2), 2.41 (s, 3H, CH_3), 2.19-2.01 (m, 2H, CH_2), 1.97-1.84 (m, 1H, CH_2), 0.97 (s, 9H, CH_3), 0.08 (s, 6H, Si-CH_3). 13C NMR (100 MHz, $CDCl_3$) δ/ppm

142.0, 140.3, 139.8, 136.5, 135.4, 130.4, 129.1, (2C), 128.0, 127.9, 125.4 (2C), 80.6, 86.7, 62.9, 34.5, 26.1, (3C), 25.9, 21.0, -5.3 (2C); EIMS (70 eV) m/z [M − 57]+ 325 (24), 233 (100), 205 (36), 179 (25), 165 (39), 75 (30). [α]20 D 8.69 (c 1.150, $CHCl_3$); Anal. Calc. for $C_{24}H_{36}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.19; H, 9.19. Phenomenex® Lux Cellulose-2, 1 mL/min hexane/i-PrOH 99:1, obs: (254 nm): retention times: 3.9 min (S-enantiomer), 4.0 min (R-enantiomer), er= 10.95-89.05.

4.4. Synthesis of tetrahydrofuran-containing biaryl 20 from (*E*)-4-(2-chlorophenyl)but-3-en-2-one 15

4.4.1. Preparation of biaryl 16

A solution of enone **15** (0.27 g, 1.5 mmol), isopropenyl acetate (0.81 mL, 7.5 mmol), and methyl propiolate (0.42 mL, 4.5 mmol) in CH_2Cl_2 was placed in a 5 mL Teflon vial. TsOH (12 mg, 4 mol%) was added and the vial was filled with the solvent. The vial was closed and kept at 9 Kbar and 45°C for 60 h. After depressurizing, the mixture was poured into saturated $NaHCO_3$ solution (10 mL) and extracted twice with 20 mL of CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated under *vacuum*. The crude residue was dissolved in toluene (20 mL) and DDQ (0.34 g, 1.5 mmol) was added. The mixture was stirred at 60°C for 24 h and then poured into saturated aqueous Na_2CO_3 and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under *vacuum.* The crude mixture was purified by silica gel column chromatography with a mixture of petroleum ether and diethyl ether 60:40 as eluent to give 0.31 g of *Methyl 5-(acetyloxy)-2'-chlorobiphenyl-2-carboxylate* (**16**) in 67% global yield. Oil; FTIR: νmax/cm^{-1} 2951, 1768, 1730, 1436, 1290, 1202, 1027, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 8.05 (d, 1H, *J* = 8.6 Hz, *H*-Ar), 7.46-7.36 (m, 1H, *H*-Ar), 7.34-7.18 (m, 4H, *H*-Ar), 7.03 (d, 1H, *J* = 2.4 Hz, *H*-Ar), 3.68 (s, 3H, OCH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 168.7, 166.4, 153.0, 142.2, 139.6, 132.5, 131.7, 130.0, 128.9, 128.8, 127.9, 126.5, 124.2, 121.0, 52.0, 21.1; EIMS (70 eV) m/z [M

– 35.5]$^+$ 269 (94), 227 (100), 211 (59), 168 (26), 139 (38); Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.06; H, 4.30. Found: C, 62.92; H, 4.57.

4.4.2. Synthesis of acid 17

To a solution of sodium methoxide prepared dissolving 0.46 g (20.0 mmol) of sodium in 100 mL of dry methanol at r.t., ester **16** (3.01 g, 10.0 mmol) was added and the resulting mixture was kept at r.t. until complete consumption of the starting material (2 h). The mixture was concentrated and after addition of 10% hydrochloric acid (10 mL) the acidic mixture was extracted three times with 30 mL of CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was dissolved in 80 mL of dry DMF at 0°C and NaH (0.31 g, 13.0 mmol) was added under inert atmosphere. After 1 h methyl iodide (0.81 mL, 13.0 mmol) was added to the resulting mixture, which was then allowed to warm to r.t. (8 h). After addition of 10% hydrochloric acid (10 mL) the acidic mixture was extracted with diethyl ether (4 x 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in a 3:1 mixture of methanol and water (40 ml) and potassium hydroxide (1.12 g, 20.0 mmol) was added. The mixture was heated to 60°C for 16 h and then allowed to cool to r.t. After addition of 10% hydrochloric acid (20 mL) the acidic mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a solid, which was triturated with diethyl ether (2x20 ml). The solid was filtered to afford *2'-Chloro-5-methoxybiphenyl-2-carboxylic acid* (**17**) as white solid (2.10 g, 72% yield). mp 48−50 °C; FTIR: νmax/cm^{-1} 3085, 2923, 1685, 1594, 1457, 1303, 1033, 755; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 10.05 (br s, 1H, *H*-Ar), 8.09 (d, 1H, *J* = 8.8 Hz, *H*-Ar), 7.47-7.10 (m, 4H, *H*-Ar), 6.95 (dd, 1H, *J* = 2.4 Hz, *H*-Ar), 6.73 (d, 1H, *J* = 2.6 Hz, *H*-Ar), 3.84 (s, 3H, OC*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 171.5, 162.8, 143.6, 140.5, 133.4, 132.6, 129.8, 128.9, 128.5, 126.3, 121.1, 116.8, 113.1, 55.5; Anal. Calcd for $C_{14}H_{11}ClO_4$: C, 64.01; H, 4.22. Found: C, 63.88; H, 4.50.

4.4.3. Preparation of ketone 18

Biaryl acid **17** (1.74 g, 6.0 mmol) was reacted with oxalyl chloride (2.54 mL, 30.0 mmol) at r.t. for 15 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (5 mL), the solvent was removed, and the crude acyl chloride obtained was immediately used for the next reaction**.** A 1M LDA solution (13.2 mL) was added to 30 mL of dry THF at –70°C. Then 0.46 mL (6 mmol) of γ-butyrolactone was added and the mixture stirred for 40 min under inert atmosphere.[48] To this mixture a solution (5 ml of dry THF) of the crude acid chloride prepared above was slowly added in 5 min. The mixture was allowed to warm to r.t. (5 h) and then quenched with 10% hydrochloric acid (10 mL). The mixture was extracted with ethyl acetate (3 x 40 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was applied to a plug of silica, eluted with CH_2Cl_2, and the solvent was removed to obtain the crude β-ketolactone intermediate sufficiently pure to be used. Thus, diphenyl diselenide (0.95 g, 3.0 mmol) and sodium (0.14 g, 6.0 mmol) were placed in an oven-dried round-bottom flask under argon. Dry THF (30 mL) and dry DMF (20 mL) were added to the contents of the flask using a syringe and the mixture was heated at 100°C for 30-45 min yielding a red solution of sodium phenylselenide. To this homogeneous solution was added the crude β-ketoester intermediate, obtained as described before, dissolved in 5 mL of DMF. The reaction was heated at 110°C for 22 h and then allowed to cool to r.t. After addition of 10% hydrochloric acid (10 mL) the acidic mixture was extracted with three 30 mL portions of ethyl acetate. The combined extracts were washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica using dichloromethane-hexane 1:1 mixture as eluent to afford 1.61 g of *1-(2'-Chloro-5-methoxybiphenyl-2-yl)-4-(phenylseleno)butan-1-one* (**18**) in 60% global yield. **L**ight yellow oil; FTIR: νmax/cm^{-1} 2936, 1684, 1600, 1473, 1214, 1022, 760, 736; ^{1}H NMR (200 MHz, $CDCl_3$) δ/ppm 7.74 (d, 1H, *J* = 8.7 Hz, *H*-Ar), 7.50-7.14 (m, 9H, *H*-Ar), 6.94 (dd, 1H, *J* = 8.7, 2.6 Hz,

H-Ar), 6.76 (d, 1H, *J* = 2.6 Hz, *H*-Ar), 3.85 (s, 3H, OC*H*$_3$), 2.83 (t, 2H, *J* = 7.2 Hz, C*H*$_2$), 2.75 (t, 1H, *J* = 7.2 Hz, C*H*$_2$), 2.72 (t, 1H, *J* = 6.8 Hz, C*H*$_2$), 1.94 (dq, 2H, *J* = 7.2,6.8 Hz, C*H*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ/ppm 200.7, 161.5, 140.7, 140.3, 132.4, 132.3, 131.4, 130.6, 130.4, 130.0, 129.3, 128.9, 128.8, 126.7, 126.6, 116.7, 112.9, 55.2, 40.0, 27.2, 24.8; Anal. Calcd for $C_{23}H_{21}ClO_2Se$: C, 62.24; H, 4.77. Found: C, 62.31; H, 5.01.

4.4.4. Asymmetric reduction of ketone 18 to alcohol 19

To a solution of (*S*)-Me-CBS 1.0 M in toluene (0.43 mL, 0.85 mmol) in dry THF (10 mL) at 0°C was added a 2.0 M borane-dimethyl sulfide complex (0.17 ml, 0.17 mmol). A solution of ketone **18** (0.38 g, 0.85 mmol) in dry THF (10 mL) was added slowly using a syringe pump over 2.5 h with vigorous stirring and the solution was allowed to warm to r.t. The mixture was stirred at r.t. until the ketone disappeared on TLC monitoring (20 h). The mixture was quenched with methanol and saturated ammonium chloride solution (2 mL). The mixture was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column with a mixture of petroleum ether and diethyl ether 60:40 as eluent to give the corresponding chiral secondary alcohol *(1R)-1-(2'-Chloro-5-methoxybiphenyl-2-yl)-4-(phenylseleno)butan-1-ol* (**19**) in 76% yield. (0.25 g) as oil. FTIR: νmax/cm^{-1} 3416, 2933, 1608, 1576, 1472, 1437, 1219, 1067, 1035, 761, 735. ^{1}H NMR (200 MHz, $CDCl_3$): approx. 3:2 mixture of conformers. δ/ppm 7.57-7.12 (overlapped, m, 10H, *H*-Ar), 6.98 (overlapped, ddd, 1H, *J* = 8.6, 3.8, 2.8 Hz, *H*-Ar), 6.68 (minor, d, 1H, *J* = 2.7, *H*-Ar), 6.62 (major, d, 1H, *J* = 2.7 Hz, *H*-Ar), 4.48-4.35 (overlapped, m, 1H, OC*H*), 3.81 (overlapped, s, 3H, OC*H*$_3$), 2.76 (minor, t, 2H, *J* = 6.9 Hz, C*H*$_2$), 2.68 (major, t, 2H, *J* = 7.1 Hz, C*H*$_2$), 1.98-1.45 (overlapped, m, 5H, O*H* and C*H*$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): approx. 3:2 mixture of conformers. δ/ppm 158.3 (major rotamer), 158.0 (minor rotamer), 139.2, 139.0, 138.9, 134.2, 132.7, 132.4 (2C), 132.3, 131.4, 131.0, 130.3, 130.2, 129.5, 129.1, 128.8,(2C); 126.9, 126.8, 126.7, 126.5, 126.4, 126.3, 114.8, 114.3 (2C), 114.2, 69.8

(major rotamer), 69.5 (minor rotamer9, 55.1, 38.2 (major rotamer), 37.6 8minor rotamer), 27.4 (minor rotamer), 27.3 (major rotamer), 26.2 (minor rotamer), 26.0 (major rotamer); EIMS (70 eV) m/z $[M]^+$ 446 (1), 271 (25), 229 (100), 207 (16), 190 (18), 165 (16), 91 (16); Anal. Calcd for $C_{23}H_{23}ClO_2Se$: C, 61.96; H, 5.20. Found: C, 61.81; H, 5.44.

4.4.5. Oxidative-cyclization of phenylseleno alcohol 19

To a solution of phenylseleno alcohol **19** (0.20 g, 0.45 mmol) in THF (20 mL) at r.t. powdered dipotassium hydrogenphosphate (0.32 g, 1.80 mmol) and *m*-chloroperoxybenzoic acid (0.24 g, 1.35 mmol) were added. The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2 h). Then powdered potassium hydroxide was added (0.19 g, 3.37 mmol). The consumption of the selenone was monitored by TLC (14 h). The mixture was then poured into 10% aqueous sodium carbonate (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with 10% aqueous sodium carbonate (10 mL), then brine, dried over sodium sulphate, and concentrated *in vacuo* to afford, after column chromatography on silica gel (diethyl ether-petroleum ether 3:7) the *(2R)-2-(2'-chloro-5-methoxybiphenyl-2-yl)tetrahydrofuran* (**20**) as oil (0.10 g, 77%). FTIR: νmax/cm^{-1} 2950, 2865, 1608, 1470, 1219, 1067, 1038, 758. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of conformers. δ/ppm 7.60-7.41 (overlapped, m, 2H, *H*-Ar), 7.40-7.20 (overlapped, m, 3H, *H*-Ar), 7.04-6.92 (overlapped, m, 1H, *H*-Ar), 6.72-6.65 (overlapped, m, 1H, *H*-Ar), 4.57 (t, 1H, *J* = 7.0 Hz, OC*H*), 4.15-3.98 (overlapped, m, 1H, OCH_2), 3.90-3.80 [(m, partly overlapped s (3H, OCH_3), m (1H, CH_2)], 2.12-1.50 (overlapped, m, 4H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): mixture of conformers. δ/ppm 158.0, 139.5, 138.8, 138.3, 134.1, 133.6, 132.4, 133.1, 131.5, 131.1, 129.4, 129.3, 128.7, 126.8, 126.5, 126.4, 126.2, 114.6, 114.2, 113.9, 78.0, 77.6, 68.6, 68.4, 55.3, 34.9 (minor rotamer), 33.9 (major rotamer), 26.3, 26.2; EIMS (70 eV) m/z $[M]^+$ 288 (79), 257 (52), 253 (79), 245 (53), 225 (42), 218 (17), 211 (100), 195 (12), 177 (40), 168 (28), 152 (33), 139 (29); Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.71; H, 5.93. Found: C, 70.65; H, 6.15.

HPLC analysis at variable temperature[49] on Phenomenex® Lux Cellulose-2 column (250 x 4.60 mm ID), n-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, 254 nm UV detector.

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Supplementary data

Supplementary data (HPLC traces and Copies of product NMR spectra) related to this article can be found at http://

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