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Enantiomerically pure organoseleno-1-arylethanols by enzymatic resolution with *Candida antarctica* lipase: Novozym 435

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Abstract—Racemic organoseleno-1-arylethanols were prepared by *ortho*-lithiation of arylethanols, followed by sequential reaction with elemental selenium and alkyl halides and by reaction of either aryldiazonium chlorides with diphenyldiselenide or with lithium and magnesium alkylselenolates. Enantiomerically enriched organoseleno-1-arylethanols were obtained by kinetic resolution of the racemic mixtures by esterification catalyzed by *Candida antarctica* lipase (Novozym 435). In some cases, enantiomeric excesses of up to 99% were obtained both for alcohols and acetates.

1. Introduction

Chiral alcohols are important intermediates in the synthesis of many pharmaceuticals and fine chemicals.[1] The biocatalyzed reduction of ketones[2] and the enzymatic kinetic resolution of racemic alcohols[3] are presently among the most employed methods for obtaining access to enantiomerically enriched alcohols. Both methods have been used by us in recent studies,[4] specially to obtain chiral compounds containing chalcogen atoms.[4a,b,f–j] Organochalcogen compounds are used in synthetic organic chemistry[5] and for pharmaceutical and toxicological studies.[6] In view of the importance of chirality in both fields,[7] it is of interest to develop synthetic routes to enantiomerically enriched organochalcogen compounds. Herein, we report the preparation and the enzymatic kinetic resolution of *ortho*-, *meta*-, and *para*-organoseleno-1-arylethanols. Two routes were employed to prepare the racemic compounds, the *ortho*-lithiation of arylethanols followed by reaction with elemental selenium and then with an alkyl halide and by reaction of *meta*- and *para*-acetophenyl diazonium chlorides with diphenyldiselenide, or with lithium methylselenolate and bromomagnesium ethylselenolate, followed by reduction of the selenoacetophenones with sodium borohydride.

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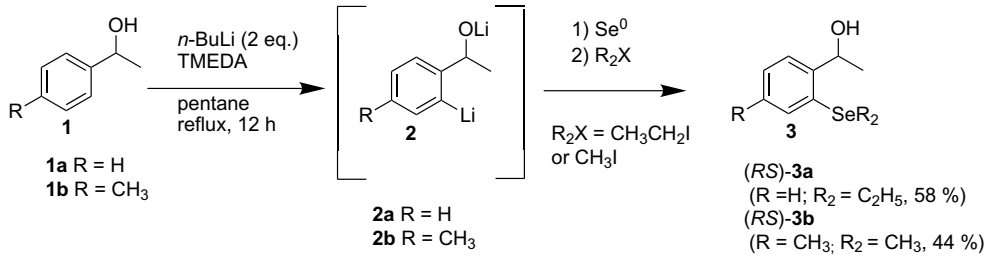
2. Results and discussion

2.1. Synthesis of organoseleno-1-arylethanols

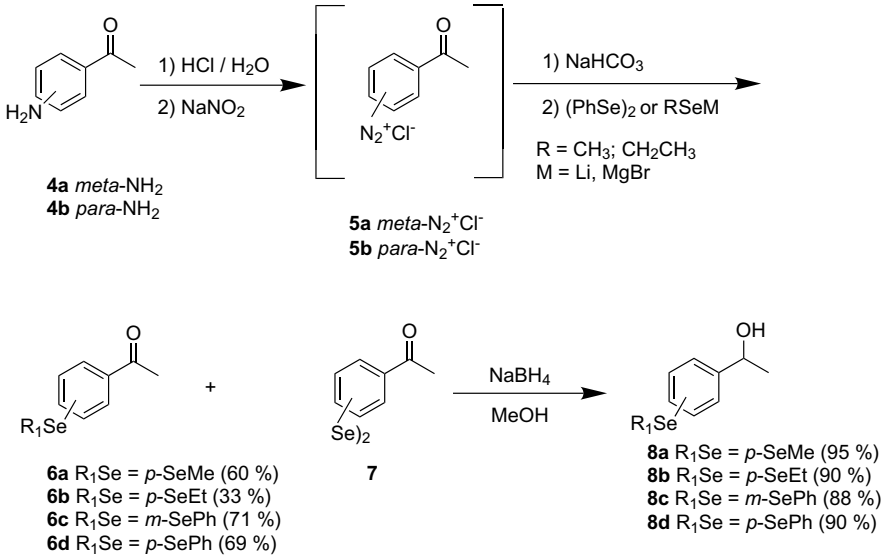
2.1.1. Synthesis by the *ortho*-metallation method. Selenides **3a** and **3b** were prepared by a one-pot sequence from racemic 1-phenylethanol **1a**. Alcohol **1a** was treated with 2 equiv of *n*-BuLi/TMEDA in dry pentane. The dilithiated intermediate **2a** was converted into compound **3a** by reaction with elemental selenium, followed by the addition of ethylbromide. In a similar way, the dilithiated intermediate **2b** was also converted to selenide **3b** by the addition of methyl iodide (Scheme 1).

2.1.2. Synthesis by the aryldiazonium method. Recently we have synthesized organoselenoacetophenones for biocatalytic studies.[4a,b] These ketones were prepared from bromoacetophenones by a laborious multistep sequence. The global yields of the organoselenoacetophenones were poor (13–43%).[4a,b] Herein, organoselenoacetophenones were prepared in a straightforward manner starting from commercially available *meta*- and *para*-aminoacetophenones **4** (Scheme 2).

The reaction was performed in an aqueous medium at 0 °C and in the presence of air. An open flask was used as the reaction vessel. The reaction consisted of the addition of an aqueous solution of aryldiazonium chloride **5** to a



Scheme 1. Organoseleno-1-arylethanols by the *ortho*-metallation method.



Scheme 2. Organoseleno-1-arylethanols by the diazonium chloride method.

solution of either diphenyldiselenide, MeSeLi or EtSeMgBr in THF. In all cases, the desired selenoacetophenones **6** were formed as the main product while diarylselenide **7** was formed as a by-product. It was observed that when the reaction mixture was stirred for several hours, the aryl- or alkylselenoacetophenones **6a**–**6d** initially formed were completely converted to the respective diarylselenoacetophenones **7**. The diazonium chloride method, in comparison to the previously reported one,[4a,b] required neither dry conditions nor protection–deprotection steps. Furthermore, the organoselenoacetophenones were obtained in better global yields (33–71%). The organoseleno-1-phenylethanols **8a**–**8d** were then prepared by reduction of the aryl- and alkylselenoacetophenones **6** with $NaBH_4$ in methanol (Scheme 2).

2.2. Enzymatic resolution

The enzymatic resolution of the organoseleno compounds **3a**–**3b** and **8a**–**8d** was performed in 24 h. As can be observed in Table 1, the resolution was very efficient with compounds **3b**, **8a**, and **8d**, which contain the organoseleno group at the *ortho*- and *para*-positions. Alcohols (*S*)-**8a**, (*S*)-**3b**, and (*S*)-**8d** and acetates (*R*)-**10a**, (*R*)-**9b**, and (*R*)-**10d** were obtained with high enantiomeric excesses (ee >99%) and in good isolated yields (Table 1, entries 1, 2, 6). When hexane was used as the solvent, selenide **3b** did not react. The reaction was then performed at higher temperature (40 °C), with no success. By changing from hexane to the more polar *t*-butylmethylether, the kinetic resolution of **3b** occurred with good conversion and enantioselectivity (ee >99%, Table 1, entry 2). On the other hand, compounds **3a** and **8b** showed a different behavior. The (*S*)-alcohols were obtained in >99% ee, but acetates **9a** and **10b** were obtained with modest enantioselectivity (Table 1, entries 3 and 5).

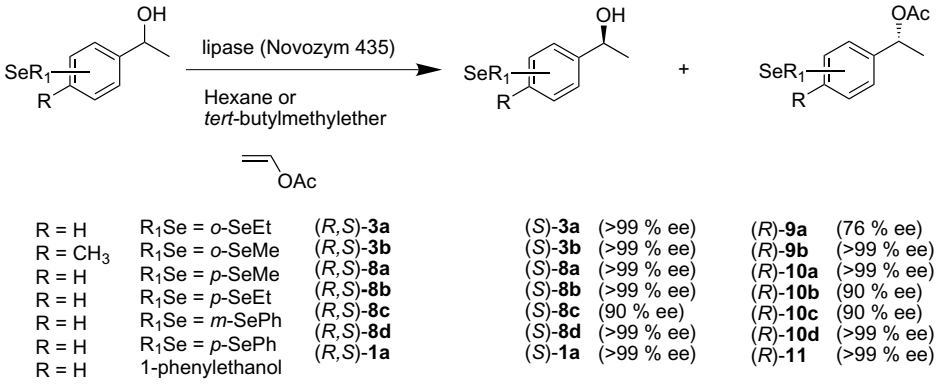
2.3. Determination of the enantiomeric excesses and absolute configuration

The enantiomeric excesses of alcohols **3a**, **3b** and **8a**, **8b** were calculated from the chiral GC chromatograms. The chromatographic separation for alcohols **8c**, **8d** was very poor. In view of this fact, compounds **8c** and **8d** were transformed into 1-phenylethanol **1a** by removing the organoselenium group with *n*-butyllithium in THF (Scheme 3). Acetates **9a**, **9b**, and **10a**–**10d** were previously hydrolyzed and subsequently reacted with *n*-BuLi to afford **1a** (Scheme 4). It was supposed that the lithium–selenium exchange reaction and the acetate hydrolysis did not affect the

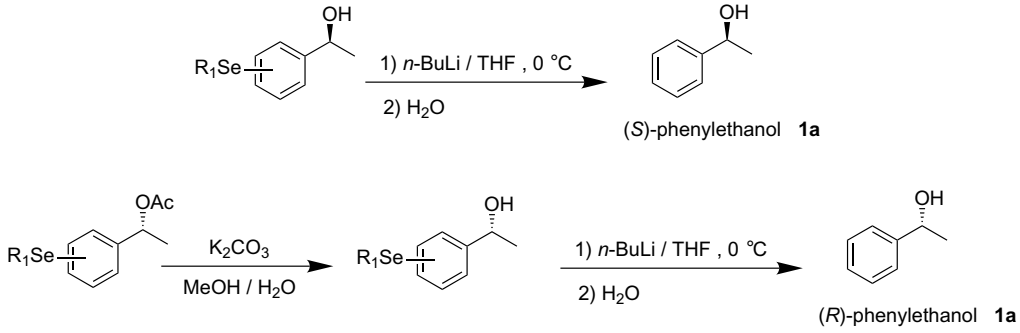
Table 1. Enzymatic resolution of organoseleno alcohols **3a**, **3b**, **8a**–**8d** and phenylethanol **1a** catalyzed by lipase from *Candida antarctica* (Novozym 435)

Entry	(*R*,*S*)-Alcohols	*c*[b] (%)	ee Alcohols (%)	Yield[a] (%)	ee Acetates (%)	Yield[a] (%)	*E*[f]
1	**8a**	50	(*S*)-**8a** (99)	40	(*R*)[d]-**10a** (99)	41	>200
2	**3b**	50	(*S*)[e]-**3b** (99)	43	(*R*)[d]-**9b** (99)	45	>200
3	**3a**	57	(*S*)-**3a** (99)	36	(*R*)[d]-**9a** (76)	43	37
4	**8b**	52	(*S*)-**8b** (99)	41	(*R*)[d]-**10b** (90)	41	99
5	**8c**	50	(*S*)[c]-**8c** (90)	40	(*R*)[d]-**10c** (90)	43	58
6	**8d**	40	(*S*)[c]-**8d** (99)	43	(*R*)[d]-**10d** (99)	40	>200
7	**1a**	50	(*S*)-**1a** (99)	43	(*R*)-**11** (99)	45	>200

The reaction was carried out at 32 °C using (*R*,*S*)-alcohols **1a**, **3** and **8**, vinyl acetate, hexane, and Novozym 435.
[a] Isolated yield.
[b] *c*: Conversion calculated from the enantiomeric excesses of the substrate (ee_S) and the product (ee_P), $c = (ee_S)/(ee_P + ee_S)$.[11]
[c] ee of 1-phenylethanol after reaction with *n*-BuLi (Scheme 4).
[d] ee of 1-phenylethanol after hydrolysis followed by reaction with *n*-BuLi (Scheme 4).
[e] *tert*-Butylmethylether was used as the solvent instead of hexane.
[f] *E*: enantiomeric ratio.



Scheme 3. Lipase-catalyzed acetylation of organoseleno-1-arylethanols **1a**, **3a**, **3b**, and **8a**–**8d**.



Scheme 4. Chemical transformations performed to transform organoseleno-1-arylethanols into (*R*)- and (*S*)-1-phenylethanol.

stereogenic center of **8c**, **8d**, **9a**, **9b**, and **10a**–**10d**. To support this assumption, alcohol (*S*)-**3a** (ee >99%) was transformed into (*S*)-**1a** by reaction with *n*-butyllithium and an identical enantiomeric excess (ee >99%) was observed for the deselenated product. The absolute configurations of alcohols **8a**, **8c**, and **8d** were determined by comparison with the optical rotation described in the literature.[4a] The absolute configurations of alcohols **3a**, **3b**, and **8b**, and acetates **9a**, **9b**, and **10a**–**10d** were attributed by chromatographic comparison with authentic samples of (*R*) and (*S*)-**1a** after removing the organoselenium group as shown in Scheme 4. The results obtained showed that the stereochemical preference of CALB for the organoselenoarylethanols was in accordance with the Kazlauskas rule.[8]

3. Conclusion

The *ortho*-metallation and the aryldiazonium chloride methods are convenient routes to organoselenoarylethanols. These compounds are efficiently resolved by the lipase from *Candida antarctica* (Novozym 435). The absolute

stereochemistry of the resolved alcohols and acetates is in accordance with the Kazlauskas rule.

4. Experimental

4.1. General

All solvents and chemicals used were previously purified according to the usual methods.[9] Column chromatography was carried out with Merck silica gel (230–400 Mesh). Thin layer chromatography (TLC) was performed on silica gel F-254 on aluminum. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian DPX-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or a Bruker DRX-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometer using as internal standard tetramethylsilane and the central peak of $CDCl_3$ at 77 ppm. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Near infrared spectra were recorded on a Bomem MB-100 spectrophotometer. Peaks are reported in cm^{-1}. Low resolution mass spectrometers were obtained in a Shimadzu GCMS-17A/QP5050A instrument equipped with capillary column HP-1 (J&W Scientific 25 m × 0.32 mm × 1.05 μm). Elemental analyses were performed at the Microanalytical Laboratory of the Chemistry Institute—University of São Paulo. The IUPAC names were obtained using the software ChemDraw Ultra®, version 8.0. Conversions and enantiomeric excesses of the enzyme-catalyzed reactions were determined using a Shimadzu GC-17A gas chromatograph equipped with a chiral capillary column Chirasil-Dex CB β-cyclodextrin (25 m × 0.25 mm)—Varian. The carrier gas was hydrogen with a pressure of 100 kPa. Optical rotations were measured in a Jasco DIP-378 polarimeter and the reported data refer to the Na-line value using a 1 dm cuvette. Novozym 435 (immobilized lipase from *Candida antarctica*) was obtained as a gift from Novo Nordisk (Paraná-Brazil). Orbital shakers, Tecnal TE-421 or Superohm G-25, were employed for the biocatalyzed transformations.

4.2. Synthesis of the substrates

4.2.1. Preparation of the organoseleno-1-arylethanols by *ortho*-metallation. The procedure was adapted from the Wirth method.[10] To a two-necked round-bottomed flask equipped with a reflux condenser and a septum under N_2 were added (*R*,*S*)-1-phenylethanol **1a** (2.44 g, 20 mmol), *N*,*N*,*N*,*N*-tetramethylethylenediamine (4.64 g, 40 mmol) and dry pentane (50 mL). The solution was cooled to 0 °C and *n*-butyllithium from a 2.0 M solution in hexane (20.5 mL, 41 mmol) was added dropwise. The bright yellow solution was refluxed for 12 h. The solution was again cooled to 0 °C and dry THF (20 mL) was added, followed by selenium (1.58 g, 20 mmol). After stirring for 3 h at room temperature, methyl iodide (2.18 g, 20 mmol) was added and the solution was stirred for an additional 30 min. A 1 M HCl solution (100 ml) was then added and the resulting solution was extracted three times with ethyl ether (3 × 40 mL). The combined organic phases were dried over $MgSO_4$. The solvents were removed in vacuum and the residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (9:1).

Compound **3b** was prepared in a similar way, using ethyl iodide instead of methyl iodide in the alkylation step.

1-(2-(Ethylselanyl)-4-methylphenyl)ethanol **3b**. Yield: 2.0 g (44%). Yellow oil. ^{1}H NMR (300 MHz) δ: 7.20 (m, 3H), 5.21 (q, $J = 6.4$ Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.00 (s, 1H), 1.48 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 142.8, 137.8, 131.0, 129.9, 127.6, 125.2, 68.7, 24.0, 21.0, 7.6. IR (film) cm^{-1}: 3377, 2971, 2925, 2868, 1480, 1448, 1424, 901, 822. MS: *m*/*z* (relative intensity): 230 (M^+, 12), 212 (9), 194 (7), 182 (6), 119 (65), 105 (15), 91 (100), 89 (26), 77 (19), 65 (37), 50 (22), 43 (98). Calculated for $C_{10}H_{14}OSe$: C, 52.41; H, 6.16. Found: C, 52.70; H, 6.28.

1-(2-(Ethylselanyl)phenyl)ethanol **3a**. Yield: 2.7 g (58%). Yellow oil. ^{1}H NMR (300 MHz) δ: 7.53–7.44 (m, 2H), 7.29–7.14 (m, 2H), 5.28 (q, $J = 6.3$ Hz, 1H), 2.90 (q, $J = 7.2$ Hz, 2H), 2.45 (br, 1H), 1.46 (d, $J = 6.3$ Hz, 3H), 1.41 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 146.9, 132.6, 128.7, 127.8, 127.3, 125.5, 69.1, 24.2, 21.2, 15.2. IR (film) cm^{-1}: 3374, 2972, 2925, 2867, 1445, 1373, 1336, 1232, 1197, 1128, 1085, 1052, 1006, 898, 754, 666. MS: *m*/*z* (relative intensity) 232 (M^++2, 5), 230 (M^+, 27), 228 (M^+−2, 14), 201 (28), 199 (17), 197 (9), 183 (34), 181 (17), 105 (46), 91 (21), 78 (29), 77 (35), 65 (7), 43 (100). Calculated for $C_{10}H_{14}OSe$: C, 52.41; H, 6.16. Found: C, 52.49; H, 5.98.

4.2.2. Preparation of organoselenoacetophenones from aryldiazonium chlorides. The appropriate aminoacetophenone (3.5 mmol), hydrochloric acid (0.8 mL) and water (0.8 mL) were mixed in a 10 mL round bottomed flask. The solution was cooled to 0 °C and an aqueous solution of sodium nitrite (256 mg, 3.7 mmol in 1 mL of H_2O) was added dropwise with vigorous stirring. The mixture was stirred for 5 min and an aqueous solution of sodium bicarbonate added slowly until pH 7. The solution was then transferred with a Pasteur pipette to another 10 mL round bottomed flask containing a solution of diphenyldiselenide or alkylselenolate (1 mmol) in THF (3 mL). The biphasic solution was continuously stirred at room temperature until the gas evolution had ceased. The mixture was then diluted with brine (20 mL) and extracted with ethyl acetate (2 × 30 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate. The organoselenoacetophenones were employed in the reduction step without further purification.

4.2.2.1. General procedure for the reduction reaction of the organoselenoacetophenones 6a–d. Organoseleno phenylethanols **8a**–**8d** were prepared by reduction of the corresponding organoselenoacetophenones **6a**–**6d** with $NaBH_4$ as previously described.[4a]

The spectral data of the compounds **8a**, **8c**, and **8d** are in agreement with those reported in the literature.[4a]

1-(4-(Methylselanyl)phenyl)ethanol **8a**. Yield: 0.194 g (90%).

1-(3-(Phenylselanyl)phenyl)ethanol **8c**. Yield: 0.253 g (91%).

1-(4-(Phenylselanyl)phenyl)ethanol **8d**. Yield: 0.244 g (88%).

1-(4-(Ethylselanyl)phenyl)ethanol **8b**. Yield: 196 g (85%). Oil. ^{1}H NMR (500 MHz) δ: 7.44 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 4.81 (q, $J = 6.3$ Hz, 1H), 2.89 (q, $J = 7.8$ Hz, 2H), 2.39 (br, 1H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.42 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (75 MHz) δ: 144.6, 132.6, 129.0, 126.1, 69.9, 25.1, 21.4, 15.5. IR (film) cm^{-1}: 3362, 2973, 2924, 2867, 1491, 1448, 1422, 1231, 1087, 1072, 898, 589, 543. MS: *m/z* (relative intensity): 232 (M^++2, 8), 230 (M^+, 44), 228 (M^+−2, 22), 215 (56), 213 (30), 187 (10), 157 (25), 107 (11), 91 (13), 78 (68), 43 (100). Calculated for $C_{10}H_{14}OSe$: C, 52.41; H, 6.16. Found: C, 52.32; H, 6.25.

4.3. Enzymatic resolutions

To a 50 mL Erlenmeyer flask containing 10 mL of hexane, 1 mL of vinyl acetate and 200 mg of Novozym 435 was added the appropriate alcohol [**3b**, **8a**–**8d** (150 mg) and **3a** (230 mg)]. The reaction mixture was stirred on a rotary shaker (32 °C, 160 rpm) for 24 h. After this time, the mixture was filtered and the solvent evaporated. The residue was purified by silica gel column chromatography using hexane/ethyl acetate as eluent. The yields and ee are shown in Table 1.

4.3.1. Evaluation of the enzymatic resolution of organoseleno-1-arylethanols by GC analysis. The reaction progress was monitored by collecting 0.1 mL samples at 24 h. These samples were analyzed by GCMS (1 μL) in a HP-1 column. After isolation and purification, the products of the biocatalyzed reactions were analyzed by GC/FID in a chiral capillary column. Organoseleno alcohols **8a**, **8b** and **3a**, **3b** were chromatographically compared with the racemic mixtures. The enantiomers of alcohols **8c** and **8d** and acetates **9a**, **9b**, and **10a**–**10d** could not be resolved by chiral capillary column chromatography (Chirasil-Dex CB—Varian). The enantiomeric excesses of these compounds were determined by chromatographic comparison with an authentic sample of (*R*,*S*)-**1a** after their transformation into **1a** by reaction with *n*-butyllithium in THF at 0 °C (Section 2.3, Scheme 4).

General GC conditions: Injector: 220 °C; detector: 220 °C; pressure: 100 kPa.

(*RS*)-1-(4-(Methylselanyl)phenyl)ethanol **8a**: 150°C, 30 min hold, retention time [(*R*)-**8a** = 17 min, (*S*)-**8a** = 18 min].

(*RS*)-1-(2-(Ethylselanyl)-4-methylphenyl)ethanol **3b**: 150 °C (30 min hold) −10 °C min −180 °C (5 min), retention time [(*R*)-**3b** = 15.5 min, (*S*)-**3b** = 19.5 min].

(*RS*)-1-(2-(Ethylselanyl)phenyl)ethanol **3a**: 80 °C, 1 °C/min up to 180 °C, retention time [(*R*)-**3a** = 66 min, (*S*)-**3a** = 68 min].

(*RS*)-1-(4-(Ethylselanyl)phenyl)ethanol **8b**: 150 °C, 30 min hold, retention time [(*R*)-**8b** = 13 min, (*S*)-**8b** = 14 min].

(*RS*)-1-(3-(Phenylselanyl)phenyl)ethanol **8c**: 150 °C, 2 °C/min up to 180 °C, retention time [(*R*)-**8c** = 32.1 min, (*S*)-**8c** = 32.8 min].

(*RS*)-1-(4-(Phenylselanyl)phenyl)ethanol **8d**: 150 °C, 2 °C/min up to 180 °C, retention time [(*R*)-**8d** = 34.2 min, (*S*)-**8d** = 34.8 min].

(*RS*)-1-Phenylethanol **1a**: 110 °C, 1 °C/min up to 118 °C, 50 °C/min up to 180 °C retention time for **7** [(*R*)-**1a** = 6.9 min; (*S*)-**1a** = 7.6 min].

4.4. Assignment of the absolute configuration

The absolute configurations of compounds **8a**, **8c**, and **8d** were determined by comparison of the sign of the measured specific rotation with those of the literature.[4a] The absolute configurations of alcohols **3a**, **3b**, and **8b** were assigned by chromatographic comparison with standard samples of (*R*)- and (*S*)-**1a** after removal of the organoselenium group of **3a**, **3b**, and **8b** with *n*-butyllithium in THF (Section 2.3). Acetates **9a**, **9b**, and **10a**–**10d** were converted into **1a** by hydrolysis with aqueous K_2CO_3 followed by reaction with *n*-butyllithium in THF, and the absolute configuration and enantiomeric excesses of the obtained samples were assigned by chromatographic comparison with authentic samples of (*R*)- and (*S*)-**1a** (Table 1).

(−)-(*S*)-1-(4-(Methylselanyl)phenyl)ethanol **8a**: $[\alpha]_D^{25} = -44.4$ (*c* 1.4, $CHCl_3$), ee 99%.

(+)-(*R*)-1-(4-(Methylselanyl)phenyl)ethyl acetate **10a**: $[\alpha]_D^{25} = +127.3$ (*c* 1.4, $CHCl_3$), ee 99%.

(−)-(*S*)-1-(2-(Ethylselanyl)-4-methylphenyl)ethanol **3b**: $[\alpha]_D^{25} = -50.7$ (*c* 1.24, $CHCl_3$), ee 99%.

(+)-(*R*)-1-(2-(Ethylselanyl)-4-methylphenyl)ethyl acetate **9b**: $[\alpha]_D^{25} = +40.8$ (*c* 1.57, $CHCl_3$), ee 99%.

(−)-(*S*)-1-(2-(Ethylselanyl)phenyl)ethanol **3a**: $[\alpha]_D^{25} = -54.2$ (*c* 1.4, $CHCl_3$), ee 99%.

(+)-(*R*)-1-(2-(Ethylselanyl)phenyl)ethyl acetate **9a**: $[\alpha]_D^{25} = +31.3$ (*c* 1.4, $CHCl_3$), ee 76%.

(−)-(*S*)-1-(4-(Ethylselanyl)phenyl)ethanol **8b**: $[\alpha]_D^{25} = -55.4$ (*c* 1.3, $CHCl_3$), ee 99%.

(+)-(*R*)-1-(4-(Ethylselanyl)phenyl)ethyl acetate **10b**: $[\alpha]_D^{25} = +88.4$ (*c* 1.3, $CHCl_3$), ee 90%.

(−)-(*S*)-1-(3-(Phenylselanyl)phenyl)ethanol **8c**: $[\alpha]_D^{25} = -30.0$ (*c* 1.2, $CHCl_3$), ee 90%.

(+)-(*R*)-1-(3-(Phenylselanyl)phenyl)ethyl acetate **10c**: $[\alpha]_D^{25} = +43.3$ (*c* 1.2, $CHCl_3$), ee 90%.

(−)-(*S*)-1-(4-(Phenylselanyl)phenyl)ethanol **8d**: $[\alpha]_D^{25} = -28.3$ (*c* 1.1, $CHCl_3$), ee 99%.

(+)-(*R*)-1-(4-(Phenylselanyl)phenyl)ethyl acetate **10d**: $[\alpha]_D^{25} = +84.4$ (*c* 1.1, $CHCl_3$), ee 99%.

(−)-(*S*)-1-Phenylethanol (*S*)-**1a**: $[\alpha]_D^{25} = -51$ (*c* 2.1, $CHCl_3$), ee 99%.

(+)-(*R*)-1-Phenylethyl acetate (*R*)-**11**: $[\alpha]_D^{25} = +45.3$ (*c* 2.0 $CHCl_3$), ee 99%.

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