Tetrahedron: *Asymmetry* 20 (2009) 2699–2703

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A large-scale synthesis of enantiomerically pure γ-hydroxy-organochalcogenides

Jefferson L. Princival, Morilo S. C. de Oliveira, Alcindo A. Dos Santos *, João V. Comasseto

Instituto de Química, Universidade de São Paulo, CP 26077, CEP 05508-000, São Paulo, SP, Brazil

ARTICLE INFO

Article history:
Received 23 September 2009
Accepted 7 October 2009
Available online 10 November 2009

ABSTRACT

Enantiomerically pure (*R*)- and (*S*)-γ-hydroxy-organochalcogenides are prepared using poly-[*R*]-3-hydroxybutanoate (PHB) as the starting material.

1. Introduction

Enantiomerically pure γ-hydroxy-organochalcogenides **1** (Fig. 1) have found use in organic synthesis.[1,2]

The sulfide **1a** (R = Ph), has been prepared by the addition of thiophenol to methyl vinyl ketone (MVK) (100% yield) followed by baker's yeast reduction to (*S*)-**1a** in 70% yield and 96% ee.[1a] In 2007, Tiecco reported an elegant methodology to prepare enantioenriched **1b**, by reacting the commercially available optically active β-hydroxy-ester with phenyl selenocyanate.[3c] Recently we have shown the preparation of the tellurides (*R*)-**1c** and (*S*)-**1c** (R = ^{n}Bu) by hydrotelluration of MVK followed by reduction of the carbonyl group (88% yield) and enzymatic kinetic resolution, giving the (*R*) and (*S*) enantiomers in 98% and 99% ee, respectively,[2a] and have demonstrated that these tellurides can be transformed into chiral dianions **2** as shown in Scheme 1.[2]

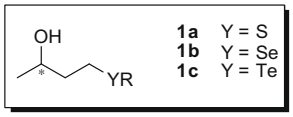
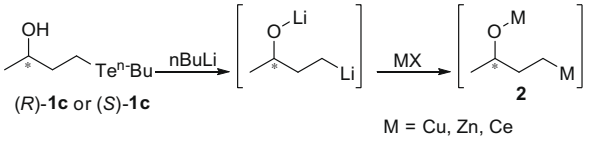


Figure 1.



Scheme 1. Preparation of reactive organometallics from γ-hydroxy-butyltelluride.

In our laboratory, the synthesis of several bioactive chiral compounds using **1c** as an optically active precursor was performed[2c] and some other syntheses are underway. In view of this fact, a large-scale preparation of **1c** was required. A retrosynthetic analysis of **1c** showed that the enantiomerically pure diol **4** should be the reagent of choice for the preparation of **1c** and its sulfur and selenium analogues (Fig. 2).

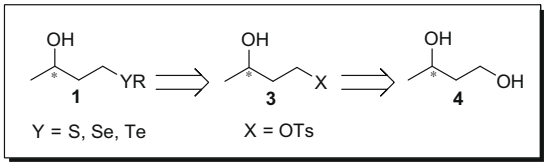


Figure 2.

Enantiomerically enriched (*R*)- and (*S*)-**4** have been prepared by enzymatic kinetic resolution of racemic **4**.[3] Alternatively, ethyl acetoacetate was bioreduced to (*S*)-3-hydroxybutanoate by baker's yeast and then reduced with $LiAlH_4$ to (*S*)-**4**.[4] Poly[*R*]-3-hydroxybutanoate (PHB) on reduction with $LiAlH_4$ gave (*R*)-**4**.[5] This last approach is attractive, since PHB is produced on a large-scale by bacteria. This phenomenon is known since 1926.[6] However, PHB has only recently become available in large-scale as a green alternative for polymeric materials derived from petrochemicals.[7] Several bacteria are able to store PHB as a food supply. Nowadays, PHB is industrially produced in high yield (up to 80–90% of dry biomass) using gram-negative bacteria such as *Alcaligenes eutrophus*, recently named *Cupriavidus necator*[8] (responsible for the highest yield production), recombinant *Escherichia coli,* and *Alcaligenes latus*.[9] PHB produced commercially by these processes has been applied for many purposes including biodegradable polymer packaging, pharmacy, medicine, food industry, and paint industry.[10] Although the major production of PHB (hundreds of tons per year) is destined for large industrial

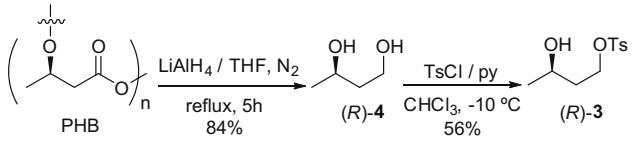
* Corresponding author. Tel.: +55 11 30911180.
E-mail address: princivalj@yahoo.com.br (A.A. Dos Santos).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.10.009

purposes, its enantiomeric purity (>99% ee) and chemical functionality make it an interesting building block for organic synthesis. For many years, its transformation into the corresponding enantiomerically pure monomer or diol has found use to generate a chiral building block in organic synthesis.[4,5] In view of this fact and based on the demonstrated application of hydroxybutyltellurides as precursors of dianions,[11] we focused our attention on the preparation of (*R*)- and (*S*)-γ-hydroxy-organochalcogenides using this polymer as the starting material, as presented herein.

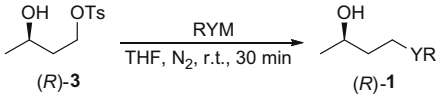
2. Results and discussion

The commercially available[12] crystalline PHB was reduced with lithium aluminum hydride in THF in 0.7 mol batches, producing 0.58 mol (84%) of (*R*)-**4** in >99% ee after distillation. The diol **4** was transformed in 56% yield into the monotosylate **3** by reaction with tosyl chloride/pyridine in $CHCl_3$[13] (Scheme 2).



Scheme 2. Preparation of the monotosylate (*R*)-**3** from PHB.

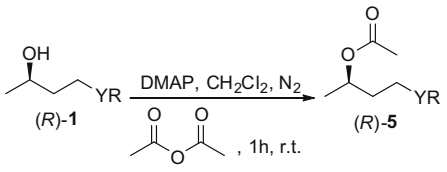
With (*R*)-**3** in hand, it was transformed into the corresponding organochalcogenides by reaction with the appropriate metal chalcogenolate as shown in Scheme 3.



		Yield (%)	e.e. (%)
1a	Y = S; M = Li; R = ^{n}Bu	62	> 99.9
1b	Y = Se; M = Li; R = ^{n}Bu	79	> 99.9
1c	Y = Te; M = Li; R = ^{n}Bu	86	> 99.9
1d	Y = S; M = MgBr; R = Ph	83	> 99.9
1e	Y = Se; M = MgBr; R = Ph	89	> 99.9
1f	Y = Te; M = MgBr; R = Ph	89	> 99.9

Scheme 3. Preparation of enantiomerically pure γ-hydroxy-organochalcogenides (*R*)-**1** from (*R*)-**3**.

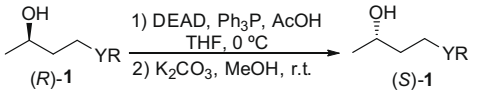
The tosylate displacement reaction can be conducted using the unprotected alcohol, due to the poor basic character of the chalcogenolates. In the case of the ^{n}Bu chalcogeno derivatives, the lithium chalcogenolates have been prepared by reaction of ^{n}BuLi in hexane with a THF suspension of the elemental chalcogen, as described recently by us.[14] When R was a phenyl group, phenylmagnesium bromide was reacted with the elemental chalcogen in THF, following the literature procedures for the preparation of magnesium selenolates[15] and tellurolates.[16] The reaction of (*R*)-**3** with the metal chalcogenolate was monitored by TLC. After work-up the γ-hydroxy-organochalcogenides were purified by column chromatography in hexane/ethyl acetate (8:2) to give **1a–f** in the yields as shown in Scheme 3. The enantiomeric excesses of **1a–f** were determined by chiral gas chromatography. To this end the alcohols **1** were transformed into the corresponding acetates to improve their chromatographic separation. In this way, the ee shown in Scheme 3 corresponds to the ee of the acetates **5** derived from **1** as shown in Scheme 4.



		Yield (%)	e.e. (%)
5a	Y = S; R = ^{n}Bu	86	> 99.9
5b	Y = Se; R = ^{n}Bu	89	> 99.9
5c	Y = Te; R = ^{n}Bu	92	> 99.9
5d	Y = S; R = Ph	87	> 99.9
5e	Y = Se; R = Ph	91	> 99.9
5f	Y = Te; R = Ph	93	> 99.9

Scheme 4. Preparation of the enantiomerically pure acetates (*R*)-**5** from (*R*)-**1**.

The (*S*)-γ-hydroxy-organochalcogenides were prepared by a Mitsunobu reaction[17] on the (*R*)-γ-hydroxy-organochalcogenides prepared above. Treatment of (*R*)-**1a–c** with DEAD, triphenylphosphine, and acetic acid in THF at 0 °C gave (*S*)-**5a–f** in good yields. Treatment of (*S*)-**5a–f** with K_2CO_3 in methanol at room temperature led to (*S*)-**1a–f**, as shown in Scheme 5.



		Overall yield (%)	e.e. (%)
(S)-**1a**	Y = S; R = ^{n}Bu	66	> 99.9
(S)-**1b**	Y = Se; R = ^{n}Bu	76	> 99.9
(S)-**1c**	Y = Te; R = ^{n}Bu	74	> 99.9
(S)-**1d**	Y = S; R = Ph	73	> 99.9
(S)-**1e**	Y = Se; R = Ph	81	> 99.9
(S)-**1f**	Y = Te; R = Ph	78	> 99.9

Scheme 5. Preparation of the (*S*)-hydroxy-organochalcogenides from the (*R*)-isomers.

3. Conclusion

In conclusion, the enantiomerically pure (*R*)- and (*S*)-hydroxy-organochalcogenides and the corresponding acetates can be prepared in good yields using the readily available and inexpensive PHB as the starting material. These chiral building blocks can be produced on a large-scale preparation as a 'one-day procedure' providing chiral functionalized organometallic equivalents.

4. Experimental

4.1. General

Poly[*R*]-3-hydroxybutanoate was kindly supplied by PHB Industrial S.A. (Serrana, São Paulo, Brazil). ^{n}BuLi 15% in hexane was purchased from Chemmetal.

All solvents and chemicals used were previously purified according to the usual methods.[18] 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 AC-200 (^{1}H: 200 MHz; ^{13}C: 50 MHz) spectrometer using tetramethylsilane and the central peak of $CDCl_3$ at 77 ppm as internal standards. 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), quint (quintuplet), sext (sextuplet), hept (heptet), 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 spectra 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). HRMS (high-resolution mass spectra) were taken with a Micro TOF-MS Bruker Daltonics ESI. The IUPAC names were obtained using the software ChemDraw Ultra®, version 8.0. The enantiomeric excesses of the organochalcogenides 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 × 0.25 μm)-Varian. The carrier gas was hydrogen with a pressure of 100 kPa. Optical rotations were measured in a Jasco DIP-370 digital polarimeter.

4.2. Synthesis of the substrates

4.2.1. Preparation of (*R*)-butane-1,3-diol by reductive depolymerization (*R*)-4

To a suspension of $LiAlH_4$ (20 g, 0.52 mol) in dry THF (1000 mL) at 0 °C, PHB was added slowly (60 g, 0.70 mol) under nitrogen and with magnetic stirring. The resulting mixture was stirred for 2 h at room temperature and then refluxed for 5 h. The mixture was cooled to 0 °C and diethyl ether (400 mL), H_2O (20 mL), NaOH (60 mL, 10% w/v solution), and H_2O (20 mL) were added in turn. The residue was filtered through a silica gel pad, which was then washed with diethyl ether (2 × 100 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by distillation under vacuum (30 mmHg/40 °C). Yield: 52 g (84%); $[\alpha]_D^{24} = -30.0$ (c 1.0, EtOH) ee >99.9%; [lit.[19] $[\alpha]_D^{20} = +30.0$ (c 1.0, EtOH) for the (*S*)-isomer]. CAS NR 6290-03-5. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.17 (3H, d, J = 5.2 Hz), 1.6 (2H, q. J = 5.2 Hz), 3.65–3.81 (1H, m), 4.05 (2H, t, J = 5.2 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ 23.4, 40.0, 60.6, 67.1. IR (film) cm^{-1}: 3362, 2967, 2964, 1134, 1088, 1054. MS *m/z* (rel int.) 91 [M+1] (58), 90 [M+] (10), 85 (1), 73 (16), 72 (22), 67 (1), 61 (3), 57 (20), 55 (32).

4.2.2. Preparation of (*R*)-3-hydroxybutyl-4-methylbenzenesulfonate (*R*)-3

To a solution of diol **4** (20 g, 0.22 mol) in dry $CHCl_3$ (460 mL) under nitrogen atmosphere and magnetic stirring, was added pyridine (54 mL). The resulting solution was cooled to 0 °C and a solution of tosyl chloride (4 mol L^{-1}, 58 g, 0.24 mol) in $CHCl_3$ was slowly added (about 1.5 h) and the mixture was stirred for 3 h. After that, cold H_2O (100 mL) was added and the phases were separated. The organic phase was washed twice with brine (20 mL) and $CuSO_4$ saturated solution until the deep blue color disappeared. The organic phases were then combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel eluting with methylene chloride. Yield: 30 g (56%). $[\alpha]_D^{23} = -14.9$ (c 1.0, CH_2Cl_2) ee >99.9%; [lit.[20] $[\alpha]_D^{20} = -14.8$ (c 1.0, CH_2Cl_2). CAS NR 75351-36-9. ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.22 (3H, d, J = 7.2 Hz), 1.67–1.89 (2H, m), 2.45 (3H, s), 3.91–3.95 (3H, m), 7.27–7.83 (4H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 9.8, 11.7, 26.0, 52.3, 56.0, 116.0, 118.0, 121.2, 133.0 IR (film) cm^{-1}: 3540, 3416, 2969, 2928, 1354, 1189, 1175, 1096. MS *m/z* (rel. int.) 245 [M+1] (14), 227 (36), 200 (3), 172 (100), 155 (28), 135 (6), 108 (32), 91 (71), 65 (35).

4.2.3. General procedure for the preparation of (*R*)-3-hydroxyorganochalcogenides 1a–f

^{n}Butyllithium in hexane (1.4 mol L^{-1}, 7.1 mL, 10 mmol) or phenylmagnesium bromide in THF (1.0 mol L^{-1}, 10 mL, 10 mmol) as appropriate, was added to a suspension of the elemental chalcogen (10 mmol) in dry THF (50 mL) under nitrogen and magnetic stirring. Then (*R*)-**3** (2.44 g, 10 mmol) was added. When the reaction reached completion (monitored by TLC), the mixture was diluted with H_2O (5 mL), treated with saturated NH_4Cl solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (80:20).

4.2.3.1. (*R*)-1-(^{n}Butylthio)-3-butanol (*R*)-1a. Oil; yield: 1.004 g (62%); ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.92 (3H, t, J = 7.0 Hz), 1.22 (3H, d, J = 6.6 Hz), 1.30–1.46 (2H, m), 1.50–1.62 (2H, m), 1.73 (2H, sext, J = 7.0 Hz), 2.02 (1H, s), 2.53 (2H, t, J = 7.4 Hz), 2.63 (2H, t, J = 7.4 Hz), 3.95 (1H, sext, J = 6.1 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 12.6, 21.9, 23.4, 28.7, 31.6, 31.7, 38.1, 67.4. IR (film) cm^{-1}: 3376, 2960, 2929, 2872, 1461, 1374, 1272, 1124, 1053, 946, 746, 664. HRMS (ESI) *m/z*; calcd for $C_8H_{18}NaOS$ $[M+Na]^+$: 185.0976, found: 185.0974.); $[\alpha]_D^{24} = -8.5$ (c 1.0, $CHCl_3$); ee >99.9%.

4.2.3.2. (*R*)-1-(^{n}Butylselanyl)-3-butanol (*R*)-1b. Oil; yield 1.659 g (79%); ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.92 (3H, t, J = 7.0 Hz), 1.21 (3H, d, J = 6.1 Hz), 1.4 (2H, sext, J = 7.0 Hz), 1.57–1.85 (4H, m), 2.0 (1H, s), 2.58 (2H, t, J = 7.4 Hz), 2.64 (2H, t, J = 7.4 Hz), 3.91 (1H, sext, J = 6.1 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 13.5, 19.9, 22.9, 23.3, 23.7, 32.5, 39.2, 67.8. IR (film) cm^{-1}: 3369, 2960, 2928, 2871, 1460, 1375, 1256, 1194, 1121, 1050, 939, 842, 737. HRMS (ESI) *m/z*; calcd for $C_8H_{18}NaOSe$ $[M+Na]^+$: 233.0421, found: 233.0420. $[\alpha]_D^{23} = -6.2$ (c 1.0, $CHCl_3$); ee >99.9%.

4.2.3.3. (*R*)-1-(^{n}Butyltellanyl)-3-butanol (*R*)-1c. Oil; yield 2.236 g (86%); CAS NR. 943643-07-0; ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.85 (3H, t, J = 6.2 Hz), 1.13 (3H, d, J = 6.3 Hz), 1.31 (2H, sext, J = 7.2 Hz); 1.65 (2H, quint, J = 7.2 Hz), 1.76–1.85 (2H, m), 2.53–2.69 (4H, m), 3.75 (1H, sext, J = 6 Hz). ^{13}C NMR (50 MHz; CDCl3) δ 2.3, 2.7, 13.4, 23.2, 25.0, 34.2, 41.1, 69.1. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 251.43. IR (film) cm^{-1} 3373, 2959, 2925, 2866, 1458, 1371, 1329, 1157, 1057, 912, 568, 448. MS *m/z* (rel int.) 260 [M^++2] (13), 258 [M+] (13), 256 (7), 255 (3), 254 (2), 215 (3), 186 (8), 72 (5), 57 (73), 55 (100), 45 (44). $[\alpha]_D^{25} = -7.9$ (c 1.0, CH_2Cl_2); ee >99.9%. [lit.[2a] $[\alpha]_D^{25} = +7.0$ (c 1.0, CH_2Cl_2) for the (*S*)-isomer, ee 99%].

4.2.3.4. (*R*)-1-(Phenylthio)-3-butanol (*R*)-1d. Oil; yield 1.51 g (83%); CAS NR. 134641-08-0; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.18 (3H, d, J = 6.6 Hz), 1.69–1.79 (2H, m); 2.25 (1H, s), 2.89–3.12 (2H, m), 3.9 (1H, sext, J = 6.1 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 23.4, 30.0, 38.0, 66.7, 125.8, 128.8, 128.9, 136.3. IR (film) cm^{-1} 3364, 3058, 2966, 2928, 2876, 1457, 1479, 1374, 1274, 1123, 740, 692, 477. HRMS (ESI) *m/z*; calcd for $C_{10}H_{14}NaOS$ $[M+Na]^+$: 205.0663, found: 205.0663. $[\alpha]_D^{24} = -29.4$ (c 1.0, $CHCl_3$) ee >99.9%; [lit.[21] $[\alpha]_D^{20} = -25.9$ (c 0.99, $CHCl_3$); ee 91.0%].

4.2.3.5. (*R*)-1-(Phenylsellanyl)-3-butanol (*R*)-1e. Oil; yield 2.047 g (89%); ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.20 (3H, d, J = 6.1 Hz), 1.75–1.86 (2H, m), 2.07 (1H, s), 2.91–3.04 (2H, m), 3.9 (1H, sext, J = 6.1 Hz), 7.22–7.27 (3H, m), 7.46–7.51 (2H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 23.4, 23.9, 39.0, 67.5, 126.7, 129.0, 132.4, 134.9. IR (film) cm^{-1}: 3366, 3070, 3056, 2967, 2929, 1578, 1477, 1437, 1120, 1072, 1023,

937, 841, 735, 691, 670, 465. HRMS (ESI) *m/z*; calcd for $C_{10}H_{14}NaOSe$ $[M+Na]^+$: 253.0108, found: 253.0103. $[\alpha]_D^{24} = -40.9$ (*c* 1.0, $CHCl_3$); ee >99.9 %. [lit.[3c] $[\alpha]_D^{22} = +40.6$ (*c* 2.19, $CHCl_3$) for the (*S*)-isomer].

4.2.3.6. (*R*)-1-(Phenyltellanyl)-3-butanol (*R*)-1f. Oil; yield 2.492 g (89%); ^1H NMR (200 MHz; $CDCl_3$) δ 1.2 (3H, d, *J* = 6.2 Hz), 1.65 (1H, d, *J* = 4.8 Hz), 1.87–1.98 (2H, m), 2.83–3.00 (2H, m), 3.84 (1H, hept, *J* = 6.2 Hz), 7.19–7.27 (3H, m), 7.69–7.74 (2H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 4.0, 23.1, 40.7, 69.1, 127.5, 129.1, 138.2, 140.2 IR (film) cm^{-1}: 3365, 3064, 3051, 2965, 2926, 1574, 1474, 1433, 1373, 1161, 1116, 1062, 1018, 928, 837, 732, 691, 654, 454. HRMS (ESI) *m/z*; calcd for $C_{10}H_{14}NaOTe$ $[M+Na]^+$: 303.005, found: 303.007. $[\alpha]_D^{24} = -9.9$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4. General procedure for the preparation of (*R*)-*O*-acetyl-1-(butylchalcogenyl)-3-butanol 5a–f

To the appropriate alcohol (*R*)-**4a–f** (2 mmol) dissolved in dry CH_2Cl_2 (10 mL) under a nitrogen atmosphere were added DMAP (0.1 mmol) and acetic anhydride (0.2 mL, 2.1 mmol). The mixture was stirred at room temperature for 1 h. After that, aqueous HCl (10% v/v, 1 mL) was added and the reaction mixture was extracted with ethyl acetate (3 mL). The organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography over silica gel eluting with hexane/ethyl acetate (9:1).

4.2.4.1. (*R*)-*O*-Acetyl-1-(*n*butylthio)-3-butanol (*R*)-5a. Oil; yield 0.350 g (86%); ^1H NMR (200 MHz; $CDCl_3$) δ 0.91 (3H, t, *J* = 7.0 Hz), 1.20 (3H, d, *J* = 6.1 Hz), 1.29–1.60 (4H, m); 1.71–1.94 (2H, m), 2.04 (3H, s), 2.47–2.54 (4H, m), 5.0 (1H, sext, *J* = 6.1 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 13.6, 19.8, 21.2, 21.9, 27.8, 31.6, 31.7, 35.9, 69.9, 170.6. IR (film) cm^{-1} 2958, 2931, 2872, 1738, 1461, 1373, 1244, 1050, 1025, 953. HRMS (ESI) *m/z*; calcd for $C_{10}H_{20}NaO_2S$ $[M+Na]^+$: 227.1082, found: 227.1082. $[\alpha]_D^{19} = +3.5$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4.2. (*R*)-*O*-Acetyl-1-(*n*butylselanyl)-3-butanol (*R*)-5b. Oil; yield 0.450 g 89(%); ^1H NMR (200 MHz; $CDCl_3$) δ 0.91 (3H, t, *J* = 7.0 Hz), 1.20 (3H, d, *J* = 6.1 Hz), 1.40 (2H, sext, *J* = 7.0 Hz), 1.64 (2H, quint., *J* = 7.0 Hz), 1.74–1.98 (2H, m), 2.04 3H, s), 2.48–2.59 (4H, m), 5.0 (1H, sext, *J* = 6.1 Hz) . ^{13}C NMR (50 MHz; $CDCl_3$) δ 13.5, 18.8, 19.6, 21.2, 22.9, 23.7, 32.5, 36.9, 70.6, 170.5. IR (film) cm^{-1} 2959, 2930, 1738, 1460, 1372, 1242, 1030, 951. HRMS (ESI) *m/z*; calcd for $C_{10}H_{20}NaO_2S$ $[M+Na]^+$: 275.0526, found: 275.0517. $[\alpha]_D^{24} = +10.1$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4.3. (*R*)-*O*-Acetyl-1-(*n*butyltellanyl)-3-butanol (*R*)-5c. Oil; yield 0.993 g (92%); CAS NR. 915040-57-2; ^1H NMR (300 MHz; $CDCl_3$) δ 0.92 (3H, t, *J* = 7.5 Hz), 1.23 (3H, d, *J* = 6.3 Hz), 1.38 (2H, sext, *J* = 7.5 Hz), 1.72 (2H, quint, *J* = 7.5 Hz), 2.04 (3H, s), 1.87–2.11 (2H, m), 2.49–2.67 (4H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ -3.6, 2.8, 13.4, 19.5, 21.3, 25.0, 34.2, 38.8, 72.2, 170.6. ^{125}Te NMR (157 MHz, 300 K, $CDCl_3$) δ 270.15. IR (film) cm^{-1} 1157, 1057, 912, 568, 448.3059, 2979, 2932, 2870, 1735, 1574, 1458, 1371, 1329, 735. MS *m/z* (rel int.) 302 (M^+, 7%); 300 (M 7%); 298 (4%); 186 (2%); 185 (3%); 184 (2%); 183 (3%); 115 (45%); 55 (100%). $[\alpha]_D^{25} = +19.5$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4.4. (*R*)-*O*-Acetyl-1-(phenylthio)-3-butanol (*R*)-5d. Oil; yield 0.390 g (87%); CAS NR. 110920-29-1; ^1H NMR (200 MHz; $CDCl_3$) δ 1.23 (3H, d, *J* = 6.6 Hz), 1.71–1.95 (2H, m), 2.03 (3H, s), 2.80–3.02 (2H, m), 5.0 (1H, sext. *J* = 6.6 Hz), 7.17–7.35 (5H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 19.8, 21.2, 29.5, 35.4, 69.7, 126.0, 128.8, 129.1, 136.0, 170.5. IR (film) cm^{-1} 3074, 3058, 3019, 2976, 2934, 2873, 1736, 1584, 1480, 1439, 1372, 1244, 1129, 1053, 1025, 953, 739, 691, 608, 475. HRMS (ESI) *m/z*; calcd for $C_{12}H_{16}NaO_2S$ $[M+Na]^+$: 247.0769, found: 247.0753. $[\alpha]_D^{24} = -7.7$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4.5. (*R*)-*O*-Acetyl-1-(phenylsellanyl)-3-butanol (*R*)-5e. Oil; yield 0.500 g (91%); CAS NR. 96004-31-3; ^1H NMR (200 MHz; $CDCl_3$) δ 1.21 (3H, d, *J* = 6.1 Hz), 1.72–1.94 (2H, m), 2.01 (3H, s), 2.77–2.99 (2H, m), 5.0 (1H, sext, *J* = 6.1 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 19.7, 21.2, 23.1, 36.4, 70.5, 126.8, 129.0, 132.5, 135.2, 170.5. IR (film) cm^{-1} 3071, 3057, 3016, 2976, 2935, 2874, 1736, 1579, 1478, 1437, 1372, 1242, 1128, 1042, 1023, 950, 737, 691, 608, 464. HRMS (ESI) *m/z*; calcd for $C_{10}H_{20}NaO_2S$ $[M+Na]^+$: 295.0213, found: 295.0207. $[\alpha]_D^{26} = +5.1$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.4.6. (*R*)-*O*-Acetyl-1-(phenyltellanyl)-3-butanol, (*R*)-5f. Oil; yield 0.600 g (93%); ^1H NMR (200 MHz; $CDCl_3$) δ 1.20 (3H, d, *J* = 6.1 Hz), 1.94–2.12 (2H, m), 2.00 (2H, s), 2.73–2.95 (2H, m), 4.9 (1H, sext., *J* = 6.1 Hz), 7.16–7.32 (3H, m), 7.68–7.73 (2H, m). ^{13}C NMR (50 MHz; $CDCl_3$) δ 2.7, 19.4, 21.2, 38.1, 72.0, 127.6, 129.1, 138.2, 140.4, 170.5. IR (film) cm^{-1}: 3065, 2975, 2934, 1735, 1574, 1474, 1433, 1372, 1243, 1126, 1022, 949, 733, 693, 608, 454. HRMS (ESI) *m/z*; calcd for $C_{12}H_{16}NaO_2Te$ $[M+Na]^+$: 345.0110, found: 345.0106. $[\alpha]_D^{24} = +16.6$ (*c* 1.0 $CHCl_3$); ee >99.9%.

4.2.5. General procedure for the preparation of (*S*)-*O*-acetyl-1-(butylchalcogenyl)-3-butanol and (*S*)-*O*-acetyl-1-(phenylchalcogenyl)-3-butanol 5a–f by Mitsunobu reaction

To a stirred solution of the alcohol (*R*)-**1a–f** (10 mmol) and triphenylphosphine (2.80 g, 12 mmol) in dry THF (30 mL) at 0 °C was slowly added DEAD (1.25 g, 12 mmol). After 5 min. acetic acid (14 mmol) was subsequently added dropwise. When the reaction had reached completion (monitored by TLC), the reaction mixture was concentrated in vacuum, the residue dissolved in a mixture of diethyl ether/pentane (50:50), and passed through a silica gel pad. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (90:10) as eluant.

4.2.5.1. (*S*)-*O*-Acetyl-1-(*n*butylthio)-3-butanol (*S*)-5a. Oil; yield: 0.70 g (73%); $[\alpha]_D^{22} = -3.5$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.5.2. (*S*)-*O*-Acetyl-1-(*n*butylselanyl)-3-butanol (*S*)-5b. Oil; yield: 1.0 g (81%); $[\alpha]_D^{25} = +10.3$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.5.3. (*S*)-*O*-Acetyl-1-(*n*butyltellanyl)-3-butanol (*S*)-5c. Oil; yield: 1.20 g (80%); $[\alpha]_D^{22} = -19.3$ (*c* 1.0, $CHCl_3$); ee >99.9 %.

4.2.5.4. (*S*)-*O*-Acetyl-1-(phenylthio)-3-butanol (*S*)-5d. Oil; yield: 1.83 g (82%); $[\alpha]_D^{23} = +7.7$ (*c* 1.0, $CHCl_3$); ee >99.9 %.

4.2.5.5. (*S*)-*O*-Acetyl-1-(phenylsellanyl)-3-butanol (*S*)-5e. Oil; yield: 2.36 g (87%); $[\alpha]_D^{24} = -5.2$ (*c* 1.0, $CHCl_3$); ee >99.9 %.

4.2.5.6. (*S*)-*O*-Acetyl-1-(Phenyltellanyl)-3-butanol (*S*)-5f. Oil; yield: 2.73 g (85%); $[\alpha]_D^{23} = -16.6$ (*c* 1.0, $CHCl_3$); ee >99.9 %.

4.2.6. General procedure for the preparation of (*S*)-3-hydroxy-organochalcogenides (1a–f)

To a suspension of K_2CO_3 (0.138 g, 1 mmol) in dry MeOH (1 mL) under a nitrogen atmosphere was slowly added the appropriate acetate (*S*)-**5a–f**. The resulting mixture was stirred for 40 min at room temperature and filtered. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (80:20).

4.2.6.1. (*S*)-1-((^{n}Butylthio)-3-butanol (*S*)-1a. Oil; yield: 0.146 g (90%); $[\alpha]_D^{23} = +8.5$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.6.2. (*S*)-1-((^{n}Butylselanyl)-3-butanol (*S*)-1b. Oil; yield: 0.197 g (94%); $[\alpha]_D^{25} = +6.3$ (*c* 1.0, $CHCl_3$); ee >99.9%.

4.2.6.3. (*S*)-1-((^{n}Butyltellanyl)-3-butanol (*S*)-1c. Oil; yield: 0.239 g (92%); $[\alpha]_D^{24} = +7.7$ (*c* 1.0, CH_2Cl_2); ee >99.9%.

4.2.6.4. (*S*)-1-(Phenylthio)-3-butanol (*S*)-1d. Oil; yield: 0.161 g (82%); $[\alpha]_D^{24} = +30.1$ (*c* 1.0, $CHCl_3$); ee >99.9%; [lit.[21] $[\alpha]_D^{20} = -25.9$ (*c* 0.99, $CHCl_3$) ee 91.0% for the (*R*)-isomer].

4.2.6.5. (*S*)-1-(Phenylselanyl)-3-butanol (*S*)-1e. Oil; yield: 0.269 g (93%); $[\alpha]_D^{25} = +42.7$ (*c* 1.0, $CHCl_3$); ee >99.9%. [lit.[3c] $[\alpha]_D^{23} = +40.6$ (*c* 2.19, $CHCl_3$)].

4.2.6.6. (*S*)-1-(Phenyltellanyl)-3-butanol (*S*)-1f. Oil; yield 0.257 g (92%); $[\alpha]_D^{24} = +9.8$ (*c* 1.0, CH_2Cl_2); ee >99.9%.

Acknowledgments

The authors thank FAPESP, CNPq, and CAPES for the support. PHB Industrial S/A is acknowledged for the donation of PHB.

References

1. (a) Cohen, T.; Liu, H. *J. Org. Chem.* **1995**, *60*, 2022; (b) Cohen, T.; Tong, S. *Tetrahedron* **1997**, *53*, 9487.
2. (a) Dos Santos, A. A.; Costa, C. E.; Princival, J. L.; Comasseto, J. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2252; (b) Dos Santos, A. A.; Princival, J. L.; Comasseto, J. V.; Barros, S. M. G.; Brainer Neto, J. E. *Tetrahedron* **2007**, *63*, 5167; (c) Wendler, E. P.; Dos Santos, A. A. *Synlett* **2009**, *7*, 1034; (d) Comasseto, J. V.; Gariani, R. A. *Tetrahedron* **2009**, *65*, 8447; (e) Ferrarini, R. S.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron: Asymmetry,* **2009**, *20*, 2043.
3. (a) Eguchi, T.; Mochida, K. *Biotech. Lett.* **1993**, *15*, 955; (b) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron: Asymmetry* **2001**, *12*, 293; (c) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Org. Biomol. Chem.* **2007**, *5*, 3510.
4. Mori, K.; Watanabe, H. *Tetrahedron* **1984**, *40*, 299.
5. (a) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495; (b) Zarbin, P. H. G.; Oliveira, A. R. M.; Delay, C. E. *Tetrahedron Lett.* **2003**, *44*, 6849.
6. Lemoigne, M. *Bull. Soc. Chem. Biol.* **1926**, *8*, 770–782.
7. (a) van der Walle, G. A. M.; de Koning, G. J. M.; Weusthuis, R. A.; Eggink, G. *Adv. Biochem. Eng. Biotechnol.* **2001**, *71*, 263–291; (b) Khanna, S.; Srivastava, A. K. *Process Biochem.* **2005**, *40*, 607.
8. Vandamme, P.; Coenye, T. *Int. J. Syst. Evol. Microbiol.* **2004**, *54*, 2285–2289.
9. Valappil, S. P.; Misra, S. K.; Boccaccini, A. R.; Keshavarz, T.; Bucke, C.; Roy, I. *J. Biotechnol.* **2007**, *132*, 251–258.
10. Anderson, A. J.; Dawes, E. A. *Microbiol. Rev.* **1990**, *54*, 450.
11. (a) Princival, J. L.; Barros, S. M. G.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2005**, *46*, 4423; (b) Bassora, B. K.; Da Costa, C. E.; Gariani, R. A.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2007**, *48*, 1485; (c) Comasseto, J. V.; Dos Santos, A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 939; (d) Princival, J. L.; Dos Santos, A. A.; Comasseto, J. V. *Tetrahedron Lett.* **2009**, *50*, 6368.
12. www.biocycle.com.br
13. Kabalka, G. W.; Varm, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.
14. Comasseto, J. V.; Gariani, R. A.; Princival, J. L.; Dos Santos, A. A.; Zinn, F. K. *J. Organomet. Chem.* **2008**, *693*, 2929.
15. Forter, D. G. *Org. Synth., Collect.* **1955**, *3*, 771.
16. Kemmitt, T.; Levanson, W. *Organometallics* **1989**, *8*, 1303.
17. For a recent review on the Mitsunobu reaction see: Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.
18. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: London, 1980.
19. (a) Huang, P.; Lan, H.; Zheng, X.; Ruan, Y. *J. Org. Chem.* **2004**, *69*, 3964; (b) Gerlach, Von H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755; (c) Murakam, S.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1356; (d) Hungerbühler, Von E.; Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1981**, *64*, 1467.
20. (a) O'Neill, J. A.; Lindell, S. D.; Simpson, T. J.; Willis, C. L. *Tetrahedron: Asymmetry* **1994**, *5*, 117; (b) Louwrier, S.; Ostendorf, M.; Bomm, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.
21. Ohtsuka, Y.; Katoh, O.; Sugai, T.; Otah, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 483.