Stereoselective Synthesis of Substituted Tetrahydropyrans and Isochromans by Cyclization of Phenylseleno Alcohols

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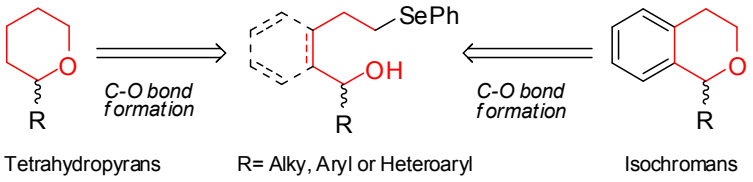


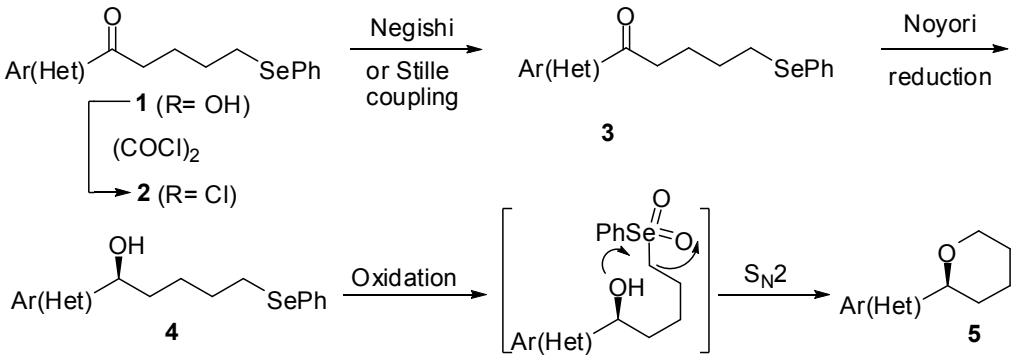
ABSTRACT: A selenium-mediated strategy for the stereoselective synthesis of substituted tetrahydropyrans and isochromans has been developed starting from δ-phenylseleno ketones. After enantioselective reduction, the chiral non-racemic phenylseleno alcohols were oxidized to the corresponding selenones which underwent an effcient 6-*exo*-tet ring-closure reaction.

INTRODUCTION

The tetrahydropyrans motif is one of the most common scaffolds found in natural products such as antibiotics,[1] marine toxins[2] and pheromones.[3] In spite of many strategies employed for the synthesis of complex tetrahydropyrans[4] (THPs), a few examples of 2-substituted THPs synthesis were accounted. Among these, C-O bond formation reactions are probably the most used methodologies, such as alkene seleno- and haloetherification,[5] acid catalyzed cyclization of vinylsilanes,[6] gold- or ytterbium-hydroalkoxylation of alkenols[7a] and allenes,[7b] palladium catalyzed allylic oxidation[8] or oxidative cyclization of alkenols,[9] water[10a] and gold- or iron-catalyzed[10b,c] cyclization of monoallylic diols, gold-catalyzed cyclic ether formation from diols,[11] copper-catalyzed O-H insertion of ω-hydroxy-α-diazoesters[12] and cycloetherification *via* intramolecular oxy-Michael addition.[13] Other approaches have focused on the formation of C-C bond as the reaction of cyclic oxonium ion with organometallic reagents,[14] the boron trifluoride-catalyzed rearrangement of 2-aryloxytetrahydropyrans,[15] the C-H arylation/alkylation at α–position of tetrahydropyran[16a] or dihydropyran[16b] and, finally, the ruthenium-catalyzed ring-closing metathesis.[17] Due to the limitation of the above mentioned synthetic methods, such as moderate yields and low stereoselectivity, development of efficient and enantioselective methods for the construction of 2-substituted THPs still represents a challenge.

Reports from our laboratory have demonstrated the utility of organochalcogen intermediates in organic synthesis[18] as well as their use in the synthesis of heterocycles.[19] We recently described the easy and stereoselective preparation of 2-substituted tetrahydrofurans[20] via intramolecular displacement of phenylselenone group by hydroxy group.

Scheme 1. General Strategy for the Stereoselective Synthesis of 2-Substituted Tetrahydropyrans



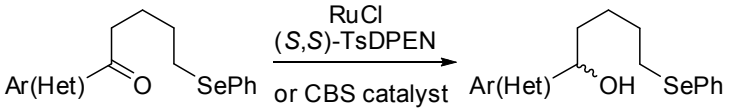
Based on this process, we envisioned a strategy for the construction of chiral non-racemic 2-substituted THPs **5** (Scheme 1), starting from enantioenriched phenylseleno alcohols **4**. The control of the stereochemistry of the secondary alcohols **4,** by using catalytic asymmetric transfer hydrogenation (ATH) reaction[21] of δ-phenylseleno ketones **3**, is the cornerstone of our strategy because it allows the expedient generation of THPs **5** in both enantiomeric forms. To the best of our knowledge, use of phenylseleno alcohol **4** as intermediate in the synthesis of 2-substituted THPs has not been previously investigated. Thus, in this study we report: i) investigation on the stereoselective synthesis of substituted tetrahydropyrans**,** based on the enantioselective reduction of δ-phenylseleno ketones and oxidation/cyclization of the corresponding alcohols; ii) application of this approach to the synthesis of variously substituted isochromans.

RESULTS AND DISCUSSION

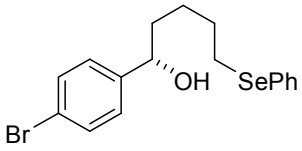
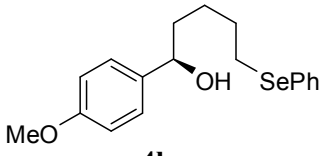
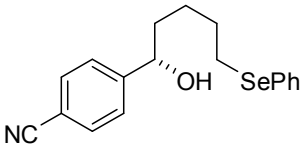
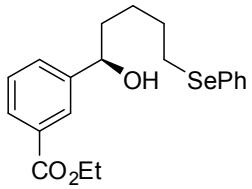
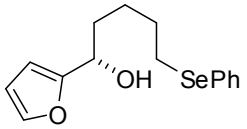
Synthesis of 2-substituted THPs. The required δ-phenylseleno ketones **3a-f** (Table 1) have been synthesized for the first time by new procedures. Treatment of 5-(phenylseleno)pentanoic acid **1** with oxalyl chloride afforded the acyl chloride **2** (Scheme 1), that was reacted with the appropriate arylzinc reagent in the presence of Pd(0) catalyst[22] (Negishi coupling). Ketones **3a-d** were obtained in 60-80% yields. The reaction of acyl chloride **2** with a suitable (hetero)aryl stannane[23] (Stille conditions) gave the ketone **3e** in 65% yield (Scheme 1). Since ketone **3f** was obtained in very low

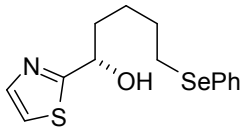
yield by the above described methodologies, it was prepared, in 69% yield, by reaction of methyl ester of acid **1** with 2-lithiothiazole.[24] Chiral non-racemic δ-phenylseleno alcohols **4** were synthesized from ketones **3** employing the commercially available RuCl[(S,S)-TsDPEN](mesitylene) as catalyst for the ATH process.[21] We selected the Noyori ATH reaction because of its efficiency and stability and low cost of the catalyst as well as for the simplicity of the experiments.

Table 1. Asymmetric Reduction of Ketones 3 into Alcohols 4



3a-f **4a-f**

entry	alcohol[a]	time (h)	yield (%)[b]	er[c]
1	 **4a**	2.5	85	---[d]
2	 **4b**	3	89[e]	---[d]
3	 **4c**	3.5	82	89.5:10.5
4	 **4d**	5	92[f]	91.4:8.6
5	 **4e**	4	92	97.2:2.8

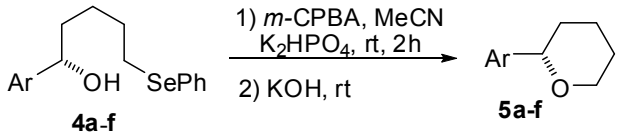
6	 **4f**	1.5	89	98.5:1.5

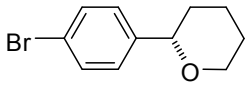
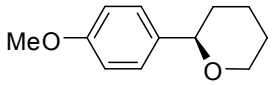
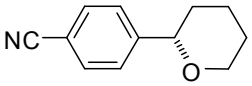
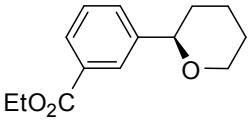
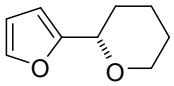
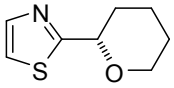
[a]Configuration of the major enantiomers of compounds **4a-f** was tentatively assumed according to the mechanism and their rotation signs.[21,22] [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Not HPLC resolved, see Table 2. [e]RuCl[(R,R)-TsDPEN](mesitylene) was employed. [f](S) Me-CBS was used

The enantioenriched δ-phenylseleno alcohols **4a-c**, **4e** and **4f** were obtained in excellent yields (Table 1) and in high enantiomeric ratio as shown by chiral HPLC analysis. However for compounds **4a** and **4b** it was not possible to obtain a good enantiomeric separation with the available chiral stationary phases. Thus, we decided to subject them, as enantioenriched mixtures, to the final cyclization step and separate the corresponding enantioenriched mixtures of tetrahydropyrans **5a** and **5b** (Table 2). Due to the instability of the ester group under the ATH conditions, alcohol **4d** was obtained by the enantioselective reduction of the corresponding ketone with borane in the presence of (*S*)-Me-CBS-oxazaborolidine catalyst[25] (Table 1, entry 4). The configuration of the major enantiomer of compounds **4a-f** was tentatively assigned according to the original mechanisms described by Noyori and Corey.[21,25] Oxidation of δ-phenylseleno alcohols **4a** in THF, with an excess of *m*-chloroperoxybenzoic acid (MCPBA) and dipotassium hydrogen phosphate at rt, gave the phenylselenone intermediate, as deduced by thin-layer chromatography (TLC). Unfortunately, the selenone intermediate was unable to turn into the desired THP ring **5a** after addition of powdered potassium hydroxide. Compound **5a** was isolated in 10% yield after 48h from addition. No significant improvement of the yield was observed with solvent changes (CH_2Cl_2 or EtOAc). The use of magnesium monoperoxyphthalate as oxidant in methanol[19a] gave THP **5a** in

moderate yield (35%) alongside the olefine derived from the β-elimination of the selenoxide intermediate.

Table 2. Oxidation/Cyclization of Alcohols 4a-f into Tetrahydropyrans 5a-f.



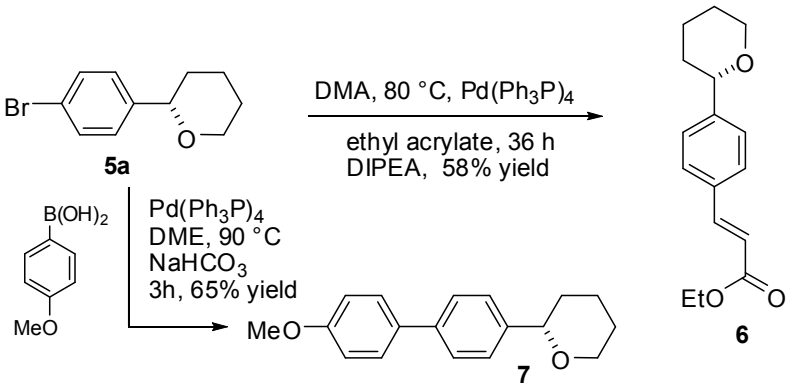
entry	tetrahydropyran	time (h)	yield (%)[a]	er[b]
1	 **5a**	8	80	97.6:2.4
2	 **5b**	5	75	88.6:11.4
3	 **5c**	7	72	89.5:10.5
4	 **5d**	2	82	---[c]
5	 **5e**	4	58	---[c]
6	 **5f**	4	67	98.5:1.5

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]Not HPLC resolved

The yield of **5a** increased up to 66% when we employed MCPBA in methanol. However, when the oxidation/cyclization of **4a** was performed in acetonitrile with an excess of MCPBA and dipotassium hydrogen phosphate, the 2-substituted THP **5a** was obtained in excellent yield (80%,

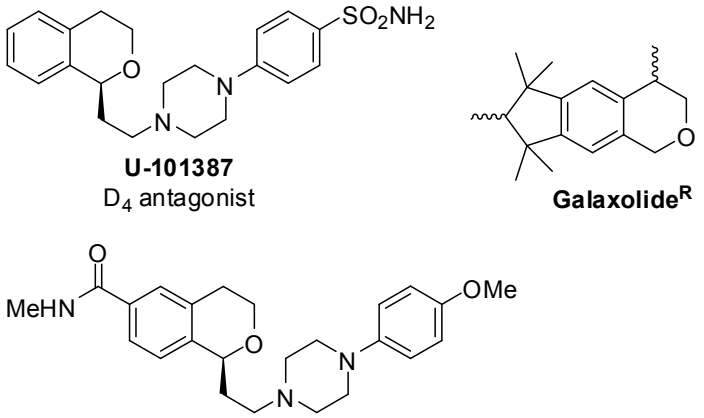
Table 2, entry 1) after addition of powdered potassium hydroxide, thus demonstrating that the cyclization step is greatly favourited by polar aprotic solvent. Oxidation/cyclization of alcohols **4b-f** was performed by using the same reaction conditions of **4a**, leading to differently 2-substituted THPs **5b-f** in good to excellent yields (Table 2, entries 2-6) and with good enantiomeric ratios. The enantiomeric composition of THPs **5c** and **5f** reflected that of the corresponding seleno-alcohols **4c** and **4f**, thus attesting that no racemization occurred in the oxidation/cyclization step. Although it was not possible to establish the enantiomeric ratios of THPs **5d** and **5e** (Table 2), the composition of the enantioenriched mixtures should be the same as that of the corresponding alcohols **4d** and **4e**, also according to our previous observations.[20] Results reported in Table 2 show that the presence of different functional groups in the aryl moiety does not significantly affect the yields of oxidation and cyclization steps. The high yields, simplicity and mildness of the experimental conditions of the procedure, make our method a general and valuable synthetic process for obtaining chiral non-racemic 2-aryl and 2-heteroaryl substituted THPs. Compounds **5b**[11] and **5e**[17] have been previously synthesized by different strategies and they were obtained in comparable or lower yields as racemic mixture. Interestingly, the presence of bromine substituent in compound **5a** allows an easy conversion into compound **6** (58% yield) by palladium(0) promoted vinylic substitution reaction,[26] or biphenyl **7** (65% yield) by palladium(0) catalyzed cross-coupling reaction[27] (Scheme 2).

Scheme 2. THP 5a involved in Palladium(0) Catalyzed Coupling Reactions



Application to the Stereoselective Synthesis of 2- and 4-substituted Isochromans. We then turned our attention to the stereoselective synthesis of various substituted isochromans, in order to explore the potential of our approach in the construction of six-membered oxygenated heterocycles. Substituted isochromans are present in drugs,[28] natural products[29] and cosmetics[30] with a wide range of activities such as analgesic, muscle relaxant, antidepressant, antihistaminic, anticoagulant and antihypertensive (Figure 1). A number of methodologies have been reported for the synthesis of isochromans, such as the oxa-Pictet-Spengler cyclization,[31] radical annulation,[32] intramolecular O-H insertion reaction of diazoesters,[12] palladium catalyzed allylic oxidation,[8] mercury-activated alkene addition,[33] cyclotrimerization[34] and the C-H alkylation or arylation at 1–position of isochromans.[35] Although these are all reliable methods, only a few enantioselective variants of the synthesis of 1- or 4-substituted isochromans have been described in literature to date.[35d,36]

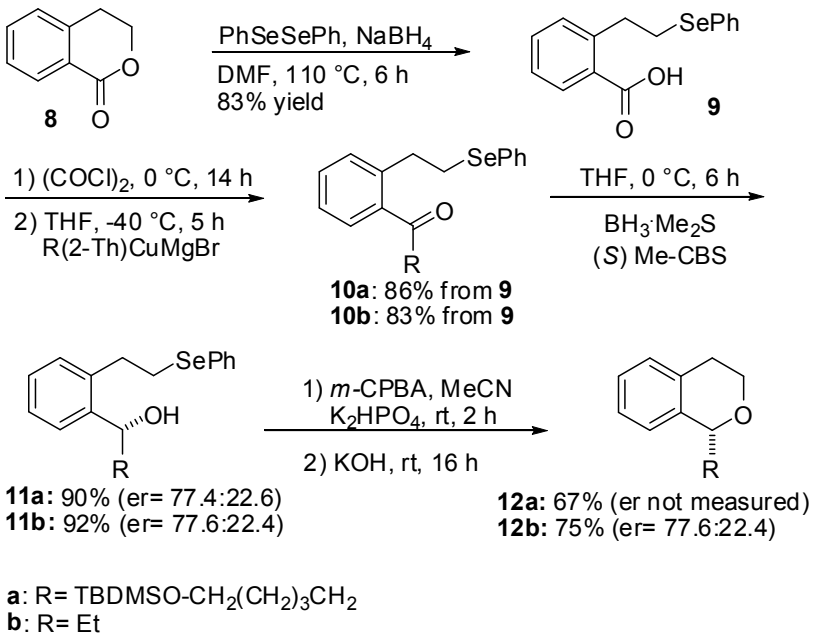
Figure 1. Selected biologically active isochromanes



We envisioned that the phenylselenone mediate ring closure reaction, proposed for the construction of THPs, could be used for the building of the six-membered oxygenated heterocycle of isochromans. Thus, the reaction sequence outlined in Scheme 3 started with the preparation of the still-unknown phenylseleno acid **9**, by cleavage of isochroman-1-one **8** with sodium

phenylselenolate. Compound **9** was reacted with oxalyl chloride to give the acyl chloride intermediate which was coupled with the appropriate mixed magnesium cuprate reagent according to our previous report[20] to furnish the new ketones **10a** and **10b** in excellent yields (Scheme 3). We also explored the direct palladium catalyzed coupling of acyl chloride of acid **9** with arylzinc reagents, as for the synthesis of **3a-d**, but the expected ketones were obtained in low yields.

Scheme 3. Synthesis of 1-substituted Isochromans 12a and 12b

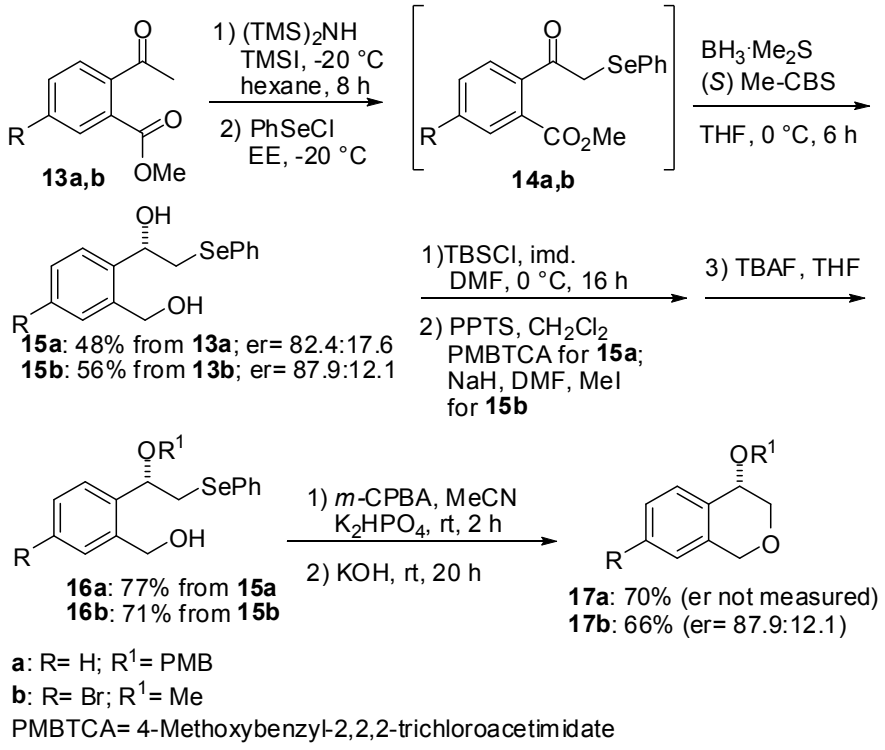


The reduction of ketones **10a** and **10b** under Noyori conditions, as described for **3a-f**, resulted in significant lesser conversion and low level of stereoselectivity. Thus, the enantioenriched phenylseleno alcohols **11a** and **11b** were obtained in excellent yields and good enantiomeric ratio via the chiral oxazaborolidine-catalyzed Corey procedure.[25] The configuration of the major enantiomer of compounds **11a** and **11b** was tentatively assigned according to the original mechanisms described by Corey.[25] The optically active 1-substituted isochromans **12a** and **12b** were finally obtained in good yields by our oxidation/cyclization procedure. Compound **12b** has been previously obtained by a different procedure in comparable yield as a racemic mixture.[35a] On

the basis of HPLC analysis on chiral stationary phase, compound **12b** showed the same enantiomeric composition of its precursor **11b,** thus supporting that no racemization occurred during the cyclization process.[20] Otherwise, for compound **12a** was not possible to obtain a clear separation of the two enantiomers by HPLC.

We next explored the enantioselective synthesis of 4-substituted isochromans **17a** and **17b** from the corresponding phenylseleno alcohols **16a** and **16b** (Scheme 4). Ketoesters **13a** and **13b** were converted, by a two steps procedure, into the intermediate α-phenylseleno ketones **14a** and **14b** which were immediately reduced with borane in the presence of (*S*)-Me-CBS oxazaborolidine to give the unexpected diols **15a** and **15b** in 48% and 56% total yield respectively, in good enantiomeric ratio (Scheme 4). It is known that ester group is stable under borane reduction conditions[37] but, in our case, the closer-in-space hydroxy group, formed in the initial reductive step, could affect the reactivity of the carbomethoxy group with borane, most probably through the formation of a lactone intermediate. A high yielding three steps procedure led to the monoprotected phenylseleno alcohols **16a** and **16b.**

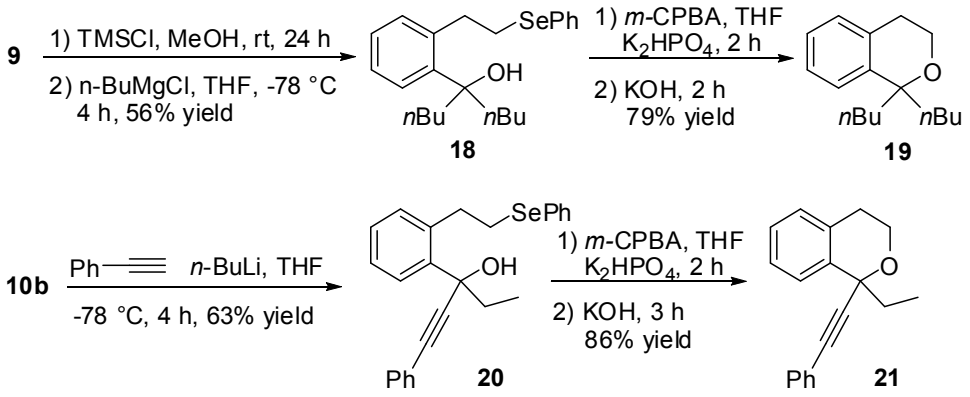
Scheme 4. Synthesis of 4-substituted Isochromans 17a and 17b



Oxidation of **16a** and **16b** with MCPBA occurred smoothly in MeCN at rt in the presence of dipotassium hydrogen phosphate to give the corresponding phenylselenone intermediates, which cyclized to the enantioenriched 4-substituted isochromans **17a** and **17b** in 70% and 66% yields, respectively, after the addition of potassium hydroxide. HPLC analysis of compound **17b** revealed the same enantiomeric composition of alcohol **16b**, whereas isochroman **17a** did not give appreciable separation with the chiral stationary phases available.

Application to the Synthesis of 1,1-disubstituted Isochromans. Our selenium-based methodology was extended to the synthesis of 1,1-disubstituted isochromans. Compound **9** was converted into the corresponding methyl ester and then treated with an excess of butylmagnesium bromide to furnish the tertiary alcohol **18** (Scheme 5). The oxidation/cyclization of alcohol **18** gave the 1,1-dialkyl isochroman **19** in high yield. Moreover, the lithium phenylacetylide addition to ketone **10b** gave the racemic tertiary alcohol **20** in 63% yield. Oxidation of **20** and cyclization of the phenylselenone intermediate gave the attractive 1-alkyl-1-alkynyl-substituted isochroman **21** in 86% yield, showing clearly that tertiary benzylic and propargylic alcohols are not affected by the reaction conditions employed for pyran ring closure.

Scheme 5. Preparation of 1,1-disubstituted Isochromans 19 and 21



CONCLUSIONS

In conclusion, we have applied the selenium-based chemistry, *via* a new 6-*exo*-tet ring-closure reaction, to the stereoselective synthesis of substituted THPs and isochromans. Our developed methodology provides a mild, stereoselective and general approach to the preparation of 2-substituted THPs and 1- or 4-substituted isochromans, from phenylseleno alcohols, that favourably compares with other previously reported methods. Within this work, a new synthetic strategy for the preparation of δ–phenylseleno ketones was developed. Further application of this new 6-*exo*-tet ring-closure reaction, directed to the synthesis of complex tetrahydropyrans as well as natural products, are currently in progress.

EXPERIMENTAL SECTION

General information. Proton nuclear magnetic resonance (^{1}H NMR) spectra and (^{13}C NMR) spectra were recorded at 200 MHz and 50.3 MHz. Unless otherwise specified $CDCl_3$ was used as the solvent and chemical shifts (δ) are reported in parts per million (ppm). The proton signal of residual, non-deuterated solvent (δ 7.27 for $CHCl_3$) was used as an internal reference for ^{1}H spectra. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broadened), coupling constants, number of protons, assignment (where possible). Coupling constant (*J*) quoted in Hertz (Hz) to the nearest 0.1 Hz. For ^{13}C spectra, chemical shifts are reported relative to the δ 77.00 resonance of $CDCl_3$ and chemical shifts are expressed in ppm. Infrared (IR) spectra were recorded on 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; for the ions containing selenium only the peaks arising from selenium-80 isotope are given. HPLC enantioseparation were performed on HPLC system equipped with a UV/Vis detector with chiral columns and solvents specified. Melting points were determined on a Kofler hotstage apparatus and are uncorrected.

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 100 mL^{-1}. Combustion analyses were carried out on elemental analyzer. Reactions were monitored by thin layer chromatography (TLC) carried out on aluminium foil sheets pre-coated with silica (Merck silica gel 60 F_{254}), which were visualized by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with 0.5% w/v potassium permanganate aqueous solution followed by heating. Column chromatography was performed using Kieselgel 60 (70-230 mesh) silica gel.

All reaction of air and water sensitive organometallics were carried out in flame-dried glassware under argon using standard techniques. The organozinc and Grignard reagents for the synthesis of compounds **3a-d**, **10b** and **18** were purchased from Aldrich and used directly from the bottle. The Grignard reagents for the preparation of ketone **10a** were synthesized in large preparation by standard method from commercially available 5-bromo-1-pentanol[38] and analyzed by the method of Knochel[39] prior to use. Freshly opened bottle of cuprous iodide was found to be satisfactory. Commercial grade tetrahydrofuran, diethyl ether, dichloromethane, acetonitrile and methanol were dried by using standard procedures. Unless indicated, all chemicals were used without further purification. 3-Chloroperbenzoic acid ≤77% from Aldrich was employed.

The starting phenylseleno acid **1** and the corresponding acyl chloride **2** were prepared as described in the literature.[20] Compounds **8**[40] and **13a**[41] have been previously described in the literature.

General Procedure for the synthesis of ketones 3a-d. Acid **1** (3.00 mmol) was reacted with oxalyl chloride (17.71 mmol) at room temperature for 14 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (5 mL), the solvent was removed and the acyl chloride **2** obtained was immediately taken in 30 mL of dry THF. The reaction mixture was cooled at 0-5 °C, protected from atmosphere moisture and powdered tetrakis(triphenylphosphine)palladium(0) (0.15 mmol), was added. Then a 0.5 M solution of organozinc reagent (7.2 mL) was added slowly along the side of the reaction flask by using a

syringe pump over 1.5 h with vigorous stirring. The dark solution was allowed to reach room temperature gradually and then stirred at this temperature for 4 h. Saturated aqueous sodium hydrogen carbonate solution (1.5 mL) was added and the slurry was filtered through a celite pad, dried over sodium sulfate, filtrated and evaporated. The residue was purified by column chromatography on silica using diethyl ether-hexane mixture as eluent afford ketone **3**.

1-(4-Bromophenyl)-5-(phenylselanyl)pentan-1-one (**3a**): Following the general procedure, **1** (0.77g, 3.00 mmol) was converted, with 4-bromophenylzinc iodide, in dry THF to **3a** (0.72 g, 61% yield); light yellow solid, mp 85-88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.54-7.44 (m, 2H), 7.35-7.15 (m, 3H), 3.08-2.82 (m, 4H), 1.98-1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.7, 135.6, 132.6 (2C), 131.9 (2C), 130.2, 129.5 (2C), 129.0 (2C), 128.1, 126.8, 37.8, 29.7, 27.5, 24.2; FTIR: 2942, 1733, 1682, 1478, 1072, 821, 732 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 396 (12), 239 (82), 183 (100), 157 (39), 91 (10), 77 (15); Anal. Calcd. for $C_{17}H_{17}BrOSe$: C, 51.54; H, 4.33. Found: C, 51.39; H, 4.57.

1-(4-Methoxyphenyl)-5-(phenylselanyl)pentan-1-one (**3b**). Following the general procedure, **1** (0.52 g, 2.00 mmol) was converted, with 4-methoxyphenylzinc iodide, in dry diethyl ether to **3b** (0.50 g, 72% yield): white solid, mp 87-89 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.56-7.48 (m, 2H), 7.32-7.23 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.05-2.86 (m, 4H), 1.98-1.72 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.5, 163.4, 132.5 (2C), 130.3 (2C), 129.9, 129.0, 128.4, 126.7 (2C), 113.7 (2C), 55.4, 37.5, 29.8, 27.5, 24.6; FTIR: 2937, 1676, 1599, 1255, 1169, 829, 733 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 348 (2), 191 (50), 135 (100), 92 (15), 77(29); Anal. Calcd. for $C_{18}H_{20}O_2Se$: C, 62.25; H, 5.80. Found: C, 62.03; H, 6.02.

4-[5-(Phenylselanyl)pentanoyl]benzonitrile (**3c**). Following the general procedure, **1** (1.03 g, 4.00 mmol) was converted, with 4-cyanophenylzinc bromide, in dry diethyl ether to **3c** (1.03 g, 73% yield): white solid, mp 80-82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.57-7.45 (m, 2H), 7.43-7.20 (m, 3H), 3.05-2.92 [t, partly overlapped t (*J* = 6.5 Hz, 2H), t (*J* = 6.4 Hz, 2H)], 2.01-1.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.3, 139.8, 132.6

(2C), 132.5 (2C), 129.6, 129.0 (2C), 128.4 (2C), 126.8, 117.9, 116.3, 38.2, 29.6, 27.4, 23.9; FTIR: 3068, 2936, 2237, 1683, 1477, 1273, 834, 731 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 343 (9), 186 (68), 157 (15), 130 (100), 102 (42), 77(14); Anal. Calcd. for $C_{18}H_{17}NOSe$: C, 63.16; H, 5.01; N, 4.09. Found: C, 62.97; H, 5.25; N, 4.23.

Ethyl 3-[5-(phenylselanyl)pentanoyl]benzoate (**3d**). Following the general procedure, **1** (1.29 g, 5.00 mmol) was converted, with 3-(ethoxycarbonyl)phenylzinc iodide, in dry THF to **3d** (1.07 g, 55% yield): amorphous solid, mp 38-40 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 1.4, 1.7 Hz, 1H), 8.24 (dt, *J* = 1.4, 7.7 Hz, 1H), 8.03 (ddd, *J* = 1.4, 1.7, 7.8 Hz, 1H), 7.61-7.43 (m, 3H), 7.32-7.19 (m, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.99-1.70 (m, 4H), 1.42 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.0, 165.8, 137.0, 133.7, 132.5 (2C), 132.0, 131.0, 130.2, 129.1 (2C), 129.0, 128.8, 126.7, 61.4, 38.0, 29.6, 27.5, 24.1, 14.3; FTIR: 2934, 1721, 1690, 1205, 1023, 748 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 390 (6), 233 (83), 177 (100), 149 (30), 120 (15), 85 (26), 71 (31), 57 (52); Anal. Calcd. for $C_{20}H_{22}O_3Se$: C, 61.70; H, 5.70. Found: C, 61.47; H, 5.94.

Preparation of ketone 3e. Acyl chloride **2** (1.00 mmol) prepared as described above from 0.258 g of acid **1** and oxalyl chloride (0.5 mL, 5.90 mmol) was dissolved in dry THF (2 mL) at room temperature. Tributyl(2-furyl)stannane (0.346 mL, 1.10 mmol) and powdered tetrakis (triphenylphosphine)palladium(0) (0.02 g, 0.03 mmol), were then added and the reaction mixture was stirred under argon atmosphere for 20 h.[42] The orange solution was then concentrated and the residue was subjected to purification by column chromatography on SiO_2 (20% diethyl ether in hexane) affording ketone **3e**.

1-(2-Furyl)-5-(phenylselanyl)pentan-1-one (**3e**): 0.20 g, 65% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 0.8, 1.8 Hz, 1H), 7.53-7.46 (m, 2H), 7.30-7.22 (m, 3H), 7.17 (dd, *J* = 0.8, 3.6 Hz, 1H), 6.54 (dd, *J* = 1.8, 3.6 Hz, 1H), 2.95 (t, *J* = 7.1 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 1.95-1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 152.6, 132.4 (2C), 130.2, 128.9 (3C), 126.6, 116.8, 112.1, 37.6, 29.6, 27.3 24.2; FTIR: 2930, 1676, 1568, 1468, 1022, 762, 736 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 308 (30), 157 (29), 151 (96), 123 (13), 95 (100), 77 (25); Anal. Calcd. for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25. Found: C, 58.51; H, 5.47.

Synthesis of ketone 3f. Dry methanol (1.0 mL) was added to a mixture of acid chloride **2** (1.36 mmol) in dry THF (10 mL) and triethyl amine (0.21 mL, 1.49 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature. After 3 h the reaction was quenched with 10 mL of 2M hydrochloric acid and 50 mL of dichloromethane. The organic phase was separated and washed with 10 mL of saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate, filtrated and evaporated to give the crude methyl ester derivative which was dissolved in 3 mL of diethyl ether and then added dropwise at -78 °C to a solution of 2-lithiothiazole (1.50 mmol) in diethyl ether (4.00 mL) prepared as described by Dondoni.[24] After ten minutes at -78 °C, the resulting mixture was allowed to warm to 25 °C (1 h) and quenched by addition of 10 mL of saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over sodium sulfate, filtrated and evaporated. The resulting oil was purified by chromatography on SiO_2 (30% diethyl ether/petroleum ether) to afford ketone **3f**.

5-(Phenylselanyl)-1-(1,3-thiazol-2-yl)pentan-1-one (**3f**): 0.72 g, 69% yield; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, *J* = 3.0 Hz, 1H), 7.67 (d, *J* = 3.0 Hz, 1H), 7.54-7.43 (m, 2H), 7.35-7.18 (m, 3H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.01-1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.5, 167.0, 144.6, 132.6 (2C), 130.2, 129.0 (2C), 126.7, 126.2, 37.8, 28.8, 27.3 24.0; FTIR: 2937, 1684, 1478, 1391, 734 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 325 (11), 168 (44), 157 (18), 140 (100), 128 (21), 112 (57), 86 (40), 77 (14); Anal. Calcd. for $C_{14}H_{15}NOSSe$: C, 51.85; H, 4.66; N, 4.32. Found: C, 51.63; H, 4.90; N, 4.11.

Typical Procedure for the Asymmetric Reduction of ketones 3a-c and 3e,f. Powdered RuCl[(*R*,*R*)-TsDPEN](mesitylene) (0.05 mmol) was added to a solution of ketone **3** (1.00 mmol) in 15 mL of degassed 2-propanol at 36 °C followed by 0.06 mmol of potassium hydroxide. The resulting dark brown mixture is stirred vigorously at 36 °C. After the appropriate reaction time (see

Table 1), the reaction mixture was quenched with 10 mL of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution, saturated NaCl solution, dried over sodium sulfate, filtrated and evaporated. The residue was purified by chromatography on SiO_2 using an ethyl acetate-petroleum ether mixture (2:8) as eluent.

(1S)-1-(4-Bromophenyl)-5-(phenylselanyl)pentan-1-ol (**4a**). Following the general procedure ketone **3a** (0.97 g, 2.45 mmol) was reduced to **4a** (0.83 g, 85% yield); amorphous solid, mp 35-37 °C; $[\alpha]_D^{23}$ -9.08 (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.42 (m, 4H), 7.31-7.14 (m, 5H), 4.59 (dd, *J* = 5.7, 7.1 Hz, 1H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.17 (br s, 1H), 1.89-1.28 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 132.4 (2C), 131.4 (2C), 130.3, 128.9 (2C), 127.5 (2C), 126.6, 121.1, 73.6, 38.3, 29.9, 27.6, 25.7; FTIR: 3396, 2932, 1578, 1478, 1009, 826, 736 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 398 (75), 223 (49), 211 (51), 198 (24), 185 (71), 169 (47), 158 (76), 144 (41), 91 (38), 77 (100), 51 (26); Anal. Calcd. for $C_{17}H_{19}BrOSe$: C, 51.28; H, 4.81. Found: C, 51.01; H, 5.05.

(1R)-1-(4-Methoxyphenyl)-5-(phenylselanyl)pentan-1-ol (**4b**). Following the general procedure ketone **3b** (0.35 g, 1.00 mmol) was reduced to **4b** (0.31 g, 89% yield); colorless oil; $[\alpha]_D^{21}$ +26.04 (*c* 1.64, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.40 (m, 2H), 7.31-7.13 (m, 5H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.58 (t, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.01 (br s, 1H), 1.88-1.29 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9, 136.7, 132.3 (2C), 130.4, 128.9 (2C), 127.0 (2C), 126.6, 113.7 (2C), 73.9, 55.2, 38.2, 30.0, 27.6, 26.0; FTIR: 3420, 2934, 1612, 1513, 1247, 884, 734 cm^{-1}; EIMS (70 eV) *m/z*: $[M-18]^+$ 332 (25), 207 (89), 159 (52), 147 (100), 121 (88), 91 (79), 78 (87); Anal. Calcd. for $C_{18}H_{22}O_2Se$: C, 61.89; H, 6.35. Found: C, 61.70; H, 6.65.

4-[(1S)-1-Hydroxy-5-(phenylselanyl)pentyl]benzonitrile (**4c**). Following the general procedure ketone **3c** (0.78 g, 2.30 mmol) was reduced to **4c** (0.64 g, 82% yield); colorless oil; $[\alpha]_D^{20}$ -9.52 (*c* 1.49, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.54-7.38 (m, 4H), 7.33-7.20 (m, 3H), 4.72 (t, *J* = 5.5 Hz, 1H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.37 (br s, 1 H), 1.89-1.35 (m, 6H); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 150.1, 132.4 (2C), 132.2 (2C), 130.3, 129.0 (2C), 126.7, 126.5 (2C), 118.8, 111.0, 73.4, 38.5, 29.9, 27.5, 25.6; FTIR: 3423, 2934, 2228, 1608, 1478, 1073, 839, 739 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 345 (54), 213 (18), 188 (33), 170 (36), 158 (100), 132 (33), 104 (51), 91 (33), 77(58); Anal. Calcd. for $C_{18}H_{19}NOSe$: C, 62.79; H, 5.56; N, 4.07. Found: C, 62.48; H, 5.90; N, 3.88. HPLC analysis on Phenomenex® Lux Cellulose-1 column (100 x 4.60 mm ID), *n*-hexane/2-propanol = 94:6, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 13.2 min, t_R (*S*-enantiomer, major) = 15.8 min, er = 10.5:89.5.

(1S)-1-(2-Furyl)-5-(phenylselanyl)pentan-1-ol (**4e**). Following the general procedure ketone **3e** (0.57 g, 1.75 mmol) was reduced to **4e** (0.53 g, 92% yield); light yellow oil; $[\alpha]_D^{24}$ -5.07 (*c* 2.43, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57-7.42 (m, 2H), 7.38 (dd, *J* = 0.8, 1.8 Hz, 1H), 7.31-7.21 (m, 3H), 6.34 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.22 (dd, *J* = 0.8, 3.2 Hz, 1H), 4.64 (t, *J* = 6.7 Hz, 1H), 2.91 (t, *J* = 7.1 Hz, 2H), 2.12 (br s, 1 H), 1.95-1.35 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.5, 132.4 (2C), 130.3, 128.9 (2C), 125.6 (2C), 110.0, 105.8, 67.4, 34.8, 29.8, 27.5, 25.6; FTIR: 3365, 2933, 1578, 1478, 1007, 736 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 310 (68), 241 (17), 157 (59), 135 (40), 123 (52), 97 (100), 91 (36), 77 (46), 55 (20); Anal. Calcd. for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87. Found: C, 57.97; H, 6.11. HPLC analysis on Phenomenex® Lux Cellulose-1 column (100 x 4.60 mm ID), *n*-hexane/2-propanol = 96:4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 10.5 min, t_R (*S*-enantiomer, major) = 11.4 min, er = 2.8:97.2.

(1S)-5-(phenylselanyl)-1-(1,3-thiazol-2-yl)pentan-1-ol (**4f**). Following the general procedure ketone **3f** (0.30 g, 0.94 mmol) was reduced to **4f** (0.27 g, 89% yield); yellow oil; $[\alpha]_D^{27}$ -10.70 (*c* 1.94, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.1 Hz, 1H), 7.54-7.42 (m, 2H), 7.32-7.20 (m, 4H), 4.99 (dd, *J* = 4.8, 7.4 Hz, 1H), 3.33 (br s, 1 H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.10-1.50 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.8, 141.9, 132.4 (2C), 130.3, 128.9 (2C), 126.6, 118.8, 71.3, 37.5, 29.8, 27.5 25.3; FTIR: 3230, 2935, 1578, 1477, 1072, 734 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 327 (14), 281 (10), 207 (36), 168 (42), 140 (100), 128 (51), 112 (75), 86 (92), 77 (30), 55 (26); Anal.

Calcd. for $C_{14}H_{17}NOSSe$: C, 51.53; H, 5.25; N, 4.29;. Found: C, 51.20; H, 5.61; N, 4.02. HPLC analysis on Phenomenex® Lux Cellulose-1 column (100 x 4.60 mm ID), *n*-hexane/2-propanol = 96:4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 15.7 min, t_R (*S*-enantiomer, major) = 18.9 min, er = 1.5:98.5

Asymmetric reduction of ketone 3d. To a solution of (*S*)-Me-CBS 1.0 M in toluene (0.33 mL, 0.33 mmol) in dry THF (20 mL) at 0 °C was added a 2.0 M borane-dimethyl sulfide complex (0.82 ml, 1.64 mmol).[25] A solution of ketone **3d** (1.64 mmol) in dry THF (13 mL) was added slowly by using a syringe pump over 2 h with vigorous stirring and the solution was allowed to warm to room temperature. The mixture was stirred at room temperature until the ketone disappeared on TLC monitoring (3 h). The mixture was quenched with methanol and saturated ammonium chloride solution (5 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), filtrated and concentrated *in vacuo.* The crude product was purified on a silica gel column with a mixture of petroleum ether and ethyl acetate 80:20 as eluent to give the corresponding chiral secondary alcohol **4d**.

Ethyl 3-[(1R)-1-hydroxy-5-(phenylselanyl)pentyl]benzoate (**4d**): 0.58 g, 90% yield; colorless oil; $[\alpha]_D^{25}$ +10.37 (*c* 1.23, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04-7.88 (m, 2H), 7.58-7.32 (m, 4H), 7.31-7.17 (m, 3H), 4.70 (dd, *J* = 5.5, 6.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.30 (br s, 1 H), 1.84-1.32 [m, partly overlapped t (*J* = 7.1 Hz, 3H), m (6H)], 1.39; ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.6, 145.0, 132.4 (2C), 130.5, 130.3, 129.6, 128.9 (2C), 128.6, 128.4, 126.9, 126.6, 73.8, 61.0, 38.4, 29.9, 27.5, 25.8, 14.3; FTIR: 3504, 2933, 1718, 1478, 1283, 1192, 740 cm^{-1}; EIMS (70 eV) *m/z*: $[M-158]^+$ 234 (3), 192 (36), 179 (100), 151 (20), 105 (23), 79 (14); Anal. Calcd. for $C_{20}H_{24}O_3Se$: C, 61.38; H, 6.18. Found: C, 61.10; H, 6.47. HPLC analysis on Phenomenex® Lux Cellulose-1 column (100 x 4.60 mm ID), *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, minor) = 17.1 min, t_R (*R*-enantiomer, major) = 21.6 min, er = 8.6:91.4.

General Procedure for the Oxidation-Cyclization of Phenylseleno alcohols 3a-f. To a solution of phenylseleno alcohol **4** (0.50 mmol) in acetonitrile (15 mL) at room temperature, powdered potassium hydrogenphosphate (2.00 mmol) and *m*-CPBA (1.50 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). Powdered potassium hydroxyde (3.75 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After the appropriate time reaction (see table 2), the mixture was then poured into water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated sodium carbonate solution, saturated NaCl solution, dried over sodium sulfate, filtrated and evaporated. The reaction product was then purified by column chromatography on silica gel (diethyl ether- petroleum ether mixture) to afford the 2-substituted THP **5**.

(2S)-2-(4-Bromophenyl)tetrahydro-2H-pyran (**5a**). Following the general procedure alcohol **4a** (0.20 g, 0.50 mmol) was converted to **5a** (97 mg, 80% yield); light yellow oil; $[\alpha]_D^{26}$ -33.90 (*c* 1.89, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.30 (dd, *J* = 1.8, 10.6 Hz, 1H), 4.21-4.08 (m, 1H), 3.70-3.52 (m, 1H), 2.02-1.43 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.4, 131.3 (2C), 127.6 (2C), 121.0, 79.3, 69.0, 34.1, 25.8, 23.9; FTIR: 2936, 2847, 1489, 1089, 909, 817 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 240 (41), 185 (73), 161 (100), 156 (32), 105 (43), 77 (35), 55 (25); Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.50; H, 5.77. HPLC analysis on Phenomenex® Lux Cellulose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 99.6:0.4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 20.7 min, t_R (*S*-enantiomer, major) = 22.2 min, er = 2.4:97.6.

(2R)-2-(4-Methoxyphenyl)tetrahydro-2H-pyran (**5b**).[43] Following the general procedure alcohol **4b** (0.31 g, 0.90 mmol) was converted to **5b** (0.13 g, 75% yield); $[\alpha]_D^{22}$ +33.51 (*c* 1.15, $CHCl_3$); HPLC analysis on Chiracel® OD-H column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, major) = 8.1 min, t_R (*S*-enantiomer, minor) = 15.6 min, er = 88.6:11.4.

4-[(2S)-Tetrahydro-2H-pyran-2-yl]benzonitrile (**5c**). Following the general procedure alcohol **4c** (0.28 g, 0.80 mmol) was converted to **5c** (0.10 g, 67%); colorless oil; $[\alpha]_D^{19}$ -51.47 (*c* 1.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.39 (dd, *J* = 2.3, 11.0 Hz, 1H), 4.22-4.10 (m, 1H), 3.70-3.53 (m, 1H), 2.10-1.31 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 132.0 (2C), 126.3 (2C), 118.9, 110.7, 78.9, 68.8, 34.0, 25.5, 23.7; FTIR: 2941, 2851, 2228, 1610, 1265, 1089, 827 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 187 (52), 158 (21), 130 (100), 116 (43), 102 (49), 84 (37), 55 (57); Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.66; H, 7.37; N, 7.20. HPLC analysis 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: t_R (*S*-enantiomer, major) = 16.3 min, t_R (*R*-enantiomer, minor) = 17.9 min, er = 89.5:10.5.

Ethyl 3-[(2R)-tetrahydro-2H-pyran-2-yl]benzoate (**5d**). Following the general procedure alcohol **4d** (0.21 g, 0.54 mmol) was converted to **5d** (0.10 g, 82% yield); colorless oil; $[\alpha]_D^{23}$ +25.69 (*c* 0.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (t, *J* = 1.6 Hz, 1H), 7.95 (dt, *J* = 1.6, 7.7 Hz), 7.56 (dt, *J* = 1.6, 7.7 Hz), 7.41 (t, *J* = 7.7 Hz), 4.45-4.34 [m, partly overlapped q (*J* = 7.1 Hz, 2H), m (1H)], 4.22-4.10 (m, 1H), 3.71-3.55 (m, 1H), 2.01-1.51 (m, 6H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6, 143.7, 130.4, 130.3, 128.4, 128.3, 126.9, 79.5, 68.9, 60.9, 34.0, 25.7, 23.9, 14.3; FTIR: 2937, 2845, 1718, 1280, 1085, 753 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 234 (37), 205 (33), 189 (47), 177 (37), 161 (100), 149 (51), 133 (66), 105 (59), 77 (30); Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.50; H, 7.98.

(2S)-2-(2-Furyl)tetrahydro-2H-pyran (**5e**).[17] Following the general procedure alcohol **4e** (0.47 g, 1.50 mmol) was converted to **5e** (0.13 g, 58% yield): colorless oil; $[\alpha]_D^{27}$ -2.42 (*c* 1.72, $CHCl_3$); FTIR: 2942, 2850, 1724, 1506, 1085, 902, 734 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 152 (57), 189 (47), 135 (24), 108 (15), 95 (100), 81 (24), 68 (17), 55 (20).

2-[(2S)-Tetrahydro-2H-pyran-2-yl]-1,3-thiazole (**5f**). Following the general procedure alcohol **4f** (0.25 g, 0.77 mmol) was converted to **5f** (85 mg, 67% yield); colorless oil; $[\alpha]_D^{19}$ -39.66 (*c* 1.54,

$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.3 Hz, 1H), 7.27 (d, *J* = 3.3 Hz, 1H), 4.77-4.70 (m, 1H), 4.22-4.09 (m, 1H), 3.76-3.55 (m, 1H), 2.30-2.10 (m, 1H), 2.07-1.90 (m, 1H), 1.80-1.50 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 142.0, 118.5, 77.6, 68.8, 32.5, 25.5, 22.9; FTIR: 2940, 2850, 1506, 1090, 1048, 902, 725 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 169 (1), 141 (34), 112 (100), 86 (30), 58 (29); Anal. Calcd. for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.49; H, 6.85; N, 8.02. HPLC analysis on Phenomenex® Lux Cellulose-1 column (100 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 4.5 min, t_R (*S*-enantiomer, major) = 6.7 min, er = 1.5:98.5.

Synthesis of compound 6. Powdered tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.005 mmol), tetrabutylammonium chloride (7 mg, 0.025 mmol), compound **5a** (0.06 g, 0.25 mmol), *N*,*N*-diisopropylethylamine (0.09 mL, 0.50 mmol), and ethyl acrylate (0.06 mL, 0.50 mmol) were dissolved in N,N-dimethylacetamide (2 mL), and the resulting mixture was heated to 80 °C for 36 h.[44] The mixture was then cooled to rt, diluted with diethyl ether (30mL), washed with brine, dried over sodium sulfate, filtrated and concentrated to afford the crude product, which was purified by column chromatography on SiO_2 (10% diethyl ether in hexane).

Ethyl (2E)-3-{4-[(2S)-tetrahydro-2H-pyran-2-yl]phenyl}acrylate (**6**): 38 mg, 58% yield: light yellow oil; $[\alpha]_D^{26}$ -60.32 (*c* 1.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 4.38-4.04 [m, partly overlapped q (*J* = 7.1 Hz, 2H), m (1H), m (1H], 4.25, 3.69-3.54 (m, 1H), 2.00-1.49 (m, 6H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.0, 145.7, 144.3, 133.4, 128.0 (2C), 126.2 (2C), 117.8, 79.6, 68.9, 60.4, 33.9, 25.7, 23.9, 14.3; FTIR: 2937, 2842, 1714, 1636, 1169, 1041, 821 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 260 (53), 214 (51), 203 (40), 187 (100), 175 (57), 159 (51), 131 (67), 103 (47), 77 (24); Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.51; H, 7.99.

Synthesis of compound 7. A 25 mL round-bottom flask was charged with compound **5a** (0.12 g, 0.50 mmol), powdered tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) and 4 mL of dimetoxyethane. The red mixture was stirred for 15 min at room temperature under argon

atmosphere, then 4-metoxyphenylboronic acid (91 mg, 0.60 mmol) and 1 mL of 2M sodium bicarbonate solution were added.[27] The mixture was stirred at 90 °C for 3 h and then allowed to slowly warm to room temperature. The slurry was filtered through a celite pad, dried over sodium sulfate, filtrated and evaporated. Purification of the crude product by chromatography on SiO_2 (10% diethyl ether in hexane) afforded 89 mg of compound **7**, 65% yield.

(2S)-2-(4'-Methoxybiphenyl-4-yl)tetrahydro-2H-pyran (**7**): white solid, mp 100-102 °C; $[\alpha]_D^{27}$ -34.86 (*c* 0.57, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.56 (m, 4H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.42-4.33 (m, 1H), 4.23-4.11 (m, 1H), 3.86 (s, 3H), 3.73-3.57 (m, 1H), 2.05-1.52 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.0, 141.7, 139.7, 133.5, 128.0 (2C), 126.5 (2C), 126.2 (2C), 114.1(2C), 79.8, 69.0, 55.3, 33.9, 25.9, 24.0; FTIR: 2934, 2837, 1607, 1499, 1250, 1039, 821 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 268 (100), 211 (65), 197 (39), 184 (31), 152 (20), 141 (20), 115 (15), 55 (9); Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.87**.**

Preparation of acid 9. Commercially available isochroman was oxidized to isochroman-1-one with a mixture of potassium permanganate and copper sulfate pentahydrate as reported in the literature.[40] Isochroman-1-one (1.18 g, 8 mmol) was then cleaved with sodium phenyl selenolate in dry dimethylformamide[20] at reflux to give 1.75 g (83% yield) of acid **9**.

2-[2-(Phenylselanyl)ethyl]benzoic acid (**9**): light yellow solid,mp 100-102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.90 (br s, 1H), 8.10 (dd, J = 1.5, 7.8 Hz, 1H), 7.68-7.52 (m, 3H), 7.50-7.10 (m, 5H), 3.55-3.38 (m, 2H), 3.24-3.17 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 143.8, 133.2, 132.4 (2C), 131.9, 131.7, 130.2, 129.0 (2C), 127.8, 126.7 (2C), 35.7, 28.2; FTIR: 3001, 2812, 1699, 1273, 930, 706 cm^{-1}; EIMS (70 eV) *m/z*: M^+ 308 (15), 157 (11), 149 (100), 135 (82), 103(33), 91 (25), 77 (39); Anal. Calcd. for $C_{15}H_{14}O_2Se$: C, 59.02; H, 4.62. Found: C, 58.70; H, 4.97.

Synthesis of Ketones 10a and 10b. The ketones **10a** and **10b** were synthesized by acylation of the appropriate mixed magnesium cuprate reagents obtained from 1-bromo-5-*tert*-butyl-dimethylsilyloxypentane[38] and ethylmagnesium bromide respectively, with the corresponding acyl chloride of acid **9** as reported in the literature.[20]

6-{[tert-Butyl(dimethyl)silyl]oxy}-1-{2-[2-(phenylselanyl)ethyl]phenyl}hexan-1-one (**10a**): 0.42 g, 86% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66-7.15 (m, 9H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.23-3.12 (m, 4H), 2.89 (t, *J* = 7.2 Hz, 2H), 1.80-1.22 (m, 6H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.5, 140.4, 138.2, 132.3 (2C), 131.5, 131.2, 130.4, 129.0 (2C), 128.5, 126.6, 126.4, 63.0, 41.7, 35.0, 32.7, 28.6, 26.0 (3C), 25.5, 24.1, 18.3, -5.3 (2C); FTIR: 2928, 1684, 1478, 1256, 1094, 835, 739 cm^{-1}; EIMS (70 eV) *m/z*: $[M-57]^+$ 433 (63), 201 (25), 183 (31), 155 (19), 141 (53), 129 (24), 103 (22), 91 (28), 75 (100); Anal. Calcd. for $C_{26}H_{38}O_2SeSi$: C, 63.78; H, 7.82. Found: C, 63.44; H, 8.09.

1-{2-[2-(Phenylselanyl)ethyl]phenyl}propan-1-one (**10b**): 2.73 g, 83% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.5, 7.5 Hz, 1H), 7.55-7.48 (m, 2H), 7.45-7.21 (m, 6H), 3.40-3.05 (m, 4H), 2.90 (q, *J* = 7.3 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.7, 140.3, 137.9, 132.1 (2C), 131.4, 131.1, 130.3 (2C), 128.9, 128.3, 126.5, 126.3, 34.9, 34.7, 28.5, 8.2; FTIR: 2936, 1648, 1478, 1216, 957, 735 cm^{-1}; EIMS (70 eV) *m/z* 318 (15), 161 (100), 157 (22), 143 (28), 128 (29), 103 (20), 91 (25), 77 (26); Anal. Calcd. for $C_{17}H_{18}OSe$: C, 64.35; H, 5.72. Found: C, 64.04; H, 6.07.

Asymmetric Reduction of Ketones 10a and 10b. The alcohols **11a** and **11b** were obtained by asymmetric reduction of the corresponding ketones with (*S*)-Me-CBS as reported above for ketone **4d**.

(1R)-6-{[tert-Butyl(dimethyl)silyl]oxy}-1-{2-[2-(phenylselanyl)ethyl]phenyl}hexan-1-ol (**11a**). As reported above, ketone **10a** (0.20 g, 0.50 mmol) was reduced to **11a** (0.36 g, 90% yield); colorless oil: $[\alpha]_D^{16}$ +10.1 (*c* 1.48, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.40 (m, 3H), 7.38-7.06 (m, 6H), 4.79 (dd, *J* = 4.9, 7.7 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.19-2.95 (m, 4H), 1.90 (br s, 1H), 1.85-1.08 (m, 8H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 137.6, 133.0 (2C), 129.8, 129.5, 129.1 (2C), 127.5, 127.1, 127.0, 125.8, 70.1, 63.1, 38.7, 33.1, 32.7, 28.8, 26.0 (3C), 25.8 (2C), 18.3, -5.3 (2C); FTIR: 3335, 2929, 1578, 1472, 1255, 1098, 835, 774 cm^{-1};

EIMS (70 eV) *m/z*: $[M-57]^+$ 435 (17), 207 (21), 185 (44), 157 (19), 143 (52), 129 (60), 117 (85), 105 (31), 91 (39), 75 (100); Anal. Calcd. for $C_{26}H_{40}O_2SeSi$: C, 63.52; H, 8.20. Found: C, 63.15; H, 8.55; HPLC analysis on Phenomenex® Lux Amylose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, major) = 12.4 min, t_R (*S*-enantiomer, minor) = 13.5 min, er = 77.4:22.6.

(1R)-1-{2-[2-(Phenylselanyl)ethyl]phenyl}propan-1-ol (**11b**). As reported above, ketone **10b** was reduced to alcohol **11b** (0.90 g, 92% yield); light yellow oil: $[\alpha]_D^{16}$ +6.00 (*c* 1.56, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.61-7.42 (m, 3H), 7.37-7.11 (m, 6H), 4.72 (dd, *J* = 5.6, 7.4 Hz, 1H), 3.21-2.92 (m, 4H), 2.01 (br s, 1H), 1.88-1.57 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.3, 137.8, 133.0, 129.4, 129.1 (3C), 127.3, 127.0, 126.9 (2C), 125.7, 71.4, 33.1, 31.4, 28.7, 10.5; FTIR: 3385, 2963, 1578, 1477, 1437, 972, 734 cm^{-1}; EIMS (70 eV) *m/z* 320 (26), 185 (12), 157 (13), 145 (79), 133 (100), 117 (38), 105 (98), 91 (64), 77 (41); Anal. Calcd. for $C_{17}H_{20}OSe$: C, 63.95; H, 6.31. Found: C, 63.58; H, 6.59; HPLC analysis on Phenomenex® Lux Celulose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, minor) = 13.9 min, t_R (*R*-enantiomer, major) = 16.1 min, er = 22.4:77.6.

General Procedure for the Oxidation-Cyclization of Phenylseleno alcohols 11a and 11b. To a solution of the appropriate phenylseleno alcohol (1.00 mmol) in acetonitrile (15 mL) at room temperature, powdered potassium hydrogenphosphate (4.00 mmol) and *m*-CPBA (3.00 mmol) were added. The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2.5 h). Powdered potassium hydroxyde (7.50 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After 16 h the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated sodium carbonate solution, saturated NaCl solution, dried over sodium sulfate, filtrated and evaporated. The reaction product was purified by column chromatography on SiO_2 (4% diethyl ether in petroleum ether).

(R)-tert-Butyl(5-(isochroman-1-yl)pentyloxy)dimethylsilane (**12a**). Following the general procedure, **11a** (0.31 g, 0.63 mmol) was converted to **12a** (0.14 g, 67% yield); colorless oil; $[\alpha]_D^{18}$ +38.5 (*c* 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.04 (m, 4H), 4.77 (dd, *J* = 2.6, 8.0 Hz, 1H), 4.16 (ddd, *J* = 3.7, 5.3, 11.2 Hz, 1H), 3.80 (ddd, *J* = 3.8, 9.6, 11.2 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.01 (ddd, *J* = 5.3, 9.6, 16.2 Hz, 1H), 2.72 (ddd, *J* = 3.7, 3.8, 16.2 Hz, 1H), 2.00-1.77 (m, 2H), 1.64-1.25 (m, 6H), 0.92 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.9, 128.8, 126.1, 126.0, 124.7, 75.8, 63.2, 63.1, 36.0, 32.8, 29.2, 26.0 (3C), 25.9, 25.1, 18.4, -5.3 (2C); FTIR: 2933, 1471, 1254, 1104, 836, 742 cm^{-1}; EIMS (70 eV) *m/z*: $[M-57]^+$ 277 (11), 185 (23), 143 (36), 133 (100), 129 (35), 117 (45), 105 (21), 75 (35); Anal. Calcd. for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.54; H, 10.59.

(1R)-1-Ethyl-isochroman (**12b**).[35a] Following the general procedure, **11b** (0.29 g, 0.9 mmol) was converted to **12b** (0.11 g, 75% yield); colorless oil; $[\alpha]_D^{23}$ +80.2 (*c* 1.50, $CHCl_3$); HPLC analysis on Phenomenex® Lux Celulose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, major) = 4.6 min, t_R (*S*-enantiomer, minor) = 5.4 min, er = 77.6:22.4.

Synthesis of ketoester 13b. Commercially available 5-bromo-2-hydroxy-benzaldehyde was converted into the corresponding 2-acetyl-5-bromobenzaldehyde **22** by the method reported in the literature.[45]

2-Acetyl-5-bromobenzaldehyde (**22**):[45] 1.52 g, 70% yield; light yellow solid, mp 73-75 °C (*n*-hexane); FTIR: 2893, 2748, 1765, 1676, 1192, 824, 710 cm^{-1}; Oxidation of **22** following the literature procedure[46] gave crude 2-acetyl-5-bromobenzoic acid which was immediately reacted with methanol[41] to give **13b**.

Methyl 2-acetyl-5-bromobenzoate (**13b**): 0.70 g, 68% yield; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 2.54 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.5, 166.2, 140.9, 134.9, 132.6, 130.8, 128.2,

124.4, 52.8, 29.8; FTIR: 2952, 1732, 1705, 1262, 967, 830, 750 cm^{-1}; EIMS (70 eV) *m/z* 256 (5), 241 (100), 225 (31), 211 (16), 198 (11), 170 (13), 153 (13), 75 (21); Anal. Calcd. for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.64; H, 3.58.

Synthesis of diols 15a and 15b. A solution of methyl 2-acetylbenzoate **13a** (0.10 g, 0.60 mmol) and hexamethyldisilazane (0.16 mL, 0.72 mmol) in hexane (8 mL) was cooled to -20 °C under argon and trimethylsilyl iodide (0.10 ml, 0,60 mmol) was added.[47] The mixture was stirred first at -20 °C for 10 min then at 25 °C for 8 h. The slurry was filtered through a celite pad and the filtrate was washed with 10 mL of cold saturated sodium hydrogen carbonate solution, dried over sodium sulfate, filtrated and evaporated to give the crude trimethylsilylenol ether derivative which was dissolved in 2 mL of dry diethyl ether at -20 °C. Phenylselenenyl chloride (0.13 g, 0.66 mmol) dissolved in dry diethyl ether (2.0 mL) was added slowly and the reaction mixture was allowed to slowly warm to room temperature. After 1 h the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (10 mL) and then extracted with diethyl ether (2 x 10 mL). The organic layer was dried over sodium sulfate, filtrated and evaporated. The residue was passed through a short column of silica gel (20% diethyl ether in petroleum ether) to give the crude α-phenylseleno-ketone intermediate **14a** (0.18 g) of sufficient purity for use in subsequent manipulation. The asymmetric reduction of crude **14a** with an equimolecular amount of (*S*)-Me-CBS in the presence of a twofold excess of borane dimethylsulfide complex[8] gave 0.09 g of the diol **15a** in 48% global yield from **13a**.

(1S)-1-[2-(Hydroxymethyl)phenyl]-2-(phenylselanyl)ethanol (**15a**): colorless oil; $[\alpha]_D^{19}$ +8.9 (*c* 1.68, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63-7.15 (m, 9H), 5.02 (dd, *J* = 5.6, 8.4 Hz, 1H), 4.58 (s, 2H), 3.48-3.10 (m, 3H), 2.60 (brs, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6, 137.8, 133.1, 133.0, 129.8, 129.7, 129.2 (2C), 128.4, 128.1, 127.4, 126.5, 69.9, 63.2, 36.6; FTIR: 3325, 2974, 1578, 1340, 762 cm^{-1}; Anal. Calcd. for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25. Found: C, 58.29; H, 5.66; HPLC analysis on Phenomenex® Lux Amylose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol

= 90:10, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 21.4 min, t_R (*S*-enantiomer, major) = 22.8 min, er = 17.6:82.4.

(1S)-1-[4-Bromo-2-(hydroxymethyl)phenyl]-2-(phenylselanyl)ethanol (**15b**). Following the above procedure, **13b** (1.52 g, 6.00 mmol) was converted to **15b** (1.30 g, 56% global yield from **13b**): light yellow oil; $[\alpha]_D^{23}$ -10.70 (*c* 1.14, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56-7.48 (m, 2H), 7.44-7.37 (m, 2H), 7.33-7.22 (m, 4H), 4.88 (dd, *J* = 4.4, 9.1 Hz, 1H), 4.48 (s, 2H), 3.20-2.90 [m, partly overlapped dd (*J* = 4.4, 12.8 Hz, 1H), dd (*J* = 9.1, 12.8 Hz, 1H), br s (2H)]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.8, 139.3, 133.3 (2C), 132.2, 131.3, 129.3 (2C), 128.7, 128.3, 127.6, 121.9, 69.3, 62.4, 36.6; FTIR: 3371, 2932, 1578, 1477, 1022, 828, 736 cm^{-1}; EIMS (70 eV) *m/z*: $[M-18]^+$ 368 (8), 170 (100), 169 (12), 118 (18), 90 (13), 77 (13); Anal. Calcd. for $C_{15}H_{15}BrO_2Se$: C, 46.66; H, 3.92. Found: C, 46.41; H, 4.22; HPLC analysis on Phenomenex® Lux Cellulose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, major) = 12.8 min, t_R (*R*-enantiomer, minor) = 22.2 min, er = 87.9:12.1.

Preparation of alcohol 16a. *tert*-Butyldiphenylsilyl chloride (0.40 mL. 1.57 mmol) was added to a stirred solution of diol **15a** (0.44 g, 1.43 mmol) and imidazole (0.12 g, 1.71 mmol) in dry dimethylformamide (5.0 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 16 h and then quenched with 10 mL of saturated aqueous ammonium chloride solution, extracted with diethyl ether (2 x 30 mL) and the organic layer was dried over sodium sulfate. The solution was filtrated, evaporated and the residue was dissolved in dichloromethane (5 mL) at room temperature. To this solution 4-methoxybenzyl 2,2,2-trichloroacetimidate (0.65 g, 2.28 mmol) and pyridinium *p*-toluensulfonate polimer bound (50 mg) were added.[48] After 24 h the mixture was filtrate through a short celite pad and evaporated. The residue was dissolved in THF (15 mL) and TBAF (0.45 g, 1.43 mmol) was added. The reaction mixture was stirred for 6 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, filtrated and evaporated. Pure **16a** (0.48 g) was isolated after

column chromatography on SiO_2 (20% diethyl ether/petroleum ether) in a 77% global yield from **15a**.

{2-[(1S)-1-[(4-Methoxybenzyl)oxy]-2-(phenylselanyl)ethyl]phenyl}methanol (**16a**): light yellow oil; $[\alpha]_D^{21}$ +29.4 (*c* 1.53, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.10 (m, 11H), 6.95-6.80 (m, 2H), 4.89 (dd, *J* = 5.2, 8.5 Hz, 1H), 4.66-4.46 (AB system, 2H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.40 (dd, *J* = 8.5, 12.4 Hz, 1H), 3.19 (dd, *J* = 5.2, 12.4 Hz, 1H), 2.39 (br s, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 139.3, 138.4, 132.8, 130.5, 129.9, 129.5, 129.4, 129.1, 129.0, 128.6, 128.4, 128.1, 127.6, 127.2, 126.9, 113.9, 113.8, 77.1, 70.5, 62.7, 55.3, 35.0; FTIR: 3370, 3245, 1696, 1512, 1247, 837, 757 cm^{-1}; Anal. Calcd. for $C_{23}H_{24}O_3Se$: C, 64.63; H, 5.66. Found: C, 64.29; H, 6.03.

Preparation of alcohol 16b. *tert*-Butyldiphenylsilyl chloride (0.56 mL. 2.20 mmol) was added to a stirred solution of diol **15b** (0.77 g, 2.00 mmol) and imidazole (0.16 g, 2.40 mmol) in dry dimethylformamide (6.0 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 16 h and then quenched with 10 mL of saturated aqueous ammonium chloride solution, extracted with diethyl ether (3 x 30 mL) and the organic layer was dried over sodium sulfate. The solution was filtrated, evaporated and the residue was dissolved in dimethylformamide (20 mL) at 0 °C. To this solution sodium hydride 60% dispersion in mineral oil (0.11 g, 2.8 mmol) was added. After 30 min, methyl iodide was added (0.16 mL, 2.60 mmol). The mixture was stirred for 8 h at rt and then quenched with 10 mL of saturated aqueous ammonium chloride solution, extracted with ethyl ether (3 x 30 mL) and the organic layer was dried over sodium sulfate. The solution was filtrated, evaporated and the residue was dissolved in THF (30 mL) and TBAF (0.63 g, 2.00 mmol) was added. The reaction mixture was stirred for 12 h, poured into saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was dried over sodium sulfate, filtrated and evaporated. Pure **16b** (0.48 g) was isolated after column chromatography on SiO_2 (40% diethyl ether/petroleum ether) in a 71% global yield from **15b**.

{5-Bromo-2-[(1S)-1-methoxy-2-(phenylselanyl)ethyl]phenyl}methanol (**16b**): yellow oil; $[\alpha]_D^{22}$ +14.95 (*c* 0.64, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53-7.40 (m, 4H), 7.35-7.19 (m, 4H), 4.64 (dd, *J* = 5.6, 8.0 Hz, 1H), 4.58 (AB system, 2H), 3.31 (dd, *J* = 8.0, 12.5 Hz, 1H), 3.23 (s, 3H); 3.11 (dd, *J* = 5.6, 12.5 Hz, 1H), 2.40 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5, 137.8, 133.0 (2C), 131.6, 131.2, 130.0, 129.1 (2C), 128.7, 127.6, 122.0, 79.4, 62.1, 57.0, 34.4; FTIR: 3381, 2931, 1578, 1477, 1091, 883, 739 cm^{-1}; EIMS (70 eV) *m/z*: 400 (15), 229 (91), 197 (100), 169 (36), 103 (18), 91 (22), 77 (15); Anal. Calcd. for $C_{16}H_{17}BrO_2Se$: C, 48.02; H, 4.28. Found: C, 47,77; H, 4.59.

Oxidation-cyclization of alcohols 16a and 16b. To a solution of phenylseleno alcohol **16a** (0.43 g, 1.00 mmol) in acetonitrile (15 mL) at room temperature, powdered potassium hydrogenphosphate (0.69 g, 4.00 mmol) and *m*-CPBA (0.52 g, 3.00 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). Powdered potassium hydroxyde (0.42 g, 7.50 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After 20 h the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated sodium carbonate solution, saturated NaCl solution, dried over sodium sulfate, filtrated and evaporated. The reaction product was purified by column chromatography on SiO_2 (15% ethyl acetate in petroleum ether) to afford **17a**.

(4S)-4-(4-Methoxybenzyloxy)isochroman (**17a**): 0.19 g, 70% yield; white gum; $[\alpha]_D^{20}$ +11.9 (*c* 1.84, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.16 (m, 5H), 7.10-6.97 (m, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.68 (d, *J* = 15.0 Hz, 1H), 4.63 (s, 2H), 4.45 (dd, *J* = 3.4, 3.6 Hz, 1H), 4.18 (dd, *J* = 3.6, 12.0 Hz, 1H), 3.90 (dd, *J* = 3.4, 12.0 Hz, 1H), 3.80 (s, 3H);^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 135.3, 133.0, 130.4, 129.5 (2C), 129.2, 127.9, 126.7, 124.0, 113.8 (2C), 70.6, 70.3, 68.2, 67.8, 55.3, FTIR: 2840, 1730, 1513, 1247, 824, 749 cm^{-1}; EIMS (70 eV) *m/z*: 270 (5), 137 (29), 121 (100), 105 (19), 91 (21), 77 (21); Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.20; H, 7.05.

(4S)-7-Bromo-4-methoxyisochroman (**17b**). Following the above procedure, alcohol **16b** (0.16 g, 0.40 mmol) was converted to **17b** (60 mg, 66%); white gum; $[\alpha]_D^{22}$ +32.85 (*c* 1.65, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 1.9 Hz, 1H), 4.74 (AB system, 2H), 4.20 (dd, *J* = 3.4, 4.1 Hz, 1H), 4.18 (dd, *J* = 3.4, 13.2 Hz, 1H), 3.83 (dd, *J* = 4.1, 13.2 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 131.6, 131.1, 129.9, 127.1, 121.9, 72.5, 67.6, 67.3, 57.5; FTIR: 2824, 1772, 1596, 1481, 1193, 1091, 821 cm^{-1}; EIMS (70 eV) *m/z*: 242 (5), 212 (100), 197 (66), 169 (32), 133 (39), 103 (31), 89 (32); Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.12; H, 4.82; HPLC analysis on Phenomenex® Lux Amylose-2 column (250 x 4.60 mm ID), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, major) = 12.4 min, t_R (*R*-enantiomer, minor) = 13.4 min, er = 87.9:12.1.

Synthesis of Isochroman 19. Acid **9** (0.37 g, 1.2 mmol) was transformed into the corresponding methyl ester derivative by reaction with trimethylsilyl chloride (0.38 mL, 3.00 mmol) in 6 ml of dry methanol for 24 h at 28 °C.[49] The crude methyl ester derivative, with sufficient purity for use in subsequent manipulation, was dissolved in 20 mL of dry THF at -18 °C (ice bath). A 2.0M butylmagnesium chloride solution in THF (1.8 mL) was added slowly. The resulting mixture was allowed to warm to 25 °C and stirred for an additional 24 h. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 x 20 mL). The organic layer was dried over sodium sulfate, filtrated and evaporated. The resulting oil was purified by chromatography on SiO_2 (20% diethyl ether/petroleum ether) to afford 0.27 g (56% yield) of compound **18**.

5-{2-[2-(phenylselanyl)ethyl]phenyl}nonan-5-ol (**18**): colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.68-7.45 (m, 2H), 7.38-7.09 (m, 7H), 3.38-3.10 (m, 4H), 1.97-1.58 (m, 5H), 1.46-1.02 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.0, 139.2, 133.0 (2C), 131.7, 130.2, 129.0 (2C), 128.0, 126.9, 126.6, 125.9, 78.5, 42.5 (2C), 35.5, 29.8, 25.9 (2C), 23.1 (2C), 14.0 (2C); FTIR: 3430, 2954, 1715, 1477, 1023, 734 cm^{-1}; EIMS (70 eV) *m/z* 404 (10), 189 (100), 157 (12),

143 (13), 133 (24), 117 (21), 91 (22); Anal. Calcd. for $C_{23}H_{32}OSe$: C, 68.47; H, 7.99. Found: C, 68.09; H, 8.30.

Alcohol **18** (0.26 g, 0.62 mmol) was dissolved in MeCN (10 mL) at room temperature and powdered potassium hydrogenphosphate (0.43 g, 2.49 mmol), and *m*-CPBA (0.32 g, 1.86 mmol) were added. The reaction mixture was stirred for 2 h (TLC analysis showed that the starting selenide was completely converted into the corresponding selenone derivative). Potassium hydroxide (0.26 g, 4.65 mmol) was added and the consumption of the selenone was monitored by TLC. After 2 h the mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with a saturated potassium carbonate solution, dried over sodium sulfate, filtrated and evaporated. Pure **19** was obtained after column chromatography on SiO_2 (5% diethyl ether/petroleum ether).

1,1-diButylisochroman (**19**): 0.12 g, 79% yield: colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28-6.92 (m, 4H), 3.93 (t, *J* = 5.5 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 1.98-1.70 (m, 4H), 1.54-1.02 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.8, 134.1, 128.5, 126.0, 125.5, 125.3, 78.6, 59.6, 40.3, 29.6 (2C), 25.6 (2C), 23.1 (2C), 14.1 (2C); FTIR: 2953, 1724, 1451, 1094, 742 cm^{-1}; EIMS (70 eV) *m/z*: $[M-57]^+$ 189 (100), 133 (38), 105 (10), 91 (8); Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.54; H, 10.98.

Synthesis of Isochroman 21. Butyllithium (3.0 mL, 2.40 mmol) was added to a stirred solution of phenylacetylene (0.24 mL, 2.20 mmol) in dry THF (16 mL) at 0 °C. The reaction was allowed to slowly warm to room temperature. After 2 h ketone **10b** (0.64 g, 2.40 mmol) was added at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for an additional 1 h, quenched by addition of 5 mL of saturated aqueous ammonium chloride solution and the aqueous phase extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtrated and concentrated. The resulting oil was purified by chromatography on SiO_2 (6% ethyl ether/petroleum ether) to afford alcohol **20**.

1-Phenyl-3-{2-[2-(phenylselanyl)ethyl]phenyl}pent-1-yn-3-ol (**20**): 0.53 g, 63% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82-7.72 (m, 1H), 7.60-7.40 (m, 4H), 7.39-7.12 (m, 9H), 3.49-3.35 (m, 2H), 3.32-3.26 (m, 2H), 2.50 (br s, 1H), 2.05 (q, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.2, 138.9, 132.8 (2C), 131.6 (2C), 131.3, 130.2, 128.9 (2C), 128.4, 128. 3 (2C), 127.8, 126.8, 126.6, 126.1, 122.4, 91.9, 86.1, 74.0, 36.7, 34.3, 29.3, 9.0; FTIR: 3453, 2971, 2225, 1577, 1478, 959, 756 cm^{-1}; EIMS (70 eV) *m/z* 420 (15), 391 (18), 289 (55), 261 (46), 233 (100), 215 (85), 189 (39), 157 (30), 129 (40), 115 (34), 91 (63), 77 (41); Anal. Calcd. for $C_{25}H_{24}OSe$: C, 71.59; H, 5.77. Found: C, 71.30; H, 6.01.

Alcohol **20** (0.13 g, 0.30 mmol) was dissolved in MeCN (10 mL) at room temperature and powdered potassium hydrogenphosphate (0.21 g, 1.20 mmol), and *m*-CPBA (0.16 g, 0.90 mmol) were added. The reaction mixture was stirred for 1 h (TLC analysis showed that the starting selenide was completely converted into the corresponding selenone derivative). Potassium hydroxide (0.13 g, 2.25 mmol) was added and the consumption of the selenone was monitored by TLC. After 3 h the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with a saturated potassium carbonate solution, dried over sodium sulfate, filtrated and evaporated. Pure **21** was obtained after column chromatography on SiO_2 (5% ethyl acetate/petroleum ether).

1-Ethyl-1-(phenylethynyl)isochroman (**21**): 68 mg, 86% yield; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.10 (m, 9H), 4.28-4.06 (m, 2H), 3.08 (ddd, *J* = 6.6, 10.8, 16.2 Hz, 1H), 2.68 (dt, *J* = 2.6, 16.2 Hz, 1H), 2.29 (dq, *J* = 7.3, 14.0 Hz, 1H), 2.11 (dq, *J* = 7.3, 14.0 Hz, 1H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 133.5, 131.7 (2C), 128.8, 128.1 (2C), 126.6, 126.4, 126.0, 125.5, 122.9, 91.7, 84.9, 74.9, 61.3, 36.3, 28.9, 8.2; FTIR: 2967, 2221, 1489, 1292, 1094, 754 cm^{-1}; EIMS (70 eV) *m/z* 262 (1), 233 (100), 215 (30), 202 (23), 189 (15), 129 (10); Anal. Calcd. for $C_{19}H_{18}O$: C, 86.90; H, 6.92. Found: C, 86.55; H, 7.28.

ASSOCIATED CONTENT

Supporting Information

^{1}H-NMR and ^{13}C-NMR spectra for all new compounds, and HPLC charts for the determination of the er values. This material is available free of charge via the Internet at http://pubs.acs.org.

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