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Synthesis of Chiral Acetals by Asymmetric Selenenylations

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Asymmetric selenenylations of (E)-ethoxystyrene are described leading to chiral acetals. An efficient synthesis of such compounds including the determination of their absolute configuration is described.

Keywords Acetals; selenium electrophiles; stereoselective synthesis

INTRODUCTION

For several decades now, selenium reagents have attracted growing interest for their applications in organic synthesis.^{1–4} The use of enantiomerically pure selenium electrophiles for the functionalization of double bonds has received particular attention, as a broad range of compounds is accessible using this methodology.⁵

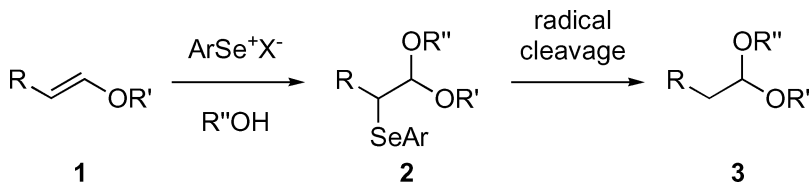
The addition of selenium electrophiles to enol ethers of type **1** leads to the formation of seleniranium cations with the higher positive charge located at the carbon atom next to the oxygen, due to resonance stabilization. Nucleophilic attack by an alcohol will then form the acetal **2**. This protocol has been known for a long time and is a well established method for glycosylation in carbohydrate chemistry.⁶ If the ether moiety is different from the attacking alcohol, a new stereogenic center will be formed. Cleavage of the selenium functionality will then yield an enantiomerically enriched acetal **3**, with the acetal carbon as the only stereocenter in the molecule (Scheme 1).

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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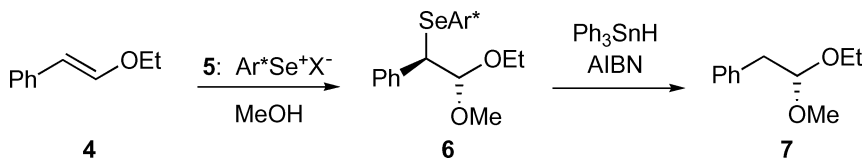


SCHEME 1

The use of chiral selenium electrophiles in such a reaction sequence will consequently allow the formation of enantiomerically enriched acetals. Although several of these compounds have already been isolated from biological systems, their optical purities and absolute configurations were not established. Only one route to this class of molecules has been reported.⁷

RESULTS AND DISCUSSION

The unsaturated compound (*E*)-ethoxystyrene **4** was applied due to its structural similarity to styrene and because of the better reactivity of (*E*)-alkenes compared to the corresponding (*Z*)-derivatives. Compound **4** was prepared in one step from phenyl acetaldehyde, sodium amide, and diethylsulfate, although a separation of the (*E*)- and (*Z*)-isomers was necessary.⁸ The subsequent reaction with the selenium electrophile **5** at -100°C yielded the addition product **6** in 87% yield with a diastereomeric excess of 80%, determined by analysis of the ^1H and ^{13}C NMR spectra. Radical cleavage of the carbon–selenium bond using triphenyltin hydride and AIBN gave the acetal **7** with 62% *ee* (Scheme 2). This observation was in agreement with the literature, where a loss of optical purity by the removal of the selenium function was observed.⁷

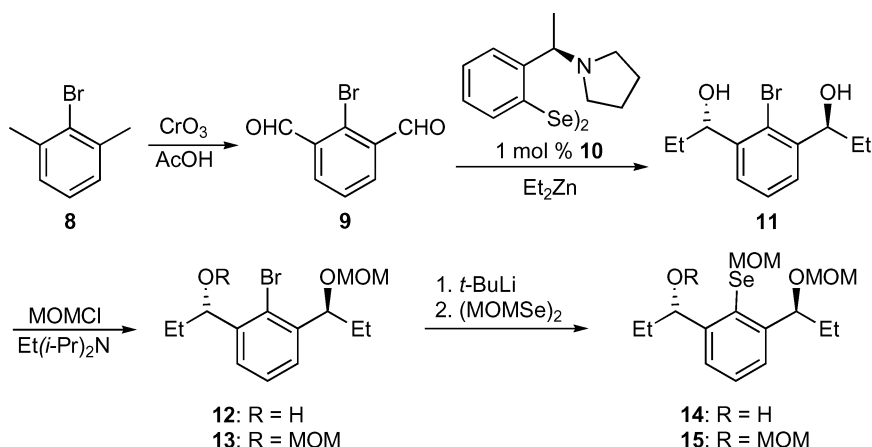


SCHEME 2

The optical purity of **7** was determined by GC using a chiral column and compared to the racemate, which was obtained by transacetalization from phenylacetaldehyde dimethylacetal and ethanol with hydrochloric acid.⁹ To obtain a higher selectivity in the methoxyseleenylation reaction, a C_2 -symmetrical reagent was developed that was able to coordinate to the selenium from two directions and therefore

have a higher influence on the direction from which the electrophilic attack will occur. Although structurally related compounds have already been described in literature,^{10,11} their long-winded and arduous synthesis recommended the design of a new approach.

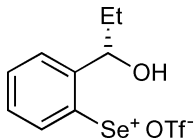
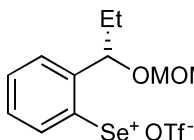
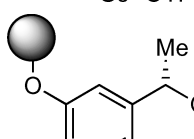
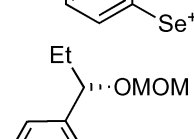
Oxidation of the two methyl groups of 2-bromoxylene **8** was achieved with chromium trioxide to give 2-bromoisophthalaldehyde **9**.¹² This was subjected to an asymmetric diethylzinc addition using 1 mol% of the nitrogen-containing diselenide **10** as a catalyst, leading to the chiral diol **11**.^{13,14} Protecting the hydroxy functionalities as the methoxymethyl ether (MOM) derivatives with chloromethyl methyl ether gave 19% of the mono- (**12**) and 76% of the dimethoxylated compound **13** (Scheme 3). Both compounds could be transferred into their corresponding mixed oxo-seleno acetals by halogen-metal exchange with *t*-BuLi and subsequent addition of the dimethoxymethyl diselenide.¹⁵ Applying the selenenyl triflate **5d** generated from **15** for the methoxyselenenylation of (*E*)-ethoxystyrene showed a somewhat decreased yield of 63%, but no other diastereomer in the NMR spectra. Therefore the diastereomeric excess was assumed to be higher than 95%. The selenium function was removed by radical cleavage, and the enantiomeric excess of the acetal **7** was determined to be 86% (Table I).



SCHEME 3

The last step was the determination of the absolute configuration of the acetal **7**. To determine the configuration at the stereogenic center of **7**, (*E*)-ethoxystyrene **4** was methoxyselenenylation, using electrophile **5a**. The obtained asymmetric acetal **6a** was hydrolyzed with aqueous trifluoroacetic acid to the corresponding aldehyde, which was

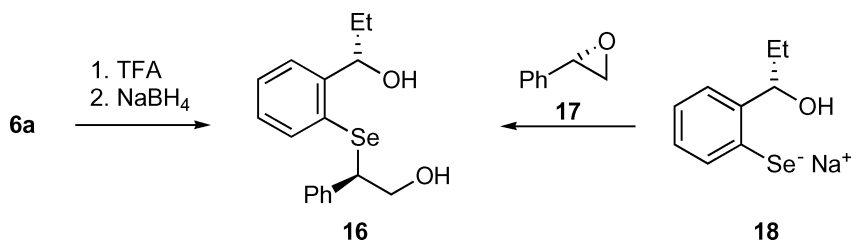
TABLE I Methoxyselenenylation of (*E*)-Ethoxystyrene

Selenium electrophile	6 Yield	6 <i>de</i>	7 <i>ee</i>	
	5a	76%	54%	n.d. ^a
	5b	87%	80%	62%
	5c	n.d. ^a	n.d. ^a	46% (70% yield)
	5d	63%	> 95%	86%

^aNot determined.

subsequently reduced to the alcohol **16** using sodium borohydride. The diastereomeric excess of **16** was found to be 54% according to the optical rotation, although the deviation was relatively high, due to a small amount of substance. The absolute configuration was assigned by comparison of the optical rotation with compound **16**, which had been obtained by selenolate opening of styrene epoxide. The nucleophilic opening of (*S*)-styrene oxide **17** by enantiomerically pure selenolate **18** leads to two different products, depending upon which carbon atom of the epoxide function will be attacked (Scheme 4). The opening at the benzylic carbon leads to the β -phenylethanol derivative **16**.¹⁶

As an interesting result, the investigations showed that the attack of the selenium electrophile occurs from the *si*-face of (*E*)-ethoxystyrene, whereas for (*E*)-methylstyrene, the attack occurs from the *re*-face. This result was in accordance with *ab initio* calculations. Thus, the changed electronic situation due to the introduction of the ethoxy moiety must be assumed to have a very strong influence on the selectivity. Furthermore,



SCHEME 4

it was possible to separate the diastereomers of **6a** by preparative TLC. To avoid hydrolysis of the acetal, it was necessary to treat the plates with triethylamine in order to eliminate acidic residues. This protocol is therefore promising to be a versatile route to obtain chiral acetals of type **7** also in enantiomerically pure form.

EXPERIMENTAL

¹H and ¹³C NMR experiments were carried out on a Varian Gemini 300 and on a Bruker 400-DPX spectrometer. IR measurements were taken using a Perkin-Elmer 1600FTIR spectrometer as a liquid film. Low resolution mass spectrometry was carried out using a Varian Saturn 2 GC-MS. Flash chromatography was carried out using Fisher Silica Gel (35–70 mesh). Preparative thin layer chromatography was carried out using Merck silica gel 60 F254 on glass plates. All solvents used were dried and purified by standard methods. Reactions requiring the exclusion of air were carried out under an atmosphere of argon in oven-dried glassware.

Addition of Selenium Electrophiles to Styrene (GP1): General Procedure

The diselenide (0.1 mmol) or methoxymethylselenide (0.2 mmol) was dissolved in dry diethyl ether (4 mL) under argon, cooled to 0°C, and treated with bromine (0.11 mmol, 0.11 mL of a 1 M solution in carbon tetrachloride). After 10 min, a solution of silver triflate (72 mg, 0.28 mmol) in methanol (0.1 mL) was added and stirred for 10 min at –78°C. The reaction mixture was cooled to –100°C and treated with styrene (0.4 mmol, 0.046 mL). After stirring for 3–4 hours at –100°C, *sym*-collidine (0.3 mmol, 0.04 mL) was added followed by water (4 mL). After extraction of the reaction mixture with *tert*.-butyl methyl ether (3 × 10 mL), drying of the combined organic phases with magnesium

sulfate, and removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel yielding the addition products as colorless oils. Enrichment of diastereomers by flash chromatography was excluded by comparison with the diastereomeric excess of the crude reaction mixtures. Spectroscopic data are given only for the major diastereomers.

Synthesis of Methoxymethyl Selenides from Bromo Precursors (GP2): General Procedure

The bromo precursor (2.0 mmol) was dissolved in dry THF (20 mL) under argon, cooled to -78°C , and treated slowly with *tert*-butyllithium (6.0 mmol, 1.6 M in hexane) (in case of a phenol functionality 8.0 mmol). After warming up and stirring for 30 min at room temperature (2 h, in case of a phenol moiety), dimethoxymethyl diselenide¹⁵ (0.55 g, 2.2 mmol) was added. The mixture was allowed to warm up to room temperature and stirred for an additional 3 h, then hydrochloric acid (20 mL, 1 M) was added. After extraction of the resulting mixture with *tert*-butyl methyl ether (3×25 mL) and drying of the combined organic phases with magnesium sulfate, powdered potassium hydroxide (0.1 g, 1.8 mmol) was added. The solvent was removed under vacuum and the residue purified by flash chromatography on silica gel.

(*E*)-Ethoxystyrene (4)

Preparation from phenylacetaldehyde, sodium amide, and diethyl sulfate. Separation from the (*Z*)-isomer was achieved by MPLC with hexane/*tert*-butyl methyl ether 300:1. Yield: 60%. Spectroscopic data see literature.⁸

5a: Generated from (*S,S*)-Bis-[2-(1-hydroxypropyl)phenyl] diselenide.¹⁷

5b: Generated from (*S,S*)-Bis-[2-(1-methoxymethoxypropyl)phenyl] diselenide.¹⁸

5c: Generated from mesoporous silica-supported (*S*)-3-(1-methoxymethoxyethyl)-4-methoxymethylselenanylphenol.¹⁹

5d: Generated from **15**.

(*S*)-1-[(*S*)-2-Ethoxy-2-methoxy-(*R*)-1-phenylethylselenyl]-phenyl}-propanol (6a)

Synthesized according to GP1. Purification by preparative TLC (plates pretreated with triethylamine) with *tert*-butyl methyl ether/pentane/triethylamine 10:40:2. Yield: 76%; colorless oil; *de* = 54%;

$[\alpha]_D^{25} = 99.1$ ($c = 1.12$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.77$ (t, $J = 7.4$ Hz, 3H, CH_3), 1.16 (t, $J = 7.1$ Hz, 3H, CH_3), 1.46 (s, 1H, OH), 1.62 (m, 2H, CH_2), 3.21 (s, 3H, OCH_3), 3.52 (dq, $J = 9.3$ Hz, $J = 7.1$ Hz, 1H, OCHHCH_3), 3.74 (dq, $J = 9.3$ Hz, $J = 7.1$ Hz, 1H, OCHHCH_3), 4.34 (d, $J = 5.8$ Hz, 1H, CHSe), 4.73 (t, $J = 5.1$ Hz, 1H, CHOH), 4.88 (d, $J = 5.9$ Hz, 1H, OCHO), 7.00–7.28 (m, 6H, arom- H), 7.19 (dt, $J = 6.5$ Hz, $J = 1.0$ Hz, 1H, arom- H), 7.25 (dd, $J = 7.8$ Hz, $J = 2.4$ Hz, 1H, arom- H), 7.49 (dd, $J = 7.0$ Hz, $J = 1.0$ Hz, 1H, arom- H); ^{13}C NMR (100.4 MHz, CDCl_3): $\delta = 10.3$ (q, CH_3), 15.0 (q, CH_3), 30.9 (t, CH_2), 52.4 (t, OCH_2), 54.1 (q, OCH_3), 63.0 (d, CHSe), 74.5 (d, ArCHOH), 105.4 (d, OCHO), 126.4 (d), 127.1 (d), 127.6 (d), 128.0 (d), 128.6 (s), 128.7 (d), 128.8 (d), 137.5 (d), 139.1 (s), 148.2 (s). IR (NaCl): 2928, 2850, 1601, 1454, 1213, 1158, 1125, 1101, 1033, 921, 700 cm^{-1} ; MS (70 eV, EI): m/z (%): 495 (6) $[\text{M}]^+$, 476 (9), 447 (32), 401 (100), 369 (71), 339 (22), 299 (21), 269 (11), 237 (30), 135 (54), 121 (8), 101 (14); HRMS for $\text{C}_{20}\text{H}_{26}\text{O}_3\text{Se}$: Calcd. 394.1047, Found 394.1058.

(S)-1-{[(S)-2-Ethoxy-2-methoxy-(R)-1-phenyl-ethylselenyl]-phenyl}-propyl Methoxymethyl Ether (6b)

Synthesized according to GP1. Purification by preparative TLC (plates pretreated with triethylamine) with *tert*-butyl methyl ether/pentane/triethylamine 10:100:2. Yield: 87%; colorless oil; $de = 80\%$; $[\alpha]_D^{25} = 42.5$ ($c = 1.48$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.89$ (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.13 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.58 (m, 2H, CH_2CH_3), 3.20 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.50 (dq, $J = 4.9$ Hz, $J = 2.1$ Hz, 1H, OCHHCH_3), 3.68 (dq, $J = 4.9$ Hz, $J = 2.0$ Hz, 1H, OCHHCH_3), 4.14 (d, $J = 6.5$ Hz, 1H, OCHHO), 4.31 (d, $J = 6.5$ Hz, 1H, OCHHO), 4.48 (d, $J = 5.8$ Hz, 1H, CHSe), 4.83 (d, $J = 5.9$ Hz, 1H, OCHO), 4.93 (dd, $J = 7.6$ Hz, $J = 5.1$ Hz, 1H, PhCH), 6.95 (t, $J = 7.5$ Hz, 1H, arom- H), 7.00–7.18 (m, 6H, arom- H), 7.27 (dd, $J = 7.7$ Hz, $J = 1.6$ Hz, 1H, arom- H), 7.35 (d, $J = 7.7$ Hz, 1H, arom- H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 10.9$ (q, CH_3), 15.5 (q, CH_3), 31.6 (t, CH_2), 52.0 (t, OCH_2), 54.4 (q, OCH_3), 56.0 (q, OCH_3), 63.4 (d, CHSe), 78.8 (d, ArCHO), 94.8 (d, OCHO), 106.1 (d, OCHO), 126.3 (d), 126.9 (d), 127.1 (d), 127.9 (d), 128.0 (d), 128.1 (d), 128.8 (d), 129.1 (s), 136.3 (d), 138.6 (s), 145.4 (s); IR (NaCl): $\nu = 3059, 3029, 2934, 2888, 1586, 1496, 1458, 1374, 1259, 1195, 1158, 1107, 1032, 919, 832, 757, 702$ cm^{-1} ; MS (CI): m/z (%): 407 (18), 375 (6), 345 (8), 317 (7), 278 (8), 216 (6), 198 (30), 166 (11), 149 (48), 136 (26), 120 (100), 108 (9), 89 (52), 52 (28); HRMS for $\text{C}_{22}\text{H}_{30}\text{O}_4\text{Se}$: Calcd. 438.1309, Found 438.1312.

(*S,S*)-1,3-Bis-(1-methoxymethoxy-propyl)-2-[(*S*)-2-ethoxy-2-methoxy-(*R*)-1-phenyl-ethylselenyl]-benzene (6d)

Synthesized from **15** according to GP1. Purification by preparative TLC (plates pretreated with triethylamine to eliminate acidic residues in the silica) with *tert*-butyl methyl ether/pentane/triethylamine 10:80:1. Yield: 63%; colorless oil; *de* > 95% (¹H NMR showed no other diastereomer); $[\alpha]_D^{25} = -64.8$ (*c* = 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.98 (t, *J* = 7.2 Hz, 6H, CH₃), 1.09 (t, *J* = 7.1 Hz, 3H, CH₃), 1.54–1.73 (m, 4H, CH₂), 3.20 (s, 3H, OCH₃), 3.24 (s, 6H, OCH₃), 3.45 (dq, *J* = 5.0 Hz, *J* = 2.0 Hz, 1H, OCHHCH₃), 3.62 (dq, *J* = 4.9 Hz, *J* = 2.1 Hz, 1H, OCHHCH₃), 4.09 (d, *J* = 6.4 Hz, 2H, OCHHO), 4.15 (d, *J* = 6.2 Hz, 1H, CHSe), 4.26 (d, *J* = 6.4 Hz, 2OCHHO), 4.77 (d, *J* = 6.2 Hz, 1H, OCHO), 5.10 (dd, *J* = 8.8 Hz, *J* = 3.2 Hz, 2H, PhCH), 7.06–7.13 (m, 5H, arom-*H*), 7.23–7.30 (m, 3H, arom-*H*); ¹³C NMR (100 MHz, CDCl₃): δ = 11.6 (q, CH₃), 15.4 (q, CH₃), 31.9 (t, CH₂), 52.8 (t, OCH₂), 54.6 (q, OCH₃), 56.0 (q, OCH₃), 63.7 (d, CHSe), 79.9 (d, ArCHO), 95.2 (d, OCHO), 106.0 (d, OCHO), 126.3 (d), 126.3 (d), 127.6 (d), 128.6 (d), 129.1 (d), 128.0(d), 129.6 (s), 139.3 (s), 147.9 (s).

rac-2-Ethoxy-2-methoxy-ethyl)-benzene (7)

To phenylacetaldehyde dimethyl acetal (166 mg, 1.0 mmol), ethanol (92 mg, 2.0 mmol) and hydrochloric acid (20 mL, 1 M in diethyl ether) were added. The mixture was stirred for 8 h, then quenched with triethylamine (50 mL). Purification by MPLC with petroleum ether/*tert*-butyl methyl ether/triethyl amine 94:5:1 gave the product in 65% yield, as well 15% of diethyl acetal and 13% of the starting material. Spectroscopic data according to the literature.⁹ Separation of the enantiomers by GC. Column: Macherey-Nagel, Hydrodex- β -3P, 50 m \times 0.25 mm, 20 psi, 115°C, 60 min, then heating 10°C/min to 200°C. *R_f*(*S*): 65.7 min, *R_f*(*R*): 66.1 min.

2-Bromobenzene-1,3-dicarbaldehyde (9)¹²

Chromium trioxide (9.9 g, 96 mmol) was dissolved in ice-cooled acetic anhydride (30 mL). At 0°C a mixture of 2,6 dimethylbromobenzene (3.0 g, 16 mmol), acetic anhydride (30 mL), and conc. sulphuric acid (8.1 mL) was added dropwise. The mixture was allowed to warm up to 15°C, stirred for 2 h, then poured on 240 g ice and left for 12 h. Extraction with dichloromethane (3 \times 25 mL), washing with aqueous potassium carbonate and water (each 50 mL), and evaporation of the solvent in vacuo yielded the tetraacetate as a brown solid. This was dissolved in dioxane (25 mL) and refluxed with conc. hydrochloric acid (6 mL) for 4 h. The mixture was concentrated in vacuo to 10% of the original volume, and

the residue was washed with water. Filtration of the residue (dissolved in 50 mL dichloromethane) through basic alumina and purification by flash chromatography on silica with dichloromethane yielded the product in 48% as colorless needles. ^1H NMR (300 MHz, CDCl_3): δ = 7.55 (t, J = 12.0, 1H, arom-*H*), 8.15 (d, J = 12.0 Hz, 2H, arom-*H*), 10.43 (s, 2H, CHO).

(*S,S*)-2,6-Bis(1-hydroxypropyl)bromobenzene (11)²⁰

Diethylzinc (0.31 g, 2.5 mmol) was added to a solution of the diselenide **10**¹⁴ (20 μmol) in toluene (10 mL) at 0°C. After stirring for 10 min, compound **9** (1.0 mmol) was added dropwise and the solution stirred for 15 h. After quenching with hydrochloric acid (5 mL, 1 M) and water (40 mL), the mixture was allowed to warm up. Extraction with *tert*-butyl methyl ether (3 \times 25 mL) and evaporation of the solvent in vacuo gave the crude product, which, if necessary, was purified by flash chromatography on silica. Purification by recrystallization from ethyl acetate. Yield 43%; mp 148.5°C; $[\alpha]_D^{25}$ = -101.2 (c = 1.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ = 1.02 (t, J = 7.9 Hz, 6H, CH_3), 1.63–1.73 (m, 2H, CH_2), 1.80–1.89 (m, 2H, CH_2), 1.93 (d, J = 3.6 Hz, 2H, OH), 5.11 (dt, J = 8.2 Hz, J = 4.2 Hz, 1H, OCHHCH₃), 7.38 (t, J = 7.7 Hz, 1H, arom-*H*), 7.48 (d, J = 7.7 Hz, 1H, arom-*H*); ^{13}C NMR (75 MHz, CDCl_3): δ = 10.6 (q, CH_3), 31.0 (t, CH_2), 74.5 (d, ArCHO), 122.1 (s), 126.5 (d), 127.8 (d), 144.4 (s); IR (NaCl): 3288 (br), 3045, 2968, 1463, 1420, 1354, 1126, 1065, 1018, 985, 779, 735, 692 cm^{-1} ; MS (70 eV, EI): m/z (%): 255 (33) $[\text{M}-\text{H}_2\text{O}]^+$, 237 (100), 211 (52), 193 (12), 175 (12), 158 (10), 135 (29), 128 (11), 121 (10), 79 (98), 75 (21), 60 (5).

(*S,S*)-2-(1-Methoxymethoxy-propyl)-6-(1-hydroxypropyl)-bromobenzene (12)

Obtained as a by-product in the synthesis of **13** in 19% yield. Colourless oil; $[\alpha]_D^{25}$ = -129.1 (c = 2.02, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ = 0.98 (d, J = 7.4 Hz, 3H, CH_3), 1.02 (d, J = 7.4 Hz, 3H, CH_3), 1.61–1.85 (m, 4H, CH_2), 3.34 (s, 3H, OCH_3), 4.50 (d, J = 6.5 Hz, 1H, OCHHO), 4.77 (d, J = 6.4 Hz, 1H, OCHHO), 5.02 (dd, J = 8.8 Hz, J = 3.2 Hz, 1H, PhCH), 5.08 (dd, J = 8.4 Hz, J = 3.1 Hz, 1H, PhCH), 7.21–7.39 (m, 3H, arom-*H*); IR (NaCl): ν = 2935, 2884, 1463, 1423, 1342, 1294, 1215, 1159, 1107, 1031, 992, 923, 796, 731 cm^{-1} ; MS (70 eV, EI): m/z (%): 287 (15), 257 (11), 225 (61), 199 (20), 171 (5), 118 (9), 91 (8), 77 (14), 45 (100); HRMS for $\text{C}_{14}\text{H}_{25}\text{BrNO}_3$ $[\text{M}+\text{NH}_4]^+$: Calcd. 334.1018, Found 334.1023.

(*S,S*)-2,6-Bis-(1-methoxymethoxy-propyl)-bromobenzene (13)

The alcohol **11** was dissolved in ethyl diisopropyl amine (15 equiv.), and the solution was cooled down to 0°C. Chloromethyl methyl ether (4 eq) was added, and the mixture was allowed to warm up. Stirring was continued for 12 h and then quenched with conc. aqueous ammonia (5 equiv.). The solvents were evaporated, and the residue was extracted with dichloromethane. Yield: 76%, colorless oil. $[\alpha]_D^{25} = -259.6$ ($c = 1.0$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.01$ (t, $J = 7.4$ Hz, 6H, CH_3), 1.61–1.85 (m, 4H, CH_2), 3.39 (s, 6H, OCH_3), 4.50 (d, $J = 6.7$ Hz, 2H, OCHHO), 4.58 (d, $J = 6.7$ Hz, 2H, OCHHO), 5.03 (dd, $J = 7.9$ Hz, $J = 3.4$ Hz, 2H, PhCH), 7.30–7.39 (m, 3H, arom-*H*); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 10.3$ (q, CH_3), 29.9 (t, CH_2), 55.7 (q, OCH_3), 78.2 (d, ArCHO), 94.7 (d, OCHO), 123.5 (s), 126.7 (d), 127.3 (d), 142.0 (s); IR (NaCl): 2933, 2882, 1463, 1341, 1215, 1159, 1125, 1106, 1030, 921, 796, 731 cm^{-1} ; MS (70 eV, EI): $m/z(\%)$: 331 (9), 301 (10), 272 (8), 227 (32), 211 (5), 197 (8), 169 (5), 131 (5), 118 (7), 91 (7), 77 (5), 45 (100); HRMS for $\text{C}_{16}\text{H}_{29}\text{BrNO}_4[\text{M}+\text{NH}_4]$: Calcd. 378.1280, Found 378.1278.

(*S,S*)-1-[3-(1-Methoxymethoxy-propyl)-2-methoxymethylselanyl-phenyl]-propan-1-ol (14)

Synthesized from **12** according to GP2. Purification by MPLC with *tert*-butyl methyl ether/pentane 1:10. Yield: 74%; pale yellow oil; $[\alpha]_D^{25} = -266.2$ ($c = 0.9$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 0.98$ (t, $J = 7.4$ Hz, 3H, CH_3), 1.03 (t, $J = 7.3$ Hz, 6H, CH_3), 1.65–1.90 (m, 4H, CH_2), 2.74 (d, $J = 3.6$ Hz, 1H, *OH*), 3.34 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 4.46 (d, $J = 6.7$ Hz, 1H, OCHHO), 4.52 (d, $J = 6.7$ Hz, 1H, OCHHO), 4.92 (d, $J = 9.3$ Hz, 1H, SeCHH), 5.01 (d, $J = 9.3$ Hz, 1H, SeCHH), 5.31–5.40 (m, 2H, PhCH), 7.37–7.47 (m, 3H, arom-*H*); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 10.7$ (q, CH_3), 10.8 (q, CH_3), 30.5 (t, CH_2), 31.0 (t, CH_2), 55.5 (q, OCH_3), 57.6 (q, OCH_3), 75.0 (d, ArCHO), 76.0 (t, SeCH_2), 79.2 (d, ArCHO), 94.4 (d, OCHO), 125.8 (d), 126.4 (d), 129.0 (s), 129.6 (d), 147.1 (s) 148.7 (s); IR (NaCl): 2932, 2880, 1729, 1463, 1288, 1213, 1159, 1125, 1100, 1032, 922, 798 cm^{-1} ; MS (70 eV, CI): $m/z(\%)$: 362 (1) $[\text{M}]^+$, 345 (27), 307 (6), 301 (31), 269 (10), 239 (100), 117 (27); HRMS for $\text{C}_{16}\text{H}_{26}\text{O}_4\text{Se}$: Calcd. 362.0996, Found 362.0991.

(*S,S*)-1,3-Bis-(1-methoxymethoxy-propyl)-2-methoxymethylselanyl-benzene (15)

Synthesized from **13** according to GP2. Purification by MPLC with *tert*-butyl methyl ether/pentane 1:10. Yield: 78%; pale yellow oil; $[\alpha]_D^{25} = -209.2$ ($c = 1.46$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.04$ (t, $J = 7.3$ Hz, 6H, CH_3), 1.70–1.75 (m, 4H, CH_2), 3.35 (s, 6H, OCH_3), 3.41 (s,

3H, OCH₃), 4.47 (d, $J = 6.7$ Hz, 2H, OCHHO), 4.53 (d, $J = 6.7$ Hz, 2H, OCHHO), 4.95 (d, $J = 8.9$ Hz, 1H, SeCHHO), 5.08 (d, $J = 8.9$ Hz, 1H, SeCHHO), 5.03 (t, $J = 6.3$ Hz, 2H, PhCH), 7.37–7.45 (m, 3H, arom-*H*); ¹³C NMR (75 MHz, CDCl₃): $\delta = 10.9$ (q, CH₃), 31.2 (t, CH₂), 55.2 (q, OCH₃), 57.7 (q, OCH₃), 76.2 (t, SeCH₂), 79.2 (d, ArCHO), 94.5 (d, OCHO), 126.2 (d), 128.4 (s), 129.3 (d), 147.1 (s); IR (NaCl): $\nu = 2932$, 2883, 2820, 1455, 1269, 1214, 1181, 1158, 1125, 1087, 1032, 924, 801 cm⁻¹; MS (70 eV, EI): m/z (%): 406 (1) [M]⁺, 330 (6), 300 (6), 225 (5), 238 (61), 223 (18), 209 (29), 15 (15), 183 (7), 156 (6), 129 (12), 115 (22), 102 (5), 91 (14), 84 (8), 57 (41), 45 (100); HRMS for C₁₈H₃₀O₅Se: Calcd. 406.158, Found 406.1257.

(*S*)-1-([(*R*)-(2-Hydroxy-1-phenyl)ethyl]seleno}phenyl)propanol (18)

Compound **6a** (20 mg, 0.05 mmol) was dissolved in chloroform (5 mL), trifluoroacetic acid (1 mL) and water (1 mL) were added, and the mixture was stirred for 2 h. The aqueous layer was discarded, and the chloroform was removed in vacuo. The remaining oil was dissolved in dry ethanol (5 mL), and sodium borohydride (2.0 mg, 0.05 mmol) was added at 0°C. The mixture was allowed to warm up to room temperature and was stirred for 1 h. The solvent was removed in vacuo, and the remaining oil was purified by preparative TLC with *tert*-butyl methyl ether/petroleum ether 1:2. Yield: 29%; colorless oil; $[\alpha]_D^{25} = -15.2$ ($c = 0.25$, CHCl₃). From this optical rotation a diastereomeric ratio of 77:23 (*S,R*):(*S,S*) (54% *de*) was calculated. (Values for the enantiomerically pure compounds (*S,R*)-**18**: $[\alpha]_D^{25} = -64.6$; (*S,S*)-**18**: $[\alpha]_D^{25} = +150.8$.)¹⁶ ¹H NMR (400 MHz, CDCl₃): $\delta = 0.88$ (t, $J = 7.4$ Hz, 3H, CH₃), 1.50–1.72 (m, 2H, CH₂), 1.95 (s (br), 1H, OH), 2.40 (s (br), 1H, OH), 3.95 (d, $J = 6.9$ Hz, 1H, CHHCOH), 4.35 (t, $J = 7.0$ Hz, 1H, CHSe), 4.92 (t, $J = 6.5$ Hz, 1H, CHOH), 7.10–7.32 (m, 6H, arom-*H*), 7.36 (td, $J = 7.4$ Hz, $J = 1.2$ Hz, 1H, arom-*H*), 7.47 (dd, $J = 7.8$ Hz, $J = 1.6$ Hz, 1H, arom-*H*), 7.60 (dd, $J = 7.7$ Hz, $J = 1.4$ Hz, 1H, arom-*H*).

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