106. Enantioselective Synthesis of (+)- and (−)-*cis*-2-Methyl-4-propyl-1,3-oxathiane and their Olfactive Properties

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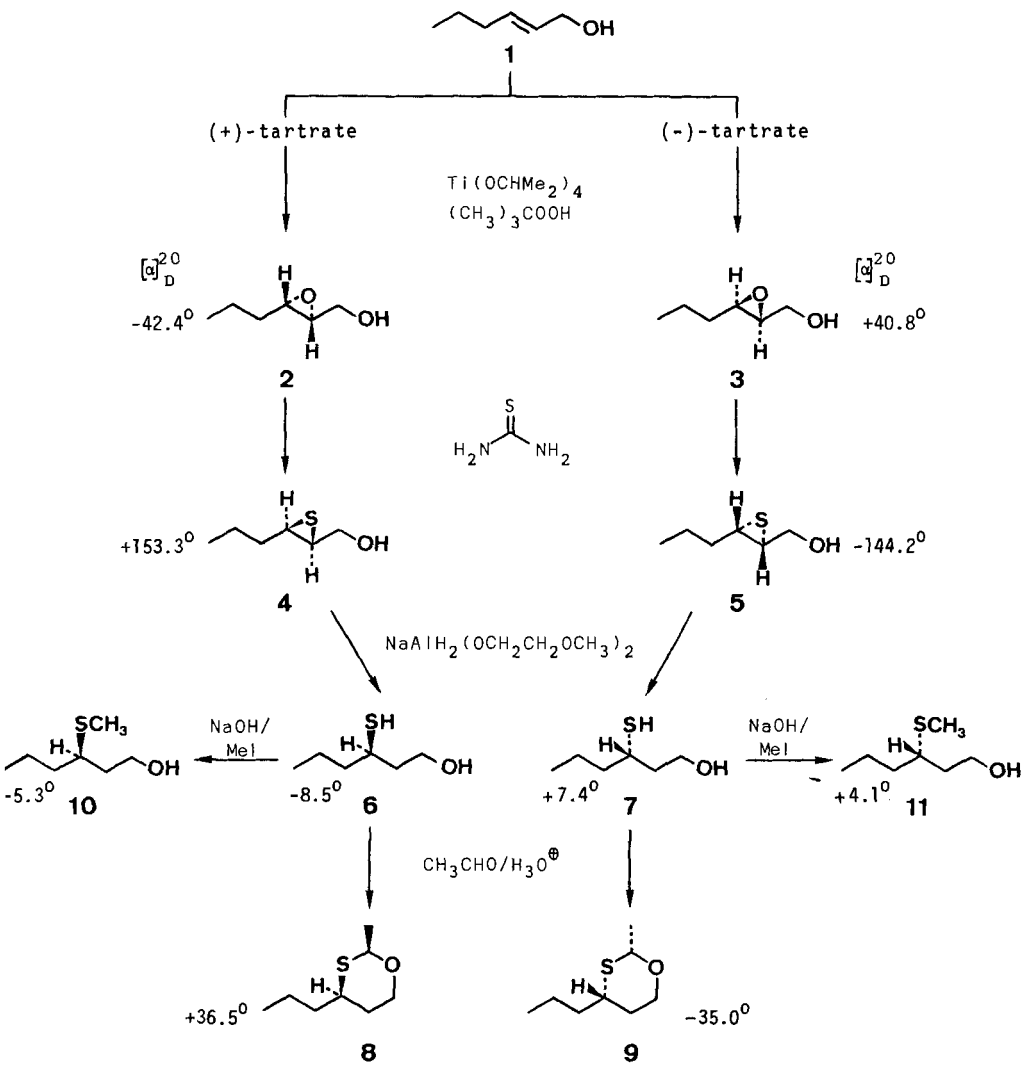
Summary

The enantioselective synthesis of (+)- and (−)-*cis*-2-methyl-4-propyl-1,3-oxathiane **8** and **9** from (*E*)-2-hexen-1-ol (**1**) as common starting material is described. The two enantiomeric forms exhibit different organoleptic properties.

2-Methyl-4-propyl-1,3-oxathiane (mixture of *cis*/*trans*-isomers, ratio *ca.* 10:1) has been isolated from the juice of the yellow passionfruit (*Passiflora edulis* f. *flavicarpa*) by *Winter et al.* [1]. Organoleptic tests of the synthetic racemic mixture established its importance as a key ingredient for the typical aroma of passionfruit and other types of flavors [2]. Due to insufficient quantities of isolated natural product, its absolute configuration has not yet been established. As part of our continuous interest in the relationship between chemical structure and olfactive properties [3], we prepared selectively from the same starting material the two enantiomers of *cis*-2-methyl-4-propyl-1,3-oxathiane (**8** and **9**, *Scheme 1*), under the epoxidation conditions of *Katsuki & Sharpless* [4] for induction of asymmetry.

Asymmetric epoxidation of (*E*)-2-hexen-1-ol (**1**) under the *Sharpless* conditions using diethyl (+)-tartrate led to (2*S*,3*S*)-2,3-epoxy-1-hexanol (**2**) and using diethyl (−)-tartrate [4] to its enantiomeric form **3**. Treatment of epoxides **2** and **3** with thiourea in the presence of H_2SO_4 and then by aqueous base [5] afforded the corresponding thiiranes **4** ($[\alpha]_D^{20} = +153.3°$) and **5**. The proposed mechanism of this reaction involves a *Walden* inversion at each asymmetric C-atom, and thus would lead to a thiirane of inverse absolute configuration. As no example was found in which an optically active epoxide has been used as substrate, we treated the (2*S*,3*S*)-2,3-epoxy-1-hexanol (**2**) with sodium thiocyanate, and obtained (2*R*,3*R*)-2,3-epithio-1-hexanol (**4**) ($[\alpha]_D^{20} = +128.5°$), with the same absolute configuration as the product from the reaction with thiourea. Because *Price & Kirk* [6] have shown that treatment of (+)-(2*S*,3*S*)-2,3-epoxybutane with potassium thiocyanate gives (−)-(2*R*,3*R*)-2,3-epithiobutane, involving a *Walden* inversion at both asymmetric C-atoms, our result confirms the proposed mechanism for the reaction with thiourea [5]. Under the acidic conditions of the reaction of **2** and **3** with thiourea, about 10% of 1,2-epithio-3-hexanol (**12**) was formed. The structure of **12** was established by its spectroscopical data and confirmed by independant synthesis. Under the neutral conditions of the reaction of **2** and **3** with

Scheme 1



sodium thiocyanate, **12** was not formed in detectable amounts. Its formation under acidic conditions can be explained by the formation of a 1,3-diol as intermediate in the proposed mechanistic scheme [5] *(Scheme 2)*, which then further reacts to either **4** involving the secondary OH-group, or to **12** involving the primary OH-group. Reduction of **4** and **5** with *Vitride*® (sodium bis(2-methoxyethoxy)aluminium hydride [7] [8]) in THF led to (*R*)-3-mercapto-1-hexanol (**6**) ($[\alpha]_D^{20} = -8.5°$) and its (*S*)-form **7** ($[\alpha]_D^{20} = +7.4°$), respectively. A small amount (7%) of 2-mercapto-1-hexanol was also formed under these conditions, and application of different reduction conditions led to differing proportions of 1,2- and 1,3-mercapto-alcohols *(Table 1)*.

Scheme 2

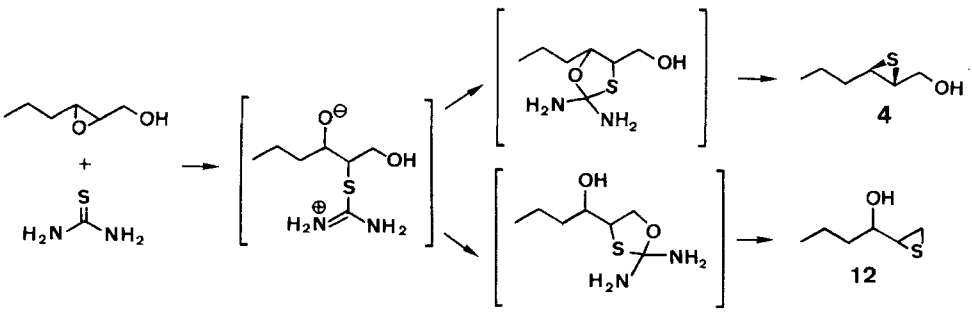


Table 1

Reducing agent	Solvent	Proportion 1,3-/1,2-mercapto-alcohols
$LiAlH_4$	Et_2O	1.2:1
$LiAlH_4$	THF	2.6:1
Vitride®	CH_2Cl_2	2.2:1
Vitride®	THF	13.0:1

These results show the same solvent and reducing-agent dependance on the regioselectivity for the reduction of 2,3-epithio-alcohols as described by *Viti* [8] for 2,3-epoxy-alcohols.

Compounds **6** and **7** were treated with acetaldehyde in the presence of TsOH to give a 9:1 mixture of the *cis*- and *trans*-2-methyl-4-propyl-1,3-oxathianes (**8** and **9**, respectively) which were purified by preparative GC. Treatment of **6** and **7** with NaOH in MeOH, followed by addition of MeI leads to (−)-(*R*)- (**10**) and (+)-(*S*)-3-methyl-thio-1-hexanol (**11**), respectively [9], compounds that occur also in the aroma of passionfruit.

Enantiomeric Purity. – The enantiomeric purity of the intermediates **2**–**11** during the synthesis was monitored using high-resolution NMR spectroscopy with $Eu(HFC)_3$ as shift reagent. *Table 2* indicates the differences in chemical shifts of pertinent signals for the enantiomeric forms of all intermediates. In all cases these differences were large enough to avoid overlapping of signals thus demonstrating unambiguously the enantiomeric purity of the products. Compounds **10** and **11** were optically impure having an e.e. of 52 and 78%, respectively[1]).

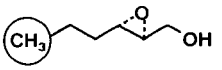
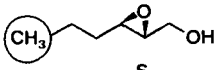
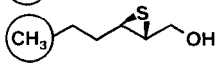
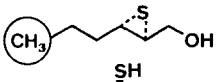
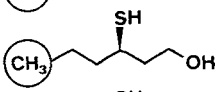
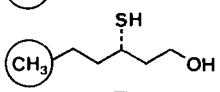
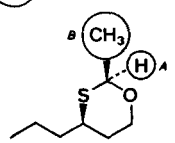
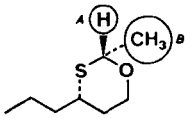
Organoleptic Properties of 8 and 9. – The compounds **8** and **9** are powerful odorants, the former having a detection threshold in water of 2 ppb and the latter 4 ppb[2]). The odor from a smelling strip[3]) is described for **8** as typical sulfurous with a rubbery

[1]) *Heusinger & Mosandl* [10] have synthesized these compounds in the optically pure form, starting from **6** and **7** which they obtained by chromatographic separation of the diastereomeric camphyl thioesters of racemic **6** followed by reduction. We thank Dr. *Mosandl* for sending us the manuscript prior to publication.

[2]) Determined by *A. Furrer* with a panel of 15–20 persons according to [11] taking 50% of the correct responses as the threshold value.

[3]) Perfumer panel of *Firmenich SA (A.F. Morris)*.

Table 2

Compound[a])		Shift without $Eu(HFC)_3$ [ppm]	Shift with $Eu(HFC)_3$ [ppm]	Shift difference $\Delta\Delta\delta$	Remarks
	**2**	0.97	1.50	+0.16	
	**3**	0.97	1.34	−0.16	
	**4**	0.97	1.40	−0.02	Fine triplet mixture of **4** and **5** gives a double triplet not baseline-resolved
	**5**	0.97	1.42	+0.02	Fine triplet
	**6**	0.92	1.30	−0.06	
	**7**	0.92	1.36	+0.06	
	**8**	4.81 *A* 1.47 *B*	4.86 1.54	−0.03	Clean *q* with no satellite from **9**
	**9**	4.81 *A* 1.47 *B*	4.89 1.56	+0.03	Clean *q* with no satellite from **8**

[a]) Corresponding signals encircled.

onion note; in addition there is a fruitness reminiscent of grapefruit peel, mango and passionfruit. Compound **9** is weaker, without the pronounced sulfur character, and possessing a fresh note with more iris character.

Tasting in water solution[4]) at 0.1 ppm showed that **8** was much stronger than **9**, having the typical sulfury notes of tropical fruits, whereas **9** was slightly camphoraceous, more woody and not very typical of tropical fruits. Tasting of **8** added at 0.5 ppm to a synthetic passionfruit flavor containing no other sulfur compounds in a sugar/acid tasting solution showed typical tropical fruit, passionfruit, sulfury notes, whereas addition of **9** at the same and elevated concentrations gave flat estery notes without the typical character of passionfruit.

[4]) Flavorist panel of *Firmenich SA (A. Y. Smith)*. We are indebted to these groups for their collaboration.

Experimental Part

General. The experimental details are identical for both enantiomeric series, so only one is described. Specific rotations ($[\alpha]_D^{20}$) were measured in $CHCl_3$ at 20° with a *Perkin-Elmer 141* polarimeter. GC: *Carlo-Erba 4160*, equipped with a 50 m × 0.27 mm glass-capillary column coated with *UCON HB 5100*. Prep. GC: *Carlo-Erba GT 200*, column 2.7 m × 4 mm, 3% SOMB on *Chromosorb*, 80–100 mesh. ^{1}H-NMR: *Bruker WH 360* (360 MHz); the spectra were recorded in $CDCl_3$ with TMS (δ = 0.00 ppm) as internal standard. Mass spectra (MS) were recorded on a *Finnigan MAT* quadrupole instrument, and fragments are quoted as *m/z* (% relative abundance).

(2S,3S)-2,3-Epoxy-1-hexanol (**2**). Under the same conditions as described in [4] the following compounds were added to 1 l CH_2Cl_2 *(Fluka, puriss.)*: 28.4 g (0.1 mol) of titanium tetraisopropoxide *(Fluka)*, 20.6 g (0.1 mol) of diethyl L(+)-tartrate *(Fluka, purum)*, 10 g (0.1 mol) of (*E*)-2-hexen-1-ol (**1**), 55 ml of a 4M solution of *tert*-butylhydroperoxide (TBHP) in CH_2Cl_2. The yellow solution was stored for 3 days at −30°. 250 ml of 10% aq. tartaric acid was added at −25° and the mixture was treated as in [4]. The excess TBHP was reduced by stirring with 10 ml of 10% aq. Na_2SO_3 solution for 1 h at r.t. After concentration, the remaining oil was rediluted with 750 ml Et_2O and stirred for 90 min at 0° with 300 ml of 1N NaOH. After separation, the aq. phase was extracted once with Et_2O, the combined org. phases were washed with brine, dried over anh. Na_2SO_4 and the solvent removed by distillation through a 10-cm *Vigreux* column to leave 12.0 g. Distillation through a 10-cm *Vigreux* column gave 6.0 g (52%) of a colorless liquid; b.p. 82–86°/12 Torr, $[\alpha]_D^{20}$ = −42.4° (*c* = 0.99). ^{1}H-NMR: 0.96 (*t*, *J* = 7, 3H), 1.42–1.60 (*m*, 4H); 1.80 (br. *s*, 1H); 2.90–3.00 (*m*, 2H); 3.66 (*m*, 1H); 3.94 (br. *d*, 1H). MS: 126 (0, M^+), 101 (trace), 73 (24), 57 (22), 55 (100), 44 (29), 43 (65), 41 (47).

(2R,3R)-2,3-Epithio-1-hexanol (**4**). To a vigorously stirred dispersion of 6.75 g (0.089 mol) of thiourea in 34 ml of H_2SO_4 (15% in H_2O) at 0° were added dropwise 10.3 g (0.089 mol) of **2** at 0 to 5°. The thiourea dissolves as the reaction proceeds. After completion of the addition, the solution was stirred 10 min at 5°, then allowed to warm up to r.t. After hydrolysis with 10% aq. Na_2CO_3, the resulting layers were separated, the aq. phase was extracted three times with Et_2O, the combined Et_2O-extracts were washed with brine, dried (Na_2SO_4) and the solvent was removed. The residue was distilled through a 10-cm *Vigreux* column to yield 5.2 g (44%) of **4**. GC analysis revealed *ca.* 10% of a compound whose spectroscopic data corresponded to 1,2-epithio-3-hexanol (**12**). A sample of **4** was purified by prep. GC. $[\alpha]_D^{20}$ = +153.3° (*c* = 1.18). ^{1}H-NMR: 0.96 (*t*, *J* = 7, 3H); 1.46–1.60 (*m*, 4H); 1.74–1.86 (*m*, 1H); 2.86 (*q*, *J* = 7, 1H); 3.0 (*q*, *J* = 5,5, 1H); 3.64–3.74 (*m*, 1H); 3.86–3.97 (*m*, 1H). MS: 132 (87, M^+), 101 (43), 99 (28), 85 (27), 81 (34), 73 (37), 67 (52), 59 (68), 57 (100), 55 (63), 45 (64), 43 (38), 41 (92).

Treatment of **2** *with Sodium Thiocyanate.* A mixture of 96 mg of **2**, 120 mg of sodium thiocyanate and 80 mg of H_2O was stirred for 30 h at r.t. After addition of 2 ml of H_2O, the mixture was extracted three times with Et_2O and the org. phases were washed with brine and dried (Na_2SO_4). After distillation of the solvent, the residue was purified by prep. GC. $[\alpha]_D^{20}$ = +128.5° (*c* = 0.21). ^{1}H-NMR and MS were identical with those of **4**.

(R)-3-Mercapto-1-hexanol (**6**). To a cooled solution (−15°) of 9.5 g (0.047 mol) of *Vitride*® in 75 ml of THF, 2.5 g (0.019 mol) of **4** in 75 ml of THF was added slowly under a flow of N_2. The mixture was stirred for 1 h at −15°, warmed to r.t. and poured onto ice-water. The aq. phase was separated, filtered and extracted twice with Et_2O. The combined org. phases were washed with brine, dried (Na_2SO_4) and concentrated. Yield: 0.95 g. A sample was purified by prep. GC for analysis. $[\alpha]_D^{20}$ = −8.5° (*c* = 0.8). ^{1}H-NMR and MS were identical with those described in [1].

(2S,4R)-2-Methyl-4-propyl-1,3-oxathiane (**8**). A mixture of 2.75 g (0.02 mmol) of **6**, 35 ml of acetaldehyde and 0.5 g of TsOH was stirred in 100 ml of dry Et_2O over 40 g of molecular sieves 4 Å. After 90 min the reaction was complete. The mixture was decanted from the molecular sieves, washed with 5% aq. Na_2CO_3, brine, and dried (Na_2SO_4). After concentration over a 10-cm *Vigreux* column, 3.2 g residue remained. Short-path distillation yielded 2.4 g of an oil which was distilled through a 10-cm *Fischer* column to give 1.4 g of a main fraction consisting of 2 peaks (GC) (ratio 9:1). A sample of the major isomer was purified by prep. GC for analysis and organoleptic evaluation. $[\alpha]_D^{20}$ = +36.5° (*c* = 1.15). ^{1}H-NMR and MS data are identical with those described in [1] for the racemic product.

(R)-3-Methylthio-1-hexanol (**10**). To a cooled solution (0–5°) of 0.3 g (7.5 mmol) of NaOH dissolved in 0.5 ml of H_2O, diluted with 5 ml of MeOH and 1 g (7.5 mmol) of **6**, 1.06 g (7.5 mmol) MeI was slowly added. The mixture was poured into H_2O, after 4 h of refluxing the aq. phase was saturated with NaCl and extracted three times with Et_2O, washed once with brine and dried ($MgSO_4$) and concentrated. Yield: 0.5 g. A sample was purified by prep. GC for analysis. $[\alpha]_D^{20}$ = −5.3° (*c* = 0.9). ^{1}H-NMR and MS were identical with those described in [1].

(2RS,3RS)-1,2-Epithio-3-hexanol (**12**). To a vigorously stirred dispersion of 2.5 g (0.033 mol) of thiourea in 13 ml of H_2SO_4 (15% in H_2O) at 0° 4 g (0.034 mol) of 1,2-epoxy-3-hexanol (prepared by peracid epoxidation of 1-hexen-3-ol) were added dropwise at 0 to 5°. Then the mixture was treated as described for **4**, to yield 3.02 g (67%) of **12**. ^{1}H-NMR: 0.96 (*t*, *J* = 7, 3H); 1.43–1.65 (*m*, 4H); 2.39 (*t*, *J* = 6.6) and 2.47 (*d*, *J* = 6.8) (total 3H); 3.07–3.17 (*m*, 1H); 3.54 (*q*, *J* = 6) and 3.72 (*q*, *J* = 6) (total 1H). MS: 132 (46, M^+), 114 (16), 99 (52), 89 (75), 61 (100), 57 (98), 55 (95), 43 (89).

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