Chiral Organometallic Reagents, XX[1]

An Enantiomerically Enriched (α-Phenylselenoalkyl)magnesium Compound

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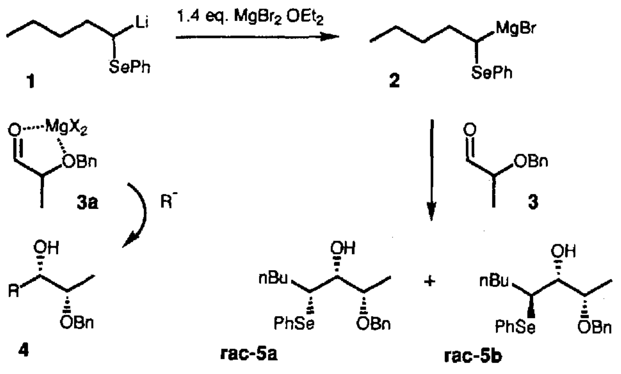
α-Selenoalkyl Grignard reagents **2** are chiral. On reaction with the magnesium chelate **3a** of α-benzyloxypropionaldehyde they show significant degrees of kinetic resolution, especially when the reactions are run in CH_2Cl_2. Under these conditions, racemic **2** was resolved by reaction with 0.59 equivalents of **3a** at temperatures below −20 °C. The remaining **2** had an enantiomer enrichment of 80−86% e.e. (as found by trapping). Hence, **2** has a considerably higher configurational stability than its lithium counterpart **1**.

α-Hetero-substituted organometallic compounds could be valuable building blocks for stereoselective synthesis, provided they possess sufficient configurational stability. Among these reagents, the α-thio-[2] and the α-selenoalkyllithium compounds[3] have a particularly high tendency to racemize rapidly at −78 °C[4]. Possibly, the corresponding α-hetero-substituted alkylmagnesium compounds could have an increased configurational stability. Indications that this could be true are sparse[5,6]. At least, ordinary secondary alkyl Grignard reagents racemize only at or above 0 °C[7]. We report here on our study of α-phenylselenopentylmagnesium bromide (**2**) and its enantiomer enrichment by kinetic resolution.

The racemic Grignard reagent **2** was generated by transmetalation of the lithium reagent **1** with magnesium bromide. Any attempts to generate enantiomerically enriched Grignard reagents would be meaningful only, if the reactions to be subsequently used to trap these reagents proceed more rapidly than the racemization of these species. The prevalence of such a situation can be established by a test, which we devised several years ago[8,9]. The test is based on kinetic resolution of the Grignard reagent in question on reaction with a chiral electrophile. As the latter we used 2-benzyloxypropionaldehyde (**3**).



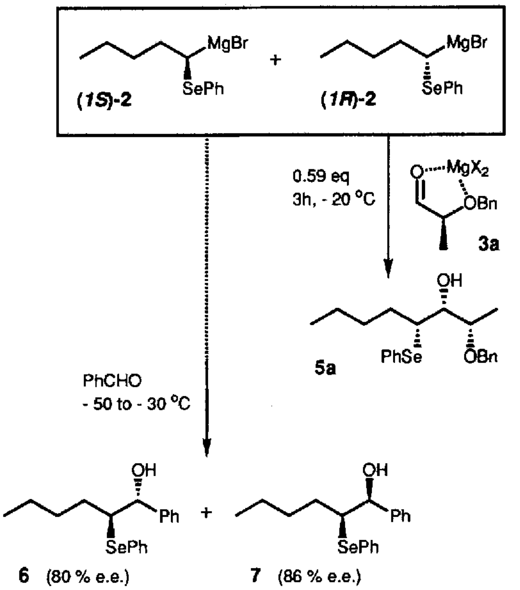
Reaction of the Grignard reagent **2** with the racemic aldehyde **3** in THF furnished the adducts **5** in 62% yield. It is remarkable that only two adducts **5a** and **5b** were formed. The relative configuration of the products **5** (for their assignment see below) suggested that chelation control[10] dominated the stereochemical course of the addition to the aldehyde **3**, cf. **3a**. The diastereomeric ratio **5a**/**5b** = 70:30 reflects the simple distereoselection on addition of the Grignard reagent **2**. While the degree of simple diastereoselectivity is not spectacular, Grignard reagents frequently show a higher simple diastereoselectivity than the reactions of the corresponding lithium reagents[6,11].

This 70:30 ratio of **5a**/**5b** likewise represents the degree of kinetic resolution that would occur on reaction of the racemic Grignard reagent **2** with the enantiomerically pure aldehyde **3**. In order to reach higher degrees of kinetic resolution, we studied the effect of various solvents on the product ratio **5a**/**5b** (Table 1).

Table 1

Entry	Aldehyde (equiv.)	Conditions			Products	
		Temp. [°C]	Time [h]	Solvent	**5a**:**5b**	Yield (%)
1	*rac*-**3** (1.25)	0	1	THF	70:30	62
2	*rac*-**3** (1.4)	-78	5	Et_2O	82:18	46
3	*rac*-**3** (1.9)	-78	5	Toluene	93: 7	57
4	*rac*-**3** (1.9)	-20	5	CH_2Cl_2	95: 5	72
5	(*S*)-**3** (1.9)	-20	5	CH_2Cl_2	64:36	64
6	(*S*)-**3** (1.0)	-20	5	CH_2Cl_2	65:35	61

The data in Table 1 show that diastereoselectivities as high as 95:5 can be attained in CH_2Cl_2 as solvent. We then chose these conditions to test, whether the Grignard reagent **2** adds to the aldehyde **3** more rapidly than it racemizes. Thus, the racemic Grignard reagent **2** was allowed to react with enantiomerically pure aldehyde **3**[12] in CH_2Cl_2 as solvent. Comparison of entries 5 and 6 with entry 4 in Table 1 shows that the addition of **2** to the enantiomerically pure aldehyde **3** resulted in a lower yield and a lower diastereoselectivity. Both are to be expected[9] when the Grignard reagent is "configurationally stable" on the time scale of its addition to the aldehyde **3**. The nomogram published in ref.[9] indicates that in this case a reduction in the diastereomeric ratio from 95:5 to 65:35 would be expected on a 75% conversion of the Grignard reagent **2** into products. We therefore conclude, that the Grignard reagent **2** is trapped by the aldehyde **3** more rapidly than racemization occurs. Moreover, the reaction was found to be subject to a substantial kinetic resolution factor of ca. 20, which opens up the chance of generating enantiomerically enriched Grignard reagent **2** by kinetic resolution[13] in the reaction with the enantiomerically pure aldehyde **3**. For this reason the Grignard reagent **2** was allowed to react with 0.59 equivalents of the enantiomerically pure aldehyde **3** in CH_2Cl_2 for 3 h at −78 °C to −20 °C. This should convert most of the (1*R*) enantiomer of **2** into the adduct **5a**.

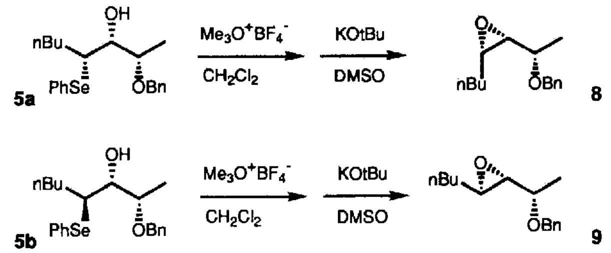


Addition of benzaldehyde at this point should trap the remaining Grignard reagent **2** to give the alcohols **6** and **7**. If the remaining Grignard reagent, enriched in (1*S*)-**2**, did not racemize between the two phases of the experiment, the alcohols **6** and **7** should be enantiomerically enriched. In fact, the enantiomeric purity in **6** and **7** exceeded 80% e.e. Thus, the Grignard reagent **2** can be generated with >80% e.e. by kinetic resolution of the racemate. With a kinetic resolution factor of 20 and 0.59 equivalents of the aldehyde **3** the remaining (1*S*)-**2** should be of ca. 95% e.e.[14]. Since the products resulting from trapping of **2** had a maximum e.e. of 86%, the degree of racemization of **2** during <3 h at −20 °C can be considered as small. Therefore, the Grignard reagent **2** has a considerably higher configurational stability than the lithium compound **1**, congeneres of which racemize rapidly at −78 °C[4,15].

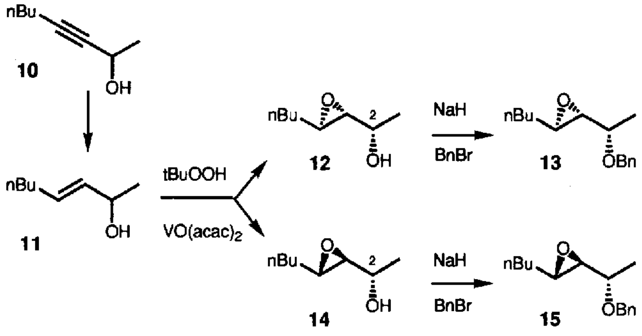
Structural and Configurational Assignment

The interpretation of the results described above has certain stereochemical implications. We therefore established the absolute and relative configuration of all the products in order to see whether the findings are consistent with the interpretation given.

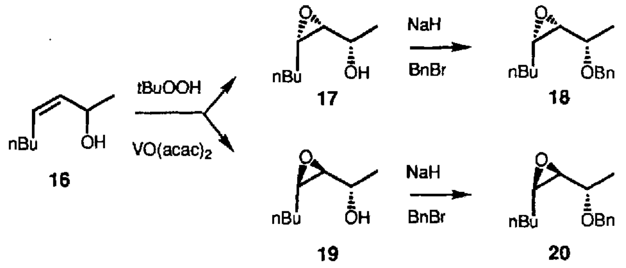
In order to establish their relative configuration, the phenylselenoalcohols **5** were separated by chromatography. The diastereomers **5a** as well as **5b** were converted into the 2-benzyloxy-3,4-epoxyoctanes **8** and **9**.



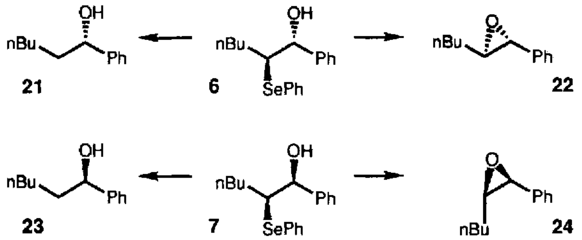
The compounds obtained were compared with the set of the four diastereomeric 2-benzyloxy-3,4-epoxyoctanes prepared from 3-octyn-2-ol (**10**)[16]. Reduction with REDAL furnished the (*E*)-allylic alcohol **11**[16]. The latter was oxidized with *t*-butyl hydroperoxide and vanadyl acetylacetonate to give a 32:68 mixture of *threo*/*erythro* epoxides **12**, **14**. This ratio falls between the 25:75 ratio found on similar epoxidation of (*E*)-3-nonen-2-ol[17] and the 36:64 ratio obtained on epoxidation of (*E*)-3-hepten-2-ol[18]. The diagnostic chemical shift of H-2 and the diagnostic coupling constant H-2/H-3[18] allowed a clear identification of **12** (δ_{H-2} = 3.54, J = 5.5 Hz) as *"threo"* and of **14** (δ_{H-2} = 3.86, J = 3.3 Hz) as *"erythro"*. Samples of **12** and **14** were enriched by gas chromatography and then benzylated to give the benzyloxyepoxides **13** and **15**, respectively. Benzylation could be accomplished by using sodium hydride and benzyl bromide in THF[19] without interference from a Payne rearrangement[20].



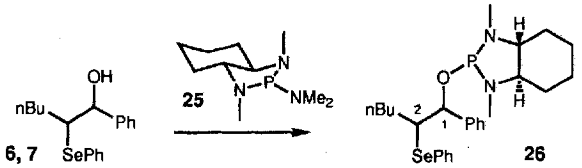
Likewise, 3-octyn-2-ol (**10**) was hydrogenated[16] to give the (*Z*)-allylic alcohol **16**. The latter was epoxidized with *t*-butyl hydroperoxide and vanadyl acetylacetonate to give an 80:20 *threo*/*erythro* mixture of **17** and **19**. This ratio corresponds to an 80:20 ratio reported for the epoxidation of (*Z*)-3-decen-2-ol[17]. Here, we rely on this analogy for the structural assignment of **17** and **19**. After (incomplete) GC separation, the enriched samples of the epoxides **17** and **19** were benzylated as above to furnish the remaining benzyloxyepoxides **18** and **20**. Comparison of the GC properties and of the spectral characteristics of the benzyloxyepoxides obtained from **4** allowed their identification as **8** = **18** and **9** = **13**.



In order to establish the relative configuration of the alcohols **6** and **7**, they were isolated by chromatography and each converted into the epoxides (**22** and **24**, respectively). These compounds show characteristic differences in the ^{13}C-NMR chemical shifts and in the ^{1}H-NMR coupling constants on the basis of which **22** was assigned as a *trans* and **24** as a *cis* epoxide.



In order to determine the enantiomeric purity of the alcohols **6** and **7** obtained, a mixture of racemic **6** and **7** was prepared by addition of 1-phenylselenopentyllithium to benzaldehyde. The isomers were separated by chromatography and converted with the Alexakis reagent **25**[21] into the diastereomeric diazaphospholidines **26**. The latter show distinct ^{31}P-NMR signals originating from the individual diastereomers.



Config.	δ ^{31}P (ppm)
1S,2R	140
1R,2S	148
1R,2R	147
1S,2S	137

Likewise, the alcohols **6** and **7** obtained from the kinetic resolution experiment were also converted to the diazaphospholidines **26**. Their enantiomeric enrichment was determined by integration of the ^{31}P-NMR spectra.

Finally, the absolute configuration of the selenoalcohols **6** and **7** was established by their reduction with triphenyltin hydride to 1-phenylhexanol. The alcohol **21** obtained from **6** is laevorotatory and should therefore have[22] the (*S*) configuration. The alcohol **23** obtained from **7** is dextrorotatory and should therefore have the (*R*) configuration. This information allowed the assignment of the ^{31}P-NMR signals of **26** to the individual diastereomers as indicated above.

The stereochemical assignments reached by these transformations are uniquely consistent with the description of the reaction of the Grignard reagent **2** with the aldehyde (*S*)-**3**. The latter reacts preferentially with (1*R*)-**2** to give the (2*S*,3*R*,4*R*) alcohol **5a**. The remaining Grignard reagent is enriched in the (1*S*) enantiomer. It is trapped to furnish the (1*R*,2*S*)- and the (1*S*,2*S*)-1-phenyl-2-phenylselenohexanols **6** and **7** as shown.

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Experimental

All temperatures quoted are not corrected. – Reactions with organolithium compounds were carried out under dry nitrogen or argon. – ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR: Bruker AC-300, WH-400, and AMX-500. – Boiling range of petroleum ether: 40–60 °C. – pH-7 buffer: 56.2 g of $NaH_2PO_4 \times 2\ H_2O$ and 213.16 g of $Na_2HPO_4 \times 2\ H_2O$ in 1.0 l of water. – Flash chromatography: Silica gel Si 60, E. Merck AG, Darmstadt, 40–63 μm. – MPLC: Silica gel Si 60, E. Merck AG, Darmstadt, 15–25 μm, 10 bar, detection by differential refractometry (Knaur). – HPLC: Merck-Hitachi, L-4000, with UV detection, L-6200 intelligent pump, D-2500 chromatointegrator, RP-18 column with Nucleosil 120-5 C-18 of CS Chromatography Service. – Analytical gas chromatography: Siemens Sichromat 3, Chromatopac C-R3A integrator 55 kPa He 0.3 mm × 30 m capillary column with SE 30. – Preparative gas chromatography: Wilkens Aerograph A-90-P3, 200 ml He/min, column A: 1.6 m × 6 mm column with 5% Apiezon on Chromosorb G-AW-DMCS 60/80 mesh; column B: 3.2 m × 6 mm with 5% QF1 on Chromosorb G-AW-DMCS; column C: 3.2 m × 6 mm column with 5% Carbowax K 20 M on Chromosorb G-AW-DMCS.

1. *2-Benzyloxy-4-phenylseleno-3-octanol* (**4**): 0.70 ml (0.84 mmol) of a 1.2 M solution of *s*-butyllithium in pentane was added at −80 °C to a solution of 274.2 mg (0.717 mmol) of 1,1-bis(phenylseleno)pentane in 10 ml of anhydrous THF. After stirring for 10 min, 1.50 ml (2.4 mmol) of a 1.6 M solution of $MgBr_2$ in ether/toluene was added slowly, leading to precipitation. The mixture was allowed to reach 0 °C with stirring for 2 h which resulted in dissolution of the precipitate. The solvents were removed at 2 Torr and the residue was triturated with 10 ml of anhydrous dichloromethane for 10 min at 0 °C. The resulting suspension was cooled to −20 °C. A solution of 224.9 mg (1.37 mmol) of 2-benzyloxypropionaldehyde and 1.5 ml (2.4 mmol) of a 1.5 M solution of $MgBr_2$ in ether/toluene in 10 ml of dichloromethane was added dropwise and the mixture was stirred for additional 5 h at this temperature. The mixture was allowed to reach 0 °C over 5 h. 10 ml of a saturated aqueous NH_4Cl solution was added, the phases were separated and the aqueous phase was extracted three times with 10 ml of ether each. The combined organic phases were washed with 10 ml of water each and brine, dried with Na_2SO_4, and concentrated. The crude product was purified by MPLC with 6% ethyl acetate in petroleum ether to give 203 mg (72%) of **5** as a 95:5 diastereomeric mixture.

In a similar manner 283.9 mg (0.76 mmol) of 1,1-bis(phenylseleno)pentane, 0.86 ml (1.03 mmol) of a 1.2 M solution of *s*-butyllithium in pentane and 0.17 g (1.0 mmol) of (2*S*)-2-benzyloxypropionaldehyde (**3**)[12] (cf. also ref.[23]) furnished 171.7 mg (58%) of **5** as a 61:39 diastereomeric mixture.

Enriched samples of **5a** and **5b** were obtained by repeated MPLC:

(2S,3R,4R)-2-Benzyloxy-4-phenylseleno-3-octanol (**5a**): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.19–1.54 (m, 4H), 1.71 (m, 1H), 1.87 (m, 1H), 3.05 (d, *J* = 2.2 Hz, 1H), 3.17 (ddd, *J* = 7.0, 7.0, and 3.5 Hz, 1H), 3.53 (ddd, *J* = 6.1, 2.7, and 2.7 Hz, 1H), 3.89 (dq, *J* = 6.2 and 6.2 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 7.21–7.58 (m, 10H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9, 15.6, 22.4, 30.2, 33.6, 50.4, 71.0, 76.5, 127.2, 127.7, 127.8, 128.4, 128.9, 129.6, 134.5, 138.2. – $[\alpha]_D^{20}$ = 22.2 (*c* = 2.44, CH$_3$OH). – C$_{21}$H$_{28}$SeO$_2$ (391.4): calcd. C 64.44, H 7.21; found C 64.52, H 7.45.

(2S,3R,4S)-2-Benzyloxy-4-phenylseleno-3-octanol (**5b**): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.87 (t, *J* = 7.3 Hz, 3H), 1.14–1.92 (m, 9H), overlayed with 1.22 (d, *J* = 6.3 Hz, 3H), 2.57 (broad s, OH), 3.27 (ddd, *J* = 9.1, 6.7, and 3.9 Hz, 1H), 3.50 (dd, *J* = 6.7 and 3.4 Hz, 1H), 3.92 (qd, *J* = 6.3 and 3.5 Hz, 1H), 4.17 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 7.18–7.56 (m, 10H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0, 16.4, 22.6, 30.1, 31.0, 51.3, 70.7, 74.7, 77.2, 127.3, 127.6, 127.8, 128.3, 129.0, 130.6, 134.4, 138.3. – $[\alpha]_D^{20}$ = 11.4 (*c* = 2.37, CH$_3$OH).

2. *Kinetic Resolution of 1-Phenylseleno-1-pentylmagnesium Bromide* (**2**): A solution of **2** in CH$_2$Cl$_2$ was obtained as described above from 1.051 g (2.75 mmol) of 1,1-bis(phenylseleno)pentane, 1.30 ml (2.91 mmol) of a 2.24 M solution of *tert*-butyllithium in cyclopentane and 2.5 ml (4.2 mmol) of a 1.68 M solution of MgBr$_2$–ether in toluene. Into this solution a solution of 264.8 mg (1.6 mmol) of (–)-(*S*)-2-benzyloxypropionaldehyde (**3**) and 2 ml (3.4 mmol) of the solution of MgBr$_2$–ether in toluene (all in 3 ml of CH$_2$Cl$_2$) were added at –80 °C by means of a cannula. The mixture was allowed to reach –20 °C over 3 h and was recooled to –50 °C. 300 μl of benzaldehyde was added and the mixture was allowed to reach –30 °C over 2 h. 10 ml of a saturated aqueous NH$_4$Cl solution was added and the mixture was purified as described under 1. MPLC separation of the crude product furnished three fractions: 652.2 mg, mainly *t*-butyl phenyl selenide and ca. 15% of pentyl phenyl selenide; 227.7 mg (0.67 mmol) of (1*R*,2*S*)-1-phenyl-2-phenylseleno-1-hexanol (**6**); 621.4 mg containing 80% of (2*S*,3*R*,4*R*)-2-benzyloxy-4-phenylseleno-3-octanol (**5a**) and 20% of (1*S*,2*S*)-1-phenyl-2-phenylseleno-1-hexanol (**7**). This corresponds to a 38% yield of **6** and **7** which were obtained in a 68:32 ratio.

(1R,2S)-1-Phenyl-2-phenylseleno-1-hexanol (**6**): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.77 (t, *J* = 7.2 Hz, 3H), 1.13–1.59 (m, 6H), 2.81 (d, *J* = 3.3 Hz, OH), 3.45 (m, 1H), 4.77 (dd, *J* = 3.3 and 3.3 Hz, 1H), 7.30–7.57 (m, 10H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8, 22.3, 28.0, 30.4, 55.9, 74.3, 126.1, 126.9, 127.3, 127.7, 128.0, 129.2, 134.7, 141.1. – C$_{18}$H$_{22}$SeO (333.3): calcd. C 64.86, H 6.65; found C 64.86, H 6.69.

(1S,2S)-1-Phenyl-2-phenylseleno-1-hexanol (**7**): ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.83 (t, *J* = 7.3 Hz, 3H), 1.15–1.66 (m, 6H), 3.29 (m, 1H), 3.40 (d, *J* = 2.4 Hz, OH), 4.49 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.29–7.60 (m, 10H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8, 22.1, 30.0, 31.2, 58.2, 75.7, 126.9, 127.4, 127.9, 128.3, 129.0, 135.5, 141.4. – C$_{18}$H$_{22}$SeO (333.3): calcd. C 64.86, H 6.65; found C 64.63, H 6.62.

The enantiomeric composition of **6** and **7** was determined in the following manner: Ca. 10 mg (0.03 mmol) of **6** or **7** was placed into an NMR tube. The tube was closed with a septum, evacuated and filled with dry nitrogen. The latter operation was repeated 3–4 times. 1.5 equivalents of a deuteriobenzene solution of (*R*,*R*)-**25**[21] were added. The mixture was allowed to stand for 12 h and the total volume was brought to ca. 0.8 ml by addition of dry toluene. The enantiomeric ratio was determined by 162-MHz, ^{31}P-NMR spectroscopy. The peak ratios for the diastereomeric products **26** were calibrated using racemic **6** and **7**.

3. *1-Hydroxy-1-phenyl-2-phenylselenohexane* (**6**, **7**): A solution of 4.14 g (10.8 mmol) of 1,1-bis(phenylseleno)pentane in 30 ml of anhydrous ether was placed in the lower compartment of a two-compartment reaction vessel[24]. The reactor was cooled to –60 °C. The upper compartment was filled with a solution of 1.76 g (16.6 mmol) of benzaldehyde in 30 ml of anhydrous ether. 11.8 ml (11.8 mmol) of a 1 M solution of *s*-butyllithium in cyclopentane was injected into the lower chamber and the content of the reactor was stirred magnetically for 15 min. The solution of the top compartment was added dropwise over 30 min to the lower compartment. After stirring for 15 min, 2 ml of methanol and 10 ml of a saturated aqueous NH$_4$Cl solution were added. The mixture was allowed to reach room temp., the phases were separated, and the aqueous phase was extracted three times with 10 ml of ether each. The combined organic phases were washed with 10 ml of water and 10 ml of brine, dried with Na$_2$SO$_4$, and concentrated. The products were isolated by MPLC (eluant: 5% ethyl acetate in petroleum ether) to give 1.31 g (36%) of **6** and 1.60 g (44%) of **7**.

4. *2-Benzyloxy-3,4-epoxyoctane* (**8**, **9**): A solution of 346.1 mg (0.88 mmol) of a 7:3 mixture of *rac*-**5a**/**5b** in 2 ml of CH$_2$Cl$_2$ was added at 0 °C to a suspension of 163.3 mg (1.1 mmol) of trimethyloxonium tetrafluoroborate in 2 ml of anhydrous CH$_2$Cl$_2$. The mixture was stirred for 12 h resulting in an orange-colored suspension. The solvent was removed in vacuo and the residue was taken up in 3 ml of anhydrous DMSO. 250 mg (2.2 mmol) of potassium *tert*-butoxide was added at 0 °C to the solution resulting in an exothermic reaction. Stirring was continued for 6 h at 0 °C. 40 ml of water was added, the phases were separated and the aqueous phase was extracted five times with 10 ml of ether each. The combined organic phases were washed with 10 ml of water and of brine, dried with Na$_2$SO$_4$, and concentrated. The crude product was separated by MPLC (eluant: 6% ethyl acetate in petroleum ether) to give 44.8 mg (22%) of (2*S**,3*S**,4*R**)-**9** and 98.7 mg (48%) of (2*S**,3*S**,4*S**)-**8**.

8: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (t, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.35–1.56 (m, 6H), 2.87–2.92 (m, 1H), 2.99 (dd, *J* = 7.9 and 4.5 Hz, 1H), 3.36–3.47 (m, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.82 (d, *J* = 11.8 Hz, 1H), 7.24–7.41 (m, 5H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0, 17.6, 22.6, 28.0, 29.1, 54.7, 60.6, 71.2, 74.0, 127.5, 127.8, 128.3, 138.7.

9: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.32–1.66 (m, 6H), 2.71 (ddd, *J* = 5.6, 5.6, and 2.3 Hz, 1H), 2.82 (dd, *J* = 6.8 and 2.3 Hz, 1H), 3.29 (dq, *J* = 6.6 and 6.6 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 7.22–7.39 (m, 5H). – ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.1, 17.5, 22.5, 28.1, 31.4, 54.8, 62.0, 71.2, 75.9, 127.4, 127.7, 128.3, 138.7.

5. *Epoxidation of* **11**: To a solution of 3.00 g (23.0 mmol) of (*E*)-2-hydroxy-3-octene (**11**)[16] and 150 mg (0.6 mmol) of vanadyl acetylacetonate in 30 ml of CH$_2$Cl$_2$, 11.7 ml (37 mmol) of a 3.2 M solution of *tert*-butyl hydroperoxide in CH$_2$Cl$_2$ was added over 15 min at 0 °C and with stirring. Stirring was continued for 1 d during

which time the mixture slowly reached room temp. Then 80 ml of ether was added and the solution was washed several times with 30-ml portions of a 5% aqueous Na_2SO_3 solution until a peroxide test was negative. The combined aqueous phases were saturated with brine and extracted three times with 40 ml of ether each. The combined organic phases were washed with 30 ml of brine and dried with $MgSO_4$. Concentration at 20 Torr was followed by bulb-to-bulb distillation at 2 Torr from a bath of 130 °C furnishing 3.18 g (96%) of a colorless liquid. The *threo*/*erythro* ratio (**12**/**14**) was determined by gas chromatography (80 °C) to be 32:68. A small sample was purified by gas chromatography (column A, 130 °C): $C_8H_{16}O_2$ (144.2): calcd. C 66.63, H 11.18; found C 66.61, H 10.98.

Samples of **12** and **14** were enriched by preparative gas chromatography (column B, 100 °C).

(2S,3R*,4R*)-2-Hydroxy-3,4-epoxyoctane* (**12**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.8 Hz, 3 H), 1.20 (d, J = 6.5 Hz, 3 H), 1.29–1.36 (m, 4 H), 1.47–1.55 (m, 2 H), 2.3 (broad s, OH), 2.65 (dd, J = 5.4 and 2.4 Hz, 1 H), 2.82 (td, J = 5.6 and 2.4 Hz, 1 H), 3.54 (dq, J = ca. 6 Hz, 1 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.7, 25.7, 28.0, 31.2, 56.9, 62.7, 67.7.

(2S,3S*,4S*)-2-Hydroxy-3,4-epoxyoctane* (**14**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.8 Hz, 3 H), 1.17 (d, J = 5.5 Hz, 3 H), 1.29–1.36 (m, 4 H), 1.47–1.55 (m, 2 H), 2.3 (broad s, OH), 2.69 (dd, J = 3.2 and 2.4 Hz, 1 H), 2.92 (td, J = 5.6 and 2.4 Hz, 1 H), 3.86 (qd, J = 6.4 and 3.3 Hz, 1 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.7, 22.4, 28.1, 31.2, 55.1, 62.7, 64.8.

6. *Benzylation of the Epoxy Alcohols* **12** *and* **14**: 288 mg (2.0 mmol) of a 32:68 mixture of **12** and **14** and 850 mg (5 mmol) of benzyl bromide were dissolved in 5 ml of THF. 4 mmol of a 80% suspension of sodium hydride in white oil was added slowly to the solution with stirring. When the exothermic reaction was finished (1.5 h), excess sodium hydride was decomposed by addition of a few drops of methanol. 10 ml of a saturated aqueous NH_4Cl solution was added and the mixture was extracted three times with 10 ml of ether each. The combined organic extracts were washed with 10 ml of brine, dried with Na_2SO_4 and concentrated. Bulb-to-bulb distillation at 2 Torr/140 °C removed excess benzyl bromide. Subsequent bulb-to-bulb distillation at 240 °C furnished 360 mg (73%) of **13** and **15** as a colorless oil. The diastereomeric ratio was determined by gas chromatography (180 °C) to be 38:62. A small sample was purified by gas chromatography (column A, 195 °C): $C_{15}H_{22}O_2$ (234.3): calcd. C 76.88, H 9.46; found C 77.00, H 9.54.

Samples of **13** and **15** were obtained by gas chromatography (column A, 170 °C).

(2S,3S*,4R*)-2-Benzyloxy-3,4-epoxyoctane* (**13**): Cf. the data of **9** under 4.

(2S,3R*,4S*)-2-Benzyloxy-3,4-epoxyoctane* (**15**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 2 H), 1.27 (d, J = 6.3 Hz, 3 H), 1.34–1.41 (m, 4 H), 1.43–1.54 (m, 2 H), 2.66 (bd, J = 5.8 and 2.2 Hz, 1 H), 2.86 (td, J = 5.5 and 2.2 Hz, 1 H), 3.34 (dq, J = ca. 6.2 Hz, 1 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 7.24–7.36 (m, 5 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 17.9, 22.5, 28.1, 31.5, 57.9, 60.6, 71.3, 74.6, 127.5, 127.7, 128.4, 138.6.

7. *Epoxidation of* **16**: 2.00 g (15.6 mmol) of (*Z*)-2-hydroxy-3-octene (**16**)[16], 100 mg (0.4 mmol) of vanadyl acetylacetonate and 7.8 ml (25 mmol) of a 3.2 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 were allowed to react as described under 4. Bulb-to-bulb distillation at 2 Torr/115 °C furnished 2.15 g (96%) of a colorless liquid. The *threo*/*erythro* ratio (**17**/**19**) was determined by gas chromatography (80 °C) to be 80:20. A sample was purified by gas chromatography (column A, 130 °C). – $C_8H_{16}O_2$ (144.2): calcd. C 66.63, H 11.18; found C 66.55, H 11.30.

Isomers of **17** and **19** were enriched by gas chromatography (column C, 135 °C).

(2S,3R*,4S*)-2-Hydroxy-3,4-epoxyoctane* (**17**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.1 Hz, 3 H), 1.21 (d, J = 6.3 Hz, 3 H), 1.30–1.55 (m, 6 H), 2.57 (broad s, OH), 2.84 (dd, J = 8.1 and 4.4 Hz, 1 H), 2.95–3.01 (m, 1 H), 3.61 (qd, J = 8.0 and 6.4 Hz, 1 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.1, 22.4, 27.8, 28.8, 57.8, 61.8, 66.3.

(2S,3S*,4R*)-2-Hydroxy-3,4-epoxyoctane* (**19**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.1 Hz, 3 H), 1.26 (d, J = 6.3 Hz, 3 H), 1.30–1.55 (m, 6 H), 2.35 (broad s, OH), 2.77 (dd, J = 7.7 and 4.1 Hz, 1 H), 2.95–3.01 (m, 1 H), 3.82 (qd, J = 9.7 and 7.1 Hz, 1 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 18.0, 21.0, 22.5, 27.4, 60.1, 64.0, 65.2.

8. *Benzylation of the Epoxy Alcohols* **17** *and* **19**: 288 mg (2.0 mmol) of a 8:2 mixture of **17** and **19** was benzylated as described under 5. to give 290 mg (56%) of a colorless liquid. The diastereomeric ratio of **18** to **20** was determined by gas chromatography (180 °C) to be 87:13. A sample was purified by gas chromatography (column A, 200 °C). – $C_{15}H_{22}O_2$ (234.4): calcd. C 76.88, H 9.46; found C 77.02, H 9.33.

(2S,3S*,4S*)-2-Benzyloxy-3,4-epoxyoctane* (**18**): Cf. the data of **8** under 4.

(2S,3R*,4R*)-2-Benzyloxy-3,4-epoxyoctane* (**20**): ^{1}H NMR (300 MHz, $CDCl_3$): The following signals could be recorded: δ = 1.29 (d, J = 6.5 Hz, 3 H), 2.66–2.69 (m, 1 H), 4.52 (d, J = 11.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.3, 22.6, 27.9, 28.9, 58.2, 59.4, 70.6, 71.6, 127.6, 127.7, 128.4.

8. *(1R*,2R*)-2-Butyl-1-phenyloxirane* (**22**): To a suspension of 254.2 mg (1.72 mmol) of trimethyloxonium tetrafluoroborate in 10 ml of CH_2Cl_2 was added at 0 °C a solution of 494.2 mg (1.48 mmol) of **6** in 20 ml of the same solvent. After stirring for 12 h the solvent was removed in vacuo and the residue was taken up in 10 ml of dry DMSO. To the solution 190 mg (1.7 mmol) of potassium *tert*-butoxide was added and the mixture was stirred for 12 h at room temp. 30 ml of water was added, the phases were separated and the aqueous phase was extracted three times with 10 ml of ether each. The combined organic phases were washed with 10 ml each of a saturated aqueous NH_4Cl solution, water, and brine, dried with Na_2SO_4, and concentrated. The remaining mixture of methyl phenyl selenide and **22** was separated by MPLC (eluant: 1% ethyl acetate in petroleum ether) to afford 120 mg (46%) of (1*R**,2*R**)-2-butyl-1-phenyloxirane (**22**) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.0 Hz, 3 H), 1.50 (m, 4 H), 1.72 (m, 2 H), 2.98 (td, J = 5.6 and 2.1 Hz, 1 H), 3.64 (d, J = 2.1 Hz, 1 H), 7.28–7.38 (m, 5 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 28.7, 32.1, 58.6, 125.5, 128.1, 128.4, 138.0. – $C_{12}H_{16}O$ (176.3): calcd. C 81.77, H 9.15; found C 81.91, H 9.01.

10. *(1S*,2R*)-2-Butyl-1-phenyloxirane* (**24**): 176.4 mg (1.20 mmol) of trimethyloxonium tetrafluoroborate, 324.5 mg (0.97 mmol) of **7** and 190 mg (1.69 mmol) of potassium *tert*-butoxide were allowed to react as described above. MPLC furnished 99.5 mg (58%) of (1S*,2R*)-2-butyl-1-phenyloxirane (**24**) as a colorless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.9 Hz, 3 H), 1.34 (m, 6 H), 3.21 (dt, J = 5.8 and 4.5 Hz, 1 H), 4.08 (d, J = 4.3 Hz, 1 H), 7.20–7.38 (m, 5 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 26.3, 28.1, 57.4, 59.5, 126.5, 127.4, 127.9, 135.8. – $C_{12}H_{16}O$ (176.3): calcd. C 81.77, H 9.15; found C 81.58, H 9.08.

11. *1-Phenylhexanol* (**21, 23**): A solution of 170.0 mg (0.51 mmol) of **6** obtained from the experiment described under 2. and 610 mg (1.7 mmol) of triphenyltin hydride in 5 ml of degassed toluene was refluxed for 12 h. 20 ml of ether and 10 ml of water were added. The phases were separated and the organic phase was washed with 10 ml of brine, dried with Na_2SO_4, and concentrated. The product was purified by MPLC (eluant: 8% ethyl acetate in petroleum ether) to furnish 75.7 mg (83%) of (−)-1-phenylhexanol (**21**). – ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.7$ Hz, 3H), 1.20–1.48 (m, 6H), 1.61–1.84 (m, 2H), 1.94 (d, $J = 3.3$ Hz, 1H), 4.63 (m, 1H), 7.22–7.35 (m, 5H). – $[\alpha]_D^{20} = -30.9$ ($c = 2.35$, cyclohexane). Cf. ref.[22]: $[\alpha]_D^{20} = 22.9$ (65% e.e.).

Likewise, 390 mg of the polar product fraction obtained under 2. containing ca. 80 mg (0.23 mmol) of **7** was reduced with 1.00 g (2.84 mmol) of triphenyltin hydride to give 33.5 mg (80%) of (+)-1-phenyl-1-hexanol (**23**). – $[\alpha]_D^{20} = 33.1$ ($c = 2.42$, cyclohexane).

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