1-Methoxyhexane-3-thiol, a Powerful Odorant of Clary Sage (*Salvia sclarea* L.)

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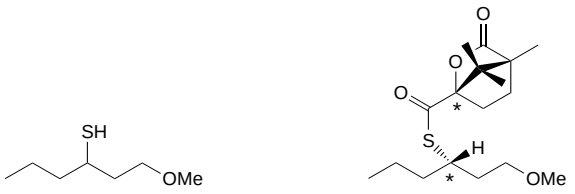
The peculiar and highly diffusive odor signal of flowering clary-sage plants (*Salvia sclarea* L.) was identified to derive from trace amounts of 1-methoxyhexane-3-thiol (**1**) by mass-spectrometry analysis and confirmed by comparison with synthetic racemic thiol (±)-**1**. The enantiomers (*S*)- and (*R*)-**1** were prepared by enantioselective synthesis, and the absolute configuration of (*S*)-**1** was fully corroborated by X-ray-diffraction analysis of the crystalline thioester (1′*S*,1*S*)-**2**. Compound (*S*)-**1** is one of the most powerful odorants known, with a detection threshold of $0.04 \cdot 10^{-3}$ ng/l air, and is, with its herbaceous-green, alliaceous, and perspiration profile, key to the fragrance of clary-sage flowers and of the freshly distilled essential oil. As a consequence of its unique odor, **1** was also suspected to be part of the volatiles of a *Ruta* species where it was subsequently identified together with its homologue, 1-methoxyheptane-3-thiol (**3**), 1-methoxy-4-methylpentane-3-thiol (**4**), and the known 4-methoxy-2-methylbutane-2-thiol (**5**). The syntheses of (±)-**3** and (±)-**4** as well as of the enantiomer (*R*)-**4** are described. In both natural fractions, the ratio (*S*)-**1**/(*R*)-**1** was slightly in favor of the (*S*)-enantiomer. Natural **4** has (*R*)-configuration.

1. Introduction. – Clary-sage (*Salvia sclarea* L.) fields in full blossom elicit a peculiar olfactory signal, both intriguing and repulsive, somewhat reminiscent of human axillary perspiration, and very distinct from the array of odors known and available to a perfumer in industry. Always attracted by novel and original scents, we became interested in this highly unusual top note. In a recent monograph on sage oils [1], *Boelens* and *Boelens* state that 'fresh plant material of *Salvia sclarea* has a strong, pungent and penetrating odor that is often disliked. This odor disappears during steam distillation and can not be recognized as the essential oil'. The monograph cites numerous references that report chemical and sensory evaluation of sage oils. Notably, *Maurer* and *Hauser* identified more than 250 chemical constituents in clary-sage oil (*S. sclarea* L.) [2a], but none of them is responsible for the pungent top notes [2b].

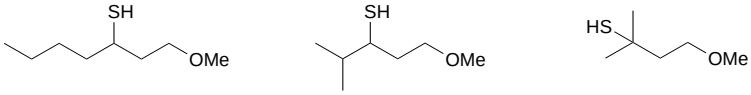
Serendipity brought us into contact with local farmers who cultivate clary sage for essential-oil production. When gently rubbing the flower panicles on a hot summer evening prior to harvest, the odor signal was strong and unambiguously recognized. The aqueous forerun from steam distillation of freshly cut aerial plant material produced a fraction which allowed isolation and identification of the target compound, 1-methoxyhexane-3-thiol (**1**), after a series of focussed separation steps combined with mass spectrometry and comparison with synthetic reference materials.

In this communication, we describe the isolation and identification of 1-methoxyhexane-3-thiol (**1**) as a new impact odorant from a steam distillate of *S. sclarea* L. The synthesis of racemic thiol (±)-**1** and its enantiomers is presented,

allowing the determination of the enantiomer ratio in the natural fractions; the absolute configuration of (*S*)-**1** is fully corroborated by X-ray-diffraction analysis of the crystalline thioester (1′*S*,1*S*)-**2**[1]). Because of the very peculiar odor characteristics of **1**, we subsequently became aware of its smell in other plants, and we document the presence of **1**, together with the related compounds **3**–**5**, in a solvent extract of a *Ruta* species[2]).



1 (1′*S*,1*S*)-**2**



3 **4** **5**

2. Results. – 2.1. *Identification of 1-Methoxyhexane-3-thiol* (**1**) *in Clary Sage.* Isolation of the target constituent **1** was achieved starting from the steam-distillation forerun of a 300-l batch of freshly cut plant material. The decanted oil layer (26.4 g), which consisted of 50% of linalyl acetate (= 3,7-dimethylocta-1,6-dienyl acetate) and 12% of linalool, was fractionally distilled *in vacuo*. Target odor fractions (> 90% linalyl acetate) were separated by medium-pressure LC (MPLC) on silica gel. Small amounts of linalyl acetate, which persisted and masked the target GC regions because of formation of elimination products, *i.e.*, 3,7-dimethylocta-1,3,6-triene and 7-methyl-3-methyleneocta-1,6-diene, were removed by chemical reduction and subsequently separated as linalool by MPLC (silica gel). The target odor remained unaffected by this operation. GC/MS Analysis on polar and apolar capillary columns revealed a small peak with the same and unreported mass spectrum. The respective retention indices corresponded well to those registered during repeated sniffing of a CH_2Cl_2 extract of fresh plant material, of the decanted oil layer, and of its fractions from packed GC columns. The key odor was particularly well perceived on a polar phase just ahead of (*Z*)-hex-3-en-1-ol. The available amount of material excluded isolation for NMR analysis, but comparison of its MS and retention indices on polar and apolar capillary column with those of authentic (±)-**1** (*vide infra*) established the structure **1** for the target constituent of clary sage. Structure **1** was given preference over the possible alternative **4** because hex-2-enal and hex-2-en-1-ol are known constituents in clary sage, in contrast to the corresponding branched compounds [2b][4][5].

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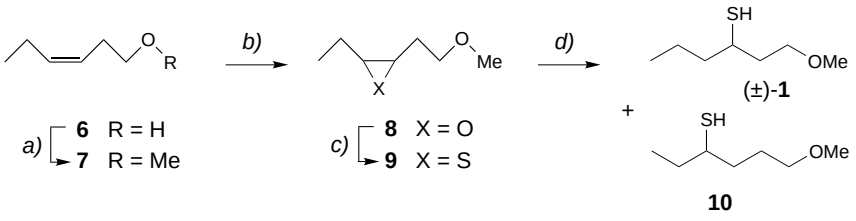
[1]) Systematic name: *S*-[(1*S*)-1-(2-methoxyethyl)butyl] (1*S*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbothioate ((1′*S*,1*S*)-**2**).

[2]) Parts of this communication are the subject of a patent application [3].

The highest mass fragment of the natural **1** was observed at *m/z* 148 (< 10%), and CI-MS confirmed it to represent M^+. Loss of 34 (*m/z* 114) suggested the presence of an S-atom in the form of a thiol. This hypothesis was substantiated by the fact that a fraction containing the target odor was also obtained after covalent chromatography on an organomercurial agarose gel [6], which is a method for specific enrichment of thiols. The presence of a tertiary thiol was excluded because no loss of SH ($[M-33]^+$) was observed. The base peak of **1** was at *m/z* 45 supporting, together with *m/z* 116 (loss of MeOH), the presence of a $MeOCH_2$ moiety. The fragment *m/z* 71 was assigned to $C_3H_4OMe^+$, formally generated upon elimination of H_2S from M^+, allylic rearrangement of the C=C bond, and allylic cleavage of the ion corresponding to 1-methoxyhex-1-ene. This is consistent with the SH group in position 1,3 relative to the MeO group. Finally, the fragment *m/z* 88 ($C_4H_8S^+$) was coherent with its generation by cleavage of the hexane chain next to the S-atom.

Authentic racemic thiol (±)-**1** was obtained in admixture with its regioisomer (±)-6-methoxyhexane-3-thiol (**10**) starting from (*Z*)-1-methoxyhex-3-ene (**7**), which, in turn, was prepared from the well known perfumery alcohol **6** (*Scheme 1*). Epoxidation of the C=C bond by 3-chloroperbenzoic acid in CH_2Cl_2 (→ **8**), subsequent opening of the oxirane ring of **8** by thiourea, followed by removal of urea from the intermediate thiouronium salt under alkaline conditions [7], afforded thiirane **9** in good yield. Reduction of **9** with $LiAlH_4$ proceeded unselectively and gave a 2:1 mixture of the two regioisomers (±)-**1** and **10** that were separated by MPLC (silica gel). The structures of (±)-**1** and **10** were unambiguously assigned by their ^{1}H-NMR data (see *Exper. Part*). Isomer **4**, the synthesis of which is outlined in *Sect. 2.3* (*vide infra*), indeed had a very similar MS but was different with respect to retention indices (and odor!) from natural **1** and authentic racemic thiol (±)-**1**.

Scheme 1

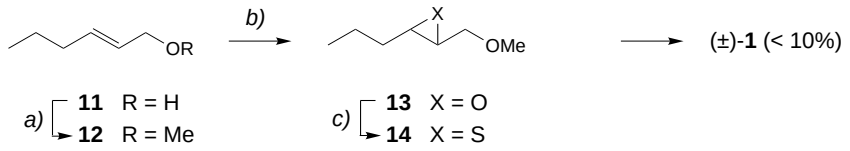


a) NaH, MeI, THF. *b*) 3-Chloroperbenzoic acid, CH_2Cl_2. *c*) 1) Thiourea, aq. H_2SO_4 soln., pH 2; 2) 10% Na_2CO_3 soln., pH 10. *d*) $LiAlH_4$, THF, reflux.

In an attempt to increase the regioselectivity of the thiirane reduction by assistance of the O-function, *trans*-2-(methoxymethyl)-3-propylthiirane (**14**) was prepared from alcohol **11** *via* methyl ether **12** and oxirane **13**, in analogy to the synthesis of thiirane **9** (*Scheme 2*). However, reduction of **14** with a variety of hydride donors and under different reaction conditions led to complex mixtures, from which (±)-**1** was isolated in only very low yield.

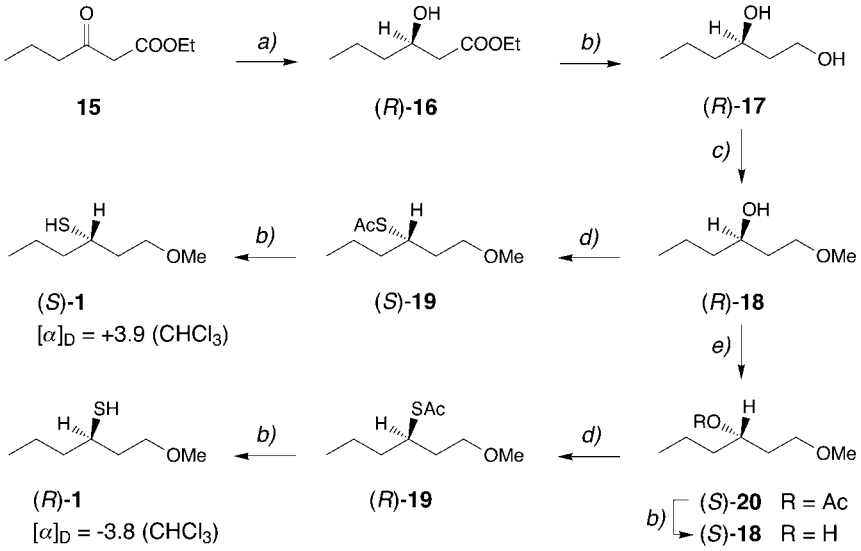
2.2. *Absolute Configuration of Natural 1-Methoxyhexane-3-thiol* (**1**). The two enantiomers of racemic thiol (±)-**1** were separated on a modified β-cyclodextrin GC capillary column (*BetaDex*™*-225*) as proposed by *Mosandl* and co-workers. for related

Scheme 2



a) NaH, MeI, THF. *b*) 3-Chloroperbenzoic acid, CH_2Cl_2. *c*) 1) Thiourea, aq. H_2SO_4 soln., pH 2; 2) 10% Na_2CO_3 soln., pH 10.

Scheme 3



a) Baker's yeast. *b*) $LiAlH_4$, Et_2O. *c*) KH, MeI, THF. *d*) Ph_3P, diisopropyl azodicarboxylate, AcSH, THF. *e)* Ph_3P, diisopropyl azodicarboxylate, AcOH, THF.

compounds [8]. The enantioselective synthesis of (*S*)- and (*R*)-**1** was accomplished by a strategy described by *Küntzel* and *Fráter* [9] (*Scheme 3*).

The key intermediate (*R*)-**18** was prepared in moderate yield by yeast-mediated reduction of ethyl 3-oxohexanoate (**15**) [10], *via* hydroxy ester (*R*)-**16** and diol (*R*)-**17**, followed by methylation of the latter with KH/MeI. The enantiomer excess (ee) of (*R*)-**18** was 96.6% as measured by ^{1}H-NMR of its *Mosher* ester [11]. *Volante* modification [12] of the *Mitsunobu* inversion procedure [13] converted (*R*)-**18** to (*S*)-**19**, which was reduced with $LiAlH_4$ to (*S*)-**1**. The ee of this material was estimated to be $>95\%$ by means of chiral GC (*vide supra*), whereas its *Mosher* ester [11] did not allow discrimination from the corresponding diastereoisomer obtained from (*R*)-**1** (see *Exper. Part*). (*S*)-**18** was obtained from (*R*)-**18** *via Mitsunobu* inversion followed by reduction of acetate (*S*)-**20**. The optical-rotation data of (*S*)-**18** mirrored well those of (*R*)-**18** (see *Exper. Part*). The ee of the *Mosher* ester of (*S*)-**18** was 95.5% (^{1}H-NMR). Further transformation of (*S*)-**18** proceeded as described for (*R*)-**18** and afforded (*R*)-**1**

with >95% ee (chiral GC). The ^{1}H-NMR spectrum of the *Mosher* ester of (*R*)-**1** confirmed an ee of 96%. The natural **1** isolated from clary sage gave rise to two peaks in a ratio of 60:40 on chiral GC. The earlier and major peak corresponded to (*S*)-**1**, the later and minor one to (*R*)-**1**, as shown by co-elution experiments with the synthetic reference samples.

The absolute configurations of (*S*)- and (*R*)-**1** were confirmed by resolution of racemic thiol (±)-**1**. Thus, reaction of (±)-**1** with (−)-(1*S*)-camphanoyl chloride in the presence of *N*,*N*-dimethylpyridin-4-amine afforded the diastereoisomeric thioesters (1′*R*,1*S*)- and (1′*S*,1*S*)-**2** (1:1 mixture) in 95% yield. Separation was effected by HPLC and, due to the higher crystallinity of (1′*S*,1*S*)-**2**, a sample was amenable to analysis by X-ray diffraction. The structure of (1′*S*,1*S*)-**2** is illustrated in the *Figure*. Reduction of (1′*R*,1*S*)- and (1′*S*,1*S*)-**2** with $LiAlH_4$ then afforded pure samples of (*R*)- and (*S*)-**1**, respectively, the optical rotations of which were identical with those recorded above.

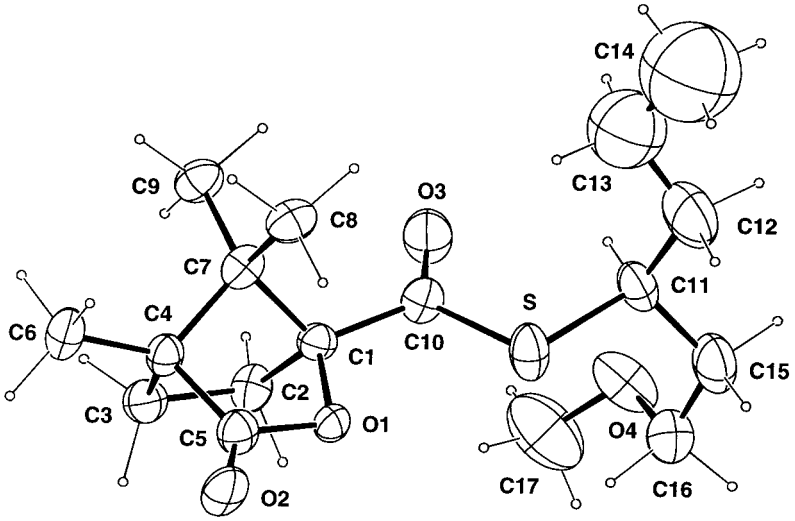


Figure. *Perspective view of the crystal structure of (1′S,1S)-***2** *with the atom numbering* (arbitrary). Ellipsoids are represented with 30% probability. For clarity, only the majoritarian (70%) disordered C(14) atom is represented.

2.3. *Identification of* **1** *and* **3**–**5** *in* Ruta *Species*[3]). The diffusive and pungent odor of twigs of a wild growing *Ruta* species (*R. chalepensis* L., sampled near San Gimigniano, Italy, in October 1999) was strongly reminiscent of 1-methoxyhexane-3-thiol (**1**). The GC of the CH_2Cl_2 extract of the plant material gave rise to several peaks arising from S-containing compounds (S-specific FPD detector). A thiol fraction was isolated by covalent chromatography [6], in which, by comparison with authentic samples, GC/MS clearly revealed the presence of **5** [15] and **1**. A third component, which was eluted before **1** and gave rise to a strikingly similar MS, was confirmed to be isomer **4** (!), which had been considered together with **1** as a hypothesis for the target molecule in clary sage.

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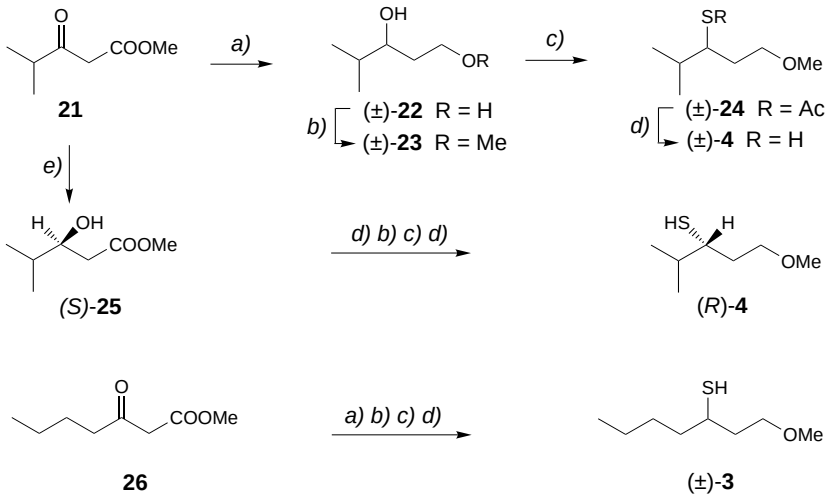
[3]) For recent analyses of essential oils of *Ruta* species, see [14].

Racemic thiol (±)-**4** was synthesized starting from methyl 4-methyl-3-oxopentanoate (**21**) (*Scheme 4*). Hydride reduction gave diol (±)-**22**, which was monomethylated to (±)-**23** in moderate yield. Introduction of the thioacetate function by the *Volante* reaction [12] proceeded poorly, and the conversion (±)-**23** → (±)-**24** was more efficient under the conditions described by *Hojo et al.* [16]. Reduction of (±)-**24** with $LiAlH_4$ then yielded thiol (±)-**4**. Enantiomer (*R*)-**4** (> 95% ee) was prepared *via* yeast-mediated reduction of keto ester **21** to (*S*)-**25** [17].

Scheme 4



a) 1) $NaBH_4$, EtOH; 2) $LiAlH_4$, Et_2O. *b*) KH, MeI, THF. *c*) 1,3-Dimethyl-2-fluoropyridinium 4-methylbenzenesulfonate, Et_3N, AcSH, acetone/benzene. *d*) $LiAlH_4$, Et_2O. *e*) Baker's yeast.

Compared to **1**, **4**, and **5**, the fourth S-component was present but in trace amounts and had a molecular weight of 162. The MS fragmentation pattern (*m/z* 130, 128, 102, 88, 71, and 45) suggested that the unknown was a homologue of **1**. Comparison of GC/MS data with those of a synthetic sample of racemic thiol (±)-**3** (prepared from methyl 3-oxoheptanoate (**26**); see *Scheme 4*) fully confirmed this hypothesis. The ratio **1**/**4**/**5** in the natural extract was estimated as 1 : 2 : 10, and the enantiomer ratio (*S*)-**1**/(*R*)-**1** was 70 : 30 as shown by chiral GC (*vide supra*). The absolute configuration of natural **4** was (*R*).

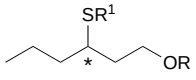
Commercial rue oils of Spanish origin are produced mainly from *R. graveolens* L. Depending on the quality of these essential oils, some were shown to contain the most abundant of these S-compounds, **5**, as verified by GC/MS experiments, whereas traces of **1** were perceived by GC/sniffing.

3. Discussion. – The sensory impression of a concentrated (0.1%) solution of the racemic thiol (±)-**1** is overpowering. Upon dilution, the individual odor qualities emerge, and that of (±)-**1** becomes different from those of the enantiomers. At 1 ppm dilution in diethyl phthalate, (±)-**1** evokes best the odor impression of the fresh plant material: sulfury, herbaceous, green, exceedingly strong, diffusive, and key to natural

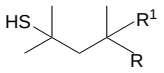
clary sage. Use levels of (±)-**1** in perfume compositions are typically in the order of 200 ppb and impart a natural sage tonality. For many panelists, (±)-**1** is extremely pungent and repulsive, even at low concentrations. The flavor of (±)-**1** in H_2O (0.5 ppb) is characterized as green and tropical fruit. In addition to herbaceous and sage odor tonalities, (*S*)-**1** has strong connotations of burnt sulfur and alliaceous notes, and evokes associations with human axillary perspiration. (*R*)-**1** is perceived as sulfury, herbaceous, and onion-like and definitely lacks the unique clary-sage signal. The detection thresholds of the series were measured in air by olfactometry [18][4]). With $0.04 \cdot 10^{-3}$ ng/l air, the detection threshold of (*S*)-**1** is among the lowest ever recorded, and is 25 times lower than that of (*R*)-**1** ($1.09 \cdot 10^{-3}$ ng/l air). Thiol (±)-**1** has a threshold of $0.36 \cdot 10^{-3}$ ng/l air.

The related constituents **3** and **4** from *Ruta* encountered less sensory interest. The odor threshold of the higher homologue of (±)-**1**, *i.e.*, the synthetic thiol (±)-**3**, has an odor threshold in air of $0.82 \cdot 10^{-3}$ ng/l. At equal dilution (1 ppm), synthetic thiol (±)-**3** smells more onion-like and is less diffusive than (±)-**1**, whereas its flavor (0.01 ppm) is characterized as tropical-fruit-like, sulfury, and lingering. At 1 ppm, the odors of synthetic thiols (±)-**4** and (*R*)-**4** are weak (odor threshold of (±)-**4** in air $4.30 \cdot 10^{-2}$ ng/l) and lack character. The flavor of (±)-**4** at 0.01 ppm is reminiscent of tropical fruit, is alliaceous and rubber-like. Both **3** and **4** are new compounds.

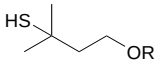
The 1-methoxyhexane-3-thiol (**1**) is a member of intensely odorous flavor molecules having in common a 1,3-positioned O,S moiety [19]. In 1976, the first members of this series of compounds, *i.e.*, 3-(methylthio)hexan-1-ol (**27**) and *Oxane*® (= *cis*- and *trans*-2-methyl-4-propyl-1,3-oxathiane; **28**), were reported by *Winter et al.* as key-impact constituents in the juice of yellow passion fruit [20], which has proven to be a rich source for similar compounds [21][22]. Among these, 3-mercaptohexyl acetate (**29**) also contributes to the varietal aroma of *Sauvignon* white wines [23], together with **31** [24], **30**, **32**, and **33** [25]. Recently, the presence of 3-mercapto-2-methylpentan-1-ol (**34**) in raw onion has been discovered by *Pickenhagen* and co-workers [26], and, at low concentrations, **34** is reported to impart a broth-like, slightly sweaty, onion-like, and leek-like flavor profile. The (2*R*,3*S*)-enantiomer of **34** has an odor threshold in air of



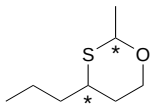
27 R = H, R^1 = Me
29 R = Ac, R^1 = H
30 R = R^1 = H



31 R, R^1 = O
32 R = OH, R^1 = H



33 R = H
35 R = CHO
5 R = Me



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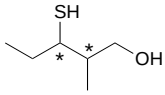

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[4]) We are indebted to Dr. *C. Vuilleumier, Firmenich SA*, for the experiments.

$0.07 - 0.2 \cdot 10^{-3}$ ng/l! Another member of this series of compounds, 3-mercapto-3-methylbutyl formate (**35**), has been identified, together with **33**, in the aroma of roasted coffee [27]. The only methoxy derivative known in this series is the impact chemical of blackcurrant buds, 4-methoxy-2-methylbutane-2-thiol (**5**) [15], which also has been identified in olive oil [28], in green tea [29], and now in *Ruta* species.

The 1-methoxyhexane-3-thiol (**1**) has not been reported to occur in nature[5]), and in commercial samples of clary-sage oil, we were neither able to perceive **1** (GC/sniffing) nor to demonstrate the presence of the corresponding MS. Albeit in even weaker concentrations, the presence of **1** was confirmed in a distillation forerun obtained from the same local farmers more recently. Fractionation of this material allowed access to a more detailed chemical profile of the volatile fractions. Among other constituents identified, the presence of the methyl ethers derived from (*Z*)-hex-3-en-1-ol, (**6**), hexan-1-ol, and linalool is of interest. The latter two derivatives are rarely encountered in essential oils, whereas, to the best of our knowledge, the methyl ether **7** has never been reported as a naturally occurring molecule. A biosynthetic route to **1** may involve *Michael* addition of a S-nucleophile [26a][30] to hex-2-enal, followed by reduction of the aldehyde and methylation of the intermediate. However, neither 3-mercaptohexanal nor **30** was perceived in our sage fractions after calibration of the respective retention times on packed GC columns with authentic samples.

We have some evidence that **1** may occur more often in nature than initially expected. Thus, the presence of **1** was clearly recognized by GC/sniffing in a steam distillate of wild growing *Mentha longifolia* L. and also suspected in a CH_2Cl_2 extract of freshly collected tomato sprouts (*Lycopersicon esculentum* MILL.).

The absolute configuration of the predominant enantiomer of **1** from both *S. sclarea* L. and *Ruta* is (*S*), which is the same as the absolute configuration established for **30** and its derivatives from passion fruit [8b][31]. In contrast to the analogous compounds isolated from passion fruit, the observed enantiomer ratios of (*S*)-**1**/(*R*)-**1** are low: in clary sage 60:40 and in the *Ruta* extract 70:30. The absolute configuration of natural thiol **4** is (*R*), in accordance with addition of the S-nucleophile to the precursors of **1** and **4** from the same face.

Experimental Part

General. Commercially available reagents and solvents of adequate quality were used without further purification. Reactions were carried out under Ar. Org. extracts were washed to neutrality with aq. H_2SO_4 soln. and/or $NaHCO_3$ and NaCl soln., dried (Na_2SO_4), and evaporated. Flash chromatography (FC): silica gel *60*, 35–70 μm (*SDS*). MPLC: prepacked silica gel *Lobar*® columns (*Merck*), size *B* (70 g) or size *C* (220 g); *Ismatec Instruments* medium-pressure pump. Anal. GC: *Hewlett-Packard-5890-II* instrument; He as carrier gas; fused-silica capillary columns *SPB-1*, *Supelcowax®10* (= *SPWax*), and *BetaDex™-225*, each 30 m × 0.25 mm i.d. with 0.25 μm film (all from *Supelco*); fused-silica capillary column *CP-Chirasil-Dex CB*, 25 m × 0.25 mm i.d. with 0.25 μm film (from *Chrompack*). The S-specific GC detector *Fison FPD-80* failed to record the target peak of the natural sage fractions, but was sufficiently sensitive for the work with the *Ruta* extract. The retention indices (*I*) were determined relative to the retention times (t_R) of a series of *n*-alkanes with linear interpolation by means of a standard GC temp. program (50° for 5 min, then 5°/min to 240°, and 20 min at 240°). Prep. GC: *Varian Star 3600* equipped with glass columns and heated sniffing ports (200°); 5% *SP-1000* or *FFAP* on

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[5]) Compound **1** has the CAS registry number 94291-50-6, but there is no reference in the generally accessible literature.

Supelcoport (100/120 mesh) and 10% *OV101* on *Supelcoport* (80/100 mesh) (all from *Supelco*). Optical rotations: *Perkin-Elmer 241* polarimeter; cell thermostatted at 20°; α_D ($l = 0.1$, neat) and/or $[\alpha]_D$ (c, solvent). IR Spectra: *HP-5890-II-GC* instrument connected to a *HP-5965B-IR* detector; $\tilde{\nu}$ in cm^{-1}. ^1H-, ^{13}C-, and ^{19}F-NMR Spectra: *Bruker-AMX-360* spectrometer; in $CDCl_3$; δ values in ppm downfield from Me_4Si (= 0 ppm), J in Hz; assignments by COSY45 and HMCQ experiments. EI-MS: *HP-5890-II* or *6890-GC* system coupled with a *HP-MSD-5972* or *-5973* quadrupole mass spectrometer; electron energy *ca.* 70 eV; fragment ions *m/z* (rel. int. in % of the base peak). CI-MS: *Finnigan MAT-4500* quadrupole instrument.

1. *Isolation of 1-Methoxyhexane-3-thiol* (**1**) *from* S. sclarea L. The plants were cultivated by local farmers for essential-oil production near the village of Bassins (canton of Vaud, Switzerland). The aerial parts were harvested and steam-distilled in batches of *ca.* 300 l on August 1, 1996. A 2-l aq. forerun was collected at the beginning of the distillation of an intermediate batch from which an oily layer (26.4 g) was decanted (= *Fr. A*). By prep. GC/sniffing of *Fr. A*, the target note was unmistakably perceived, both on polar and apolar phase. Part of *Fr. A* (15.8 g) was distilled in a *Teflon*®-lined still (*Fischer*) under reduced pressure, and the fractions were monitored by prep. GC/sniffing. Odor-positive material was combined (= *Fr. A-1*; 2.42 g; 60–100°/15 mbar), and part (1.47 g) of this material was submitted to MPLC (size *B*, pentane/Et_2O 96:4). The combined odor-positive fraction (*Fr. A-11*; solvent only partially distilled off) was consistently accompanied by small amounts of linalyl acetate. Under GC/MS conditions, linalyl acetate gave rise to minor amounts of the elimination products 3,7-dimethylocta-1,3,6-triene and 7-methyl-3-methyleneocta-1,6-diene, which, on *SPWax*, were eluted in the target region and thus masked the target MS. In a preliminary experiment, it was shown that treatment of the mixture with $LiAlH_4$ did not destroy the target odor. Therefore, *Fr. A-11* was slightly diluted with Et_2O, and the soln. was exposed for 1 h to a few mg of $LiAlH_4$ to reduce the linalyl acetate. After hydrolysis with ice-water and workup with Et_2O, the resulting mixture was chromatographed under the same conditions as above. The target fraction (*Fr. A-111*) was now obtained free of linalool and of its acetate. *Fr. A-111* (only partially concentrated) was used for GC/MS experiments. On both *SPWax* and *SPB-1* columns, a small peak was detected with the same characteristic and unreported MS. The respective retention indices corresponded to the ones registered during repeated prep. GC/sniffing: $I_{SPB\text{-}1}$1041 and I_{SPWax}1360; *cf.* I_{SPWax}(hexan-1-ol) 1342 and I_{SPWax}((*Z*)-hex-3-en-1-ol; **6**) 1370. CI-MS (NH_3): 166 (100). Retention indices (*SPWax* and *SPB-1*) and EI-MS were in agreement with a synthetic sample of (±)-**1**, but in disagreement with (±)-**4**.

2. *Absolute Configuration of Natural* **1**. In analogy to [6], a *Pasteur* pipette was loaded with *Affi-Gel 501* (*Bio-Rad*; 3 ml). This organomercurial agarose gel was conditioned with ^{i}PrOH (5 ml) followed by CH_2Cl_2 (5 ml). *Fr. A-1* (300 mg) was applied in CH_2Cl_2 (1 ml), and the bed was eluted with further CH_2Cl_2 (20 ml). The thiol fraction was then removed from the gel by eluting with 10 mM 1,4-dithioerithreitol in CH_2Cl_2 (5 ml). This fraction (strong smell of **1**) was carefully concentrated and passed through a plug of SiO_2 (3 g) with pentane/Et_2O 95:5. The resulting material (*A-1S*) was analyzed by GC/MS (*BetaDex*™*-225*; 40° for 5 min, then 0.5°/min to 80°). Two peaks in a ratio 60:40 were observed after 67 min of elution whose MS were identical with that of (±)-**1**. The first peak arouse from (*S*)-**1** (t_R 67.8 min), the second one from (*R*)-**1** (t_R 68.1 min), as established by coelution with synthetic (*S*)- and (*R*)-**1**, resp.

3. *Racemic Thiol* (±)-**1**. 3.1. *(Z)-1-Methoxyhex-3-ene* (**7**). To a *ca.* 80% suspension of NaH (17.16 g, *ca.* 572 mmol) in THF (600 ml), MeI (84.80 g, 596 mmol) was rapidly added. A soln. of (*Z*)-hex-3-en-1-ol (**6**; obtained from the plant, 52.0 g, 520 mmol) in THF (200 ml) was added dropwise (caution: delayed strongly exothermic reaction). The mixture was temporarily cooled in an ice-bath to maintain the internal temp. < 35°. After complete addition (35 min), the mixture was stirred at r.t. overnight (→ white voluminous precipitate). The mixture was then cautiously poured onto ice-water to destroy unreacted NaH. After workup (Et_2O), the solvent was removed under normal pressure and the residue fractionated over a 15-cm *Vigreux* column: **7** (39.83 g, 67%). B.p. 90–95°/15 mbar. ^1H-NMR: 5.48, 5.34 (2 *m*, H–C(3), H–C(4)); 3.38 (*t*, $J = 7.1$, 2 H–C(1)); 3.36 (*s*, MeO); 2.33 (*q*, $J = 7.1$, 2 H–C(2)); 2.06 (*quint.*, $J = 7.5$, 2 H–C(5)); 0.97 (*t*, $J = 7.5$, 3 H–C(6)). MS: 115 (1, $[M+1]^+$), 82 (7), 67 (48), 45 (100).

3.2. *(±)*-cis-*2-Ethyl-3-(2-methoxyethyl)oxirane* (**8**). A soln. of **7** (27.36 g, 240 mmol) in CH_2Cl_2 (850 ml) was cooled in an ice-water bath to 10°. While stirring, *ca.* 70% 3-chloroperbenzoic acid (62 g, *ca.* 252 mmol) was added portionwise. The mixture was stirred at r.t. overnight. After workup (CH_2Cl_2), the org. layer gave a negative peroxide test. The crude residue was distilled (*Vigreux* column): **8** (24.87 g, 79.7%). B.p. 51–52°/15 mbar. ^1H-NMR: 3.55 (*dd*, $J = 6.7$, 5.5, CH_2O); 3.37 (*s*, MeO); 3.05 (*m*, H–C(3)); 2.90 (*m*, H–C(2)); 1.79 (*m*, CH_2–C(3)); 1.55 (*m*, CH_2–C(2)); 1.13 (*t*, $J = 6.2$, *Me*CH_2). ^{13}C-NMR: 70.09 (*t*, CH_2O); 58.81 (*q*, MeO); 58.15 (*d*, C(2)); 54.82 (*d*, C(3)); 28.39 (*t*, *C*–C(3)); 21.23 (*t*, *C*–C(2)); 10.49 (*q*, *Me*CH_2). MS: 129 (1, $[M-1]^+$), 115 (1, $[M-Me]^+$), 99 (4, $[M-MeO]^+$), 85 (26, $[M-MeOCH_2]^+$), 72 (16), 67 (12), 59 (26), 45 (100), 41 (68).

3.3. *(±)*-cis-*2-Ethyl-3-(2-methoxyethyl)thiirane* (**9**). Adapted from [7]: To a stirred ice-cooled soln. of thiourea (14.53 g, 191 mmol) in H_2O (66 ml) and conc. H_2SO_4 soln. (4.7 ml), **8** (24.85 g, 191 mmol) was added dropwise during 20 min. The mixture was allowed to warm to r.t., and the clear soln. (pH 2) was stirred overnight. After cooling in an ice-water bath, the pH of the mixture was adjusted to 10 with 10% aq. Na_2CO_3 soln. (106 ml). Heating the mixture at 40° for 40 min effected complete removal of urea from the intermediate thiouronium salt. After workup (Et_2O), the crude product was distilled (*Vigreux* column): **9** (25.01 g, 89.7%). Colorless liquid. B.p. 69–73°/15 mbar (99.1% pure by GC). Odor: herbal, sulfur, alliaceous. IR: 1124*s*. ^{1}H-NMR: 3.57 (*m*, CH_2O); 3.38 (*s*, MeO); 3.09 (*m*, H–C(3)); 2.95 (*m*, H–C(2)); 2.20 (*m*, 1 H, CH_2–C(3)); 1.88 (*m*, 1 H, CH_2–C(2)); 1.67 (*m*, 1 H, CH_2–C(3)); 1.52 (*m*, 1 H, CH_2–C(2)); 1.05 (*t*, J = 6.2, *Me*CH_2). ^{13}C-NMR: 72.32 (*t*, CH_2O); 58.81 (*q*, MeO); 43.36 (*d*, C(2)); 38.94 (*d*, C(3)); 31.06 (*t*, *C*–C(3)); 24.45 (*t*, *C*–C(2)); 13.79 (*q*, *Me*CH_2). MS: 148 (0.5, $[M+2]^+$), 147 (0.5, $[M+1]^+$), 146 (7, M^+), 113 (28, $[M-SH]^+$), 101 (2), 99 (2), 81 (20), 71 (38), 67 (13), 59 (18), 45 (100).

3.4. *(±)-1-Methoxyhexane-3-thiol* ((±)-**1**) *and (±)-6-Methoxyhexane-3-thiol* (**10**). To a suspension of $LiAlH_4$ (1.90 g, 50 mmol) in THF (200 ml), a soln. of **9** (15.04 g, 103 mmol) in THF (50 ml) was added dropwise. The mixture was then heated to reflux for 4 h (8% of **9** left). Stirring was continued at r.t. overnight (5% of **9** left). The mixture was poured onto ice and worked up with Et_2O. Evaporation at 50°/400 mbar yielded 14.30 g of crude mixture. Anal. GC (*SPWax*): (±)-**1** (58.7%), **10** (39.8%), and unreacted **9** (1.1%). The crude mixture was separated (2 batches of 7 g each) by MPLC (size *C*, hexane/Et_2O 95:5, GC monitoring). The combined GC-pure fractions of (±)-**1** and **10** were each freed from solvent by bulb-to-bulb distillation at 70°/15 mbar. The mixed fractions amounted to 3.30 g (21.9%).

Data of (±)-**1**: 3.50 g (23.7%). $I_{SPB\text{-}1}$1041, I_{SPWax}1360. IR: 2591*w*, 1124*s*. ^{1}H-NMR: 3.53 (*m*, 2 H–C(1)); 3.34 (*s*, MeO); 2.94 (*m*, H–C(3)); 1.97 (*m*, 1 H–C(2)); 1.65 (*m*, 1 H–C(2)); 1.60–1.40 (*m*, 2 H–C(4), 2 H–C(5)); 1.38 (*d*, J = 6.2, SH); 0.93 (*t*, J = 6.2, 3 H–C(6)). ^{13}C-NMR: 70.30 (*t*, C(1)); 58.68 (*q*, MeO); 41.47 (*t*, C(4) ?); 38.82 (*t*, C(2)); 37.58 (*d*, C(3)); 20.18 (*t*, C(5) ?); 13.76 (*q*, C(6)). MS: 150 (0.5, $[M+2]^+$), 149 (0.5, $[M+1]^+$), 148 (6, M^+), 116 (22, $[M-MeOH]^+$), 114 (10, $[M-H_2S]^+$), 101 (4), 88 (26), 83 (22), 71 (61), 67 (14), 58 (10), 55 (39), 47 (12), 45 (100), 41 (34).

Data of **10**: 3.40 g (22.6%). Odor: sulfur, green, herbal. $I_{SPB\text{-}1}$1062, I_{SPWax}1406. IR: 2591*w*, 1125*s*. ^{1}H-NMR: 3.38 (*m*, 2 H–C(6)); 3.33 (*s*, MeO); 2.73 (*m*, H–C(3)); 1.70 (*m*, 4 H); 1.52 (*m*, 2 H); 1.34 (*d*, J = 6.2, SH); 1.00 (*t*, J = 6.2, 3 H–C(1)). ^{13}C-NMR: 72.49 (*t*, C(6)); 58.57 (*q*, MeO); 42.76 (*d*, C(3)); 35.16 (*t*); 31.91 (*t*); 27.29 (*t*); 11.49 (*q*, C(1)). MS: 150 (0.2, $[M+2]^+$), 149 (0.2, $[M+1]^+$), 148 (4, M^+), 116 (32, $[M-MeOH]^+$), 114 (0.5, $[M-H_2S]^+$), 101 (1), 88 (36), 87 (78), 75 (26), 71 (10), 67 (12), 58 (58), 55 (50), 47 (18), 45 (100), 41 (50).

4. *(±)*-trans-*2-(Methoxymethyl)-3-propylthiirane* (**14**). From **11** *via* **12** and oxirane **13** as described in *Exper. 3.1–3.3*. ^{1}H-NMR: 3.59 (*dd*, J = 10.7, 5.6, 1 H, CH_2–C(2)); 3.39 (*s*, MeO); 3.37 (*dd*, J = 10.7, 7.1, 1 H, CH_2–C(2)); 2.73 (*ddd*, J = 7.1, 5.6, 5.1, H–C(2)); 2.70 (*m*, H–C(3)); 1.85 (*m*, 1 H, $MeCH_2CH_2$); 1.51 (*m*, 1 H of $MeCH_2CH_2$, $MeCH_2CH_2$)); 0.97 (*t*, J = 7.5, *Me*CH_2CH_2)). ^{13}C-NMR: 76.69 (*t*, *C*–C(2)); 58.78 (*q*, MeO); 41.96 (*d*, C(3)); 39.70 (*d*, C(2)); 37.79 (*t*, *C*–C(3)); 22.40 (*t*); 13.65 (*q*). MS: 148 (2, $[M+2]^+$), 147 (3, $[M+1]^+$), 146 (30, M^+), 113 (27), 101 (11), 85 (18), 81 (20), 71 (49), 59 (23), 45 (100), 41 (30).

5. *Enantioselective Synthesis of (*S*)- and (*R*)-***1***.* 5.1. *Ethyl (3*R*)-3-Hydroxyhexanoate* ((*R*)-**16**). From ethyl 3-oxohexanoate (**15**; 10.00 g, 63.3 mmol) in the presence of baker's yeast (50.0 g), and sucrose (2 × 100 g) in H_2O (1 l) [10]. The crude product was purified by FC (cyclohexane/AcOEt 7:3) and bulb-to-bulb distilled: (*R*)-**16** (7.08 g, 70%). B.p. 130–140°/15 mbar. $[\alpha]_D = -27.2$ (c = 1.00, $CHCl_3$), $\alpha_D = -7.77$ (neat); 97.4% ee by anal. GC (*CP-Chirasil-Dex CB*) ([10]: $[\alpha]_D = -22.1$ (c = 1.04, $CHCl_3$), 90% ee; [9]: $[\alpha]_D = -25.8$ (c = 1.0, $CHCl_3$), 96% ee).

Mosher ester from (*R*)-**16** with (*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride ((*S*)-MTBA-Cl) [11]: ^{19}F-NMR: −71.808 (96.8%); −71.919 (3.2%); 93.6% ee.

5.2. *(3*R*)-Hexane-1,3-diol* ((*R*)-**17**). To a suspension of $LiAlH_4$ (3.8 g, 100 mmol) in anh. Et_2O (250 ml), (*R*)-**16** (16.00 g, 100 mmol) in Et_2O (200 ml) was added dropwise at 5–10° (sluggish conversion as shown by GC). Further $LiAlH_4$ (1.2 g) was added after 3 h at r.t. and then after one night (1.0 g). The mixture was subsequently refluxed for 3 h to complete the reduction. The suspension was cooled to 5° and carefully hydrolyzed by consecutive addition of H_2O (6 ml), 15% NaOH soln. (6 ml), and H_2O (18 ml). After 40 min stirring at r.t., Na_2SO_4 was added and the mixture filtered through a glass frit. The filtrate was concentrated and distilled (*Vigreux* column): (*R*)-**17** (11.36 g, 96.3%). B.p. 143–145°/15 mbar. $\alpha_D = +10.9$ (neat) ([9]: $[\alpha]_D = -11.4$ (c = 1.6, EtOH); −1.34 (c = 1.0, $CHCl_3$)). ^{1}H-NMR (after exchange with D_2O): 3.90–3.75 (*m*, 1 H–C(3), 2 H–C(1)); 1.75–1.55 (*m*, 2 H–C(2)); 1.55–1.25 (*m*, 2 H–C(4), 2 H–(C(5)); 0.93 (*t*, J = 6.9, 3 H–C(6)). ^{13}C-NMR: 71.55 (*d*, C(3)); 61.35 (*t*, C(1)); 39.84 (*t*); 38.17 (*t*, C(2)); 18.74 (*t*); 14.09 (*q*, C(6)). MS: 119 (0.5, $[M+1]^+$), 117 (0.5, $[M-1]^+$), 100 (15, $[M-H_2O]^+$), 85 (10), 75 (100), 57 (81), 45 (50), 43 (55).

5.3. *(3*R*)-1-Methoxyhexan-3-ol* ((*R*)-**18**). A *ca.* 35% KH dispersion (11.0 g, *ca.* 95 mmol; freed from mineral oil by washing with 3 portions of anh. pentane) was suspended in anh. THF (180 ml). Diol (*R*)-**17** (10.62 g, 90 mmol) in THF (180 ml) was added dropwise. After 90 min stirring at r.t., MeI (5.6 ml, 90 mmol) was added at such a rate that the internal temp. did not rise above 30° (ice-water bath). The mixture was stirred at r.t. for 2 h. After workup and evaporation, the crude product (11.23 g) was analyzed by GC (*SPWax*): (*R*)-**18** (49.7%), (*R*)-**17** (37.6%), and tentatively 3-methoxyhexan-1-ol (9.4%). The product was isolated by FC (cyclohexane/Et_2O 7:3). The homogeneous fractions (by GC) were distilled (*Vigreux* column): (*R*)-**18** (4.20 g, 35%). B.p. 90–92°/15 mbar. $\alpha_D = -9.87$ (neat), $[\alpha]_D = +11.0$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR: 3.78 (*m*, H–C(3)); 3.63, 3.55 (2*m*, 2 H–C(1)); 3.36 (*s*, MeO); 1.77–1.61 (*m*, 2 H–C(2)); 1.54–1.28 (*m*, 2 H–C(4), 2 H–C(5)); 0.93 (*t*, $J = 6.9$, 3 H–C(6)). ^{13}C-NMR: 71.73 (*t*, C(1)); 71.06 (*d*, C(3)); 58.88 (*q*, MeO); 39.70 (*t*); 36.37 (*t*); 18.79 (*t*); 14.13 (*q*, C(6)). MS: 133 (0.5, $[M+1]^+$), 131 (0.5, $[M-1]^+$), 114 (10, $[M-\text{MeOH}]^+$), 89 (88), 71 (47), 60 (19), 45 (100).

Mosher ester from (*R*)-**18** with (*R*)-MTBA-Cl: no separation by GC (*SPWax* and *SPB-1*) from *Mosher* ester of (*S*)-**18** (see *Exper. 5.7*) with (*R*)-MTBA-Cl. ^{1}H-NMR: 3.23 (*s*, MeO–C(1)); 0.93 (*t*, $J = 7.3$, 3 H–C(6); 98.3%); 0.86 (*t*, 3 H–C(6) of diastereoisomer; 1.7%); 96.6% ee. ^{19}F-NMR: diastereoisomers not discriminated.

5.4. S-*[(1*S*)-1-(2-Methoxyethyl)butyl] Ethanethioate* ((*S*)-**19**). Adapted from [12]: to a cooled (0° internal temp.) soln. of triphenylphosphine (10.5 g, 40 mmol) in anh. THF (100 ml), 95% diisopropyl azodicarboxylate (8.3 ml, *ca.* 40 mmol) was added (slightly exothermic reaction). After 40 min stirring at 0° (→ white precipitate), a soln. of (*R*)-**18** (2.64 g, 20 mmol) and thioacetic acid (3.04 g, 40 mmol) in THF (50 ml) was introduced dropwise. Stirring was continued at 0° for 1 h, then at r.t. overnight. The now brownish-clear soln. was evaporated, diluted with pentane to precipitate triphenylphosphine oxide, and filtered. The filtrate was evaporated, and the residue purified by FC (cyclohexane/Et_2O 9:1) followed by bulb-to-bulb distillation: GC-pure (*S*)-**19** (2.06 g, 54.2%). B.p. 150°/15 mbar. $[\alpha]_D = +0.10$ ($c = 1.00$, $CHCl_3$). IR: 1706*s*, 1123*s*, 945*m*. ^{1}H-NMR: 3.62 (*m*, H–C(1)); 3.42 (*m*, CH_2O); 3.32 (*s*, MeO); 2.32 (*s*, MeCO); 1.85 (*m*, CH_2–C(1)); 1.58 (*m*, 2 H–C(2)); 1.38 (*m*, 2 H–C(3)); 0.91 (*t*, $J = 6.2$, 3 H–C(4)). ^{13}C-NMR: 198.71 (*s*, CO); 70.24 (*t*, CH_2O); 58.65 (*q*, MeO); 41.49 (*d*, C(1)); 37.30 (*t*, C(2)); 34.72 (*t*, *C*–C(1)); 30.75 (*q*, *Me*CO); 20.00 (*t*, C(3)); 13.87 (*q*, C(4)). MS: 192 (0.2, $[M+2]^+$), 191 (0.2, $[M+1]^+$), 190 (3, M^+), 147 (41, $[M-\text{MeCO}]^+$), 115 (19), 88 (24), 71 (47), 55 (43), 47 (8), 45 (100), 43 (98).

5.5. *(3*S*)-1-Methoxyhexane-3-thiol* ((*S*)-**1**). To an ice-cooled suspension of $LiAlH_4$ (200 mg, 5.3 mmol) in anh. Et_2O (20 ml), (*S*)-**19** (1.00 g, 5.3 mmol) in Et_2O (10 ml) was added dropwise. The mixture was allowed to warm to r.t. and stirred overnight. After hydrolysis with 10% HCl soln. and workup with Et_2O, the residue was purified by FC (pentane/Et_2O 95:5). Bulb-to-bulb distillation (100°/20 mbar) of the GC-pure fractions afforded (*S*)-**1** (550 mg, 70.6%). Colorless liquid. GC (*SPB-1* and *SPWax*), NMR, and MS data: identical with those of (±)-**1**. $[\alpha]_D = +3.9$ ($c = 1.00$, $CHCl_3$); >95% ee by anal. GC (*BetaDex*™*-225*).

Mosher ester from (*S*)-**1** with (*S*)-MTBA-Cl: no discrimination of the diastereoisomers by GC and ^{1}H- and ^{19}F-NMR. The ^{1}H-NMR *s* at 3.32 of the diastereoisomer (see *Exper. 5.9*) coincides with a *m*.

5.6. *(1*S*)-1-(2-Methoxyethyl)butyl Acetate* ((*S*)-**20**). Transformation of (*R*)-**18** (2.64 g, 20 mmol) as described in *Exper. 5.4*, but in the presence of AcOH, afforded (*S*)-**20** (2.50 g, 71.8%). $\alpha_D = +7.35$ (neat). ^{1}H-NMR: 5.00 (*quint.*, $J = 6.3$, H–C(1)); 3.39 (*dt*, $J = 10.3, 6.3$, CH_2O); 3.31 (*s*, MeO); 2.04 (*s*, MeCO); 1.81 (*q*, $J = 6.3$, CH_2–C(1)); 1.65–1.45 (*m*, 2 H–C(2)); 1.45–1.22 (*m*, 2 H–C(3)); 0.91 (*t*, $J = 7.3$, 3 H–C(4)). ^{13}C-NMR: 170.79 (*s*, CO); 71.65 (*d*, C(1)); 58.67 (*q*, MeO); 36.61 (*t*); 34.32 (*t*); 21.21 (*q*, *Me*CO); 18.53 (*t*, C(2)); 13.94 (*q*, C(4)). MS: 131 (3, $[M-\text{MeCO}]^+$), 114 (3), 99 (2), 89 (9), 71 (37), 55 (11), 45 (50), 43 (100).

5.7. *(3*S*)-1-Methoxyhexan-3-ol* ((*S*)-**18**). Acetate (*S*)-**20** (1.25 g, 7.2 mmol) in anh. Et_2O (20 ml) was added to an ice-cooled suspension of $LiAlH_4$ (300 mg, 7.9 mmol) in Et_2O (30 ml). The mixture was stirred at r.t. overnight and hydrolyzed with H_2O (0.3 ml), 10% NaOH soln. (0.3 ml), and H_2O (0.9 ml). After 40 min stirring, Na_2SO_4 was added, and the white solid was filtered off. The crude product was purified by FC (cyclohexane/Et_2O 65:35) and freed from solvent by bulb-to-bulb distillation: (*S*)-**18** (550 mg, 57.9%). B.p. 120°/15 mbar. $\alpha_D = +9.95$ (neat), $[\alpha]_D = -10.8$ ($c = 1.00$, $CHCl_3$). GC (*SPWax* and *SPB-1*), ^{1}H-NMR and MS data: identical with those of (*R*)-**18**.

Mosher ester from (*S*)-**18** with (*R*)-MTBA-Cl: ^{1}H-NMR: 3.32 (*s*, MeO–C(1); 98.0%); 3.25 (*s*, MeO–C(1) of diastereoisomer; 2%); 0.93 (*t*, $J = 7.3$, 3 H–C(6) of diastereoisomer; 2.1%); 0.86 (*t*, $J = 7.5$, 3 H–C(6); 97.9%); 95.8% ee. ^{19}F-NMR: diastereoisomers not discriminated.

5.8. S-*[(1*R*)-1-(2-Methoxyethyl)butyl] Ethanethioate* ((*R*)-**19**). Alcohol (*S*)-**18** (2.19 g, 16.6 mmol) was submitted to the *Volante* inversion [12] as described for (*R*)-**18** (*Exper. 5.4*): 1.33 g (42.2%) of GC-pure (*R*)-**19**. $[\alpha]_D = -0.4$ ($c = 1.00$, $CHCl_3$). GC (*SPWax*), NMR, and MS data: identical with those of (*S*)-**19**.

5.9. *(3*R*)-1-Methoxyhexane-3-thiol* ((*R*)-**1**). (*R*)-**19** (1.00 g, 5.3 mmol) was reduced as described for (*S*)-**19** (see *Exper. 5.5*): (*R*)-**1** (590 mg, 75.7%). Colorless liquid. GC (*SPB-1* and *SPWax*), NMR, and MS data: identical with those of (±)-**1**. $[\alpha]_D = -3.8$ ($c = 1.00$, $CHCl_3$); >95% ee by anal. GC (*BetaDex*™*-225*).

Mosher ester from (*R*)-**1** with (*S*)-MTBA-Cl: ^{1}H-NMR: 3.32 (*s*, MeO–C(1); 98%); 3.25 (*s*, MeO–C(1) of diastereoisomer; 2%); 96% ee. ^{19}F-NMR: diastereoisomers not discriminated.

6. *Resolution of Racemic Thiol (±)-***1**. (Experiments by Mr. *P. Sonnay*, *Firmenich SA*). 6.1. A mixture of (–)-(1*S*)-camphanoyl chloride (530 mg, 2.5 mmol), (±)-**1** (300 mg, 2.0 mmol), and *N*,*N*-dimethylpyridin-4-amine (300 mg, 2.5 mmol) in CCl_4 (7.5 ml) was stirred at 40° for 3 h. The cooled mixture was diluted with Et_2O (30 ml) and filtered through *Hyflo*. Concentration and bulb-to-bulb distillation followed by FC (cyclohexane/AcOEt 7:3) and redistillation *in vacuo* afforded a 1:1 diastereoisomer mixture of (1′*R*,1*S*)-**2** and (1′*S*,1*S*)-**2** as a semicrystalline solid (630 mg, 95%) of m.p. 38–42°. Separation was effected by HPLC (*Nucleosil* 50-7, 250 mm × 10 mm (*Macherey-Nagel*), cyclohexane/THF 96:4, flow 5 ml/min)[6]: pure (1′*R*,1*S*)-**2** (240 mg) and (1′*S*,1*S*)-**2** (240 mg).

S-*[(1*R*)-1-(2-Methoxyethyl)butyl] (1*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbothioate* ((1′*R*,1*S*)-**2**): M.p. 33°. $[\alpha]_D = -54.7$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR: 3.73 (*m*, 1 H); 3.42 (*m*, 2 H); 3.30 (*s*, 3 H); 2.43 (*m*, 1 H); 2.02–1.23 (9 H); 1.10 (*s*, 3 H); 1.04 (*s*, 3 H); 0.95 (*s*, 3 H); 0.90 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR: 196.31 (*s*); 177.84 (*s*); 96.25 (*s*); 70.06 (*t*); 58.67 (*q*); 55.42 (*q*); 54.50 (*s*); 40.68 (*d*); 36.99 (*t*); 34.55 (*t*); 31.08 (*t*); 28.95 (*t*); 20.04 (*t*); 16.75 (*q*); 16.62 (*q*); 13.85 (*q*); 9.69 (*q*). MS: 328 (20, M^+), 296 (11), 182 (52), 164 (41), 114 (78), 83 (100).

S-*[(1*S*)-1-(2-Methoxyethyl)butyl] (1*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbothioate* ((1′*S*,1*S*)-**2**): M.p. 59–61°. $[\alpha]_D = -51.4$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR: 3.73 (*m*, 1 H); 3.43 (*m*, 2 H); 3.30 (*s*, 3 H); 2.44 (*m*, 1 H); 2.02–1.23 (9 H); 1.10 (*s*, 3 H); 1.04 (*s*, 3 H); 0.96 (*s*, 3 H); 0.90 (*t*, $J = 7.1$, 3 H). ^{13}C-NMR: 196.27 (*s*); 177.86 (*s*); 96.27 (*s*); 70.03 (*t*); 58.67 (*q*); 55.42 (*s*); 54.50 (*s*); 40.65 (*d*); 36.99 (*t*); 34.58 (*t*); 31.06 (*t*); 28.97 (*t*); 20.06 (*t*); 16.75 (*q*); 16.60 (*q*); 13.84 (*q*); 9.71 (*q*). MS: 328 (30, M^+), 296 (18), 182 (60), 164 (52), 114 (81), 83 (100).

Recrystallization of (1′*S*,1*S*)-**2** from MeOH/H_2O 5:1 afforded crystals suitable for a structure determination by X-ray-diffraction analysis (see *Exper. 7*).

6.2. A soln. of (1′*R*,1*S*)-**2** (80 mg, 0.24 mmol) in Et_2O was reduced with $LiAlH_4$: (*R*)-**1** (29 mg, 80%). $[\alpha]_D = -3.8$ ($c = 0.50$, $CHCl_3$). ^{1}H-NMR and MS: identical with those of (±)-**1**.

6.3. A soln. of (1′*S*,1*S*)-**2** (170 mg, 0.52 mmol) in Et_2O was reduced with $LiAlH_4$: (*S*)-**1** (62 mg, 80%). $[\alpha]_D = +3.8$ ($c = 0.50$, $CHCl_3$). ^{1}H-NMR and MS: identical with those of (±)-**1**.

7. *Crystal Structure of (1′*S*,1*S*)-***2**. $C_{17}H_{28}O_4S$, M_r 328.5; $\mu = 1.616$ mm^{-1}, $F(000) = 712$, $d_x = 1.140$ g/cm^{-3}, orthorhombic, $P2_12_12_1$, $Z = 4$, $a = 6.3374(4)$, $b = 15.919(1)$, $c = 18.968(1)$ Å, $V = 1913.6(2)$ Å^3, from 32 reflections ($44° < 2\theta < 51°$). A colorless prism, dimension 0.18 × 0.23 × 0.50 mm, was obtained by crystallization from MeOH/H_2O. Since the compound showed crystal crack at low temp. (until 250K), cell dimensions and intensities were measured at 293K. *Stoe-STADI4* diffractometer, graphite-monochromated CuK_α radiation (λ 1.5418 Å); $\omega - 2\theta$ scans, scan width 1.05° + 0.35 tg θ, scan speed 0.075 °/s; $0 < h < 6$, $0 < k < 16$, $0 < l < 19$, and all antireflections of these; 2862 measured reflections, 2344 unique reflections of which 1884 were observables $|F_o| > 4\,\sigma(F_o)$); R_{int} for equivalent reflections 0.032. Data were corrected for *Lorentz* and polarization effects and for absorption [32] (A^* min, max = 1.310, 1.553). The structure was solved by direct methods using MULTAN 87 [33]; all other calculations used the XTAL [34] system. Full-matrix least-squares refinement based on F with weight of $1/[\sigma^2(F_o) + 0.0005\ (F_o)^2]$ gave final values $R = 0.067$, $\omega R = 0.078$ for 195 variables and 1884 contributing reflections. The final difference electron density map showed a maximum of +0.30 and a minimum of −0.36 eÅ^{-3}. The *Flack* parameter [35][36] converged to $x = 0.04(7)$. The crystals showed low density, and the structure exhibited large displacements parameters of the terminal MeO (O(4), C(17)) and propyl (C(12)–C(14)) substituents. The C(14) methyl group was disordered and was refined on two atomic sites with occupancy factors of 0.70 and 0.30, resp., and isotropic displacement parameters. These phenomena and the instability of the crystals at low temperature could explain the large R values.

Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* (deposition No. CCDC 149373). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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[6] We thank Dr. *E. Frérot, Firmenich SA*, for performing this separation.

8. *Identification of* **1** *and* **3**–**5** *in a* Ruta *Species.* Two twigs with flowers (*R. chalepensis* L.; 40 g; collected near San Gimignano, Italy, in October 1999) were cut and macerated in CH_2Cl_2 (300 ml) for 18 h. The extract was dried (Na_2SO_4, $CaCl_2$), filtered, and concentrated at 40° to *ca.* 5 ml. The concentrate was analyzed by GC/sniffing and revealed, besides further sulfury odors, the presence of **1**. GC/FPD gave rise to several sulfur signals (experiment by Mr. *A. Jaquier*, *Firmenich SA*). A 1-ml sample of the concentrate was treated with *Affi-Gel 501* [6] (see *Exper. 2*), and the eluate was analyzed by GC/MS (polar and apolar phase). Four related MS were recorded, two of which matched **1** and **5**, resp., present in our spectra library. The structures of the two unknowns were deduced from their MS and retention indices and confirmed by comparison with the synthetic samples (±)-**3** and (±)-**4**, see *Exper. 9*. Retention indices ($I_{SPB\text{-}1}$, I_{SPWax}): **5** (900, 1209), **4** (1029, 1345), **1** (1041, 1360), and **3** (1140, 1458); ratio **5**/**4**/**1** *ca.* 10 : 2 : 1. Chiral GC (*BetaDex*™*-225*) resolved **1** (ratio (*S*)-**1**/(*R*)-**1** 70 : 30), whereas **4** gave rise to one peak (→ (*R*)-**4**). Under the GC conditions applied (see *Exper. 2*), **3** was not observed.

9. *Racemic Thiols (±)-***3** *and (±)-***4**. 9.1. *(±)-1-Methoxy-4-methylpentan-3-ol* ((±)-**23**). Methyl 4-methyl-3-oxopentanoate (**21**; 21.6 g, 150 mmol) in EtOH (75 ml) was first reduced with $NaBH_4$ (2.04 g, 53.7 mmol) in EtOH (175 ml) to the intermediate ethyl hydroxy ester (20.0 g; transesterification!), which, without purification, was diluted in Et_2O (150 ml) and reduced with $LiAlH_4$ (5.70 g, 150 mmol) in Et_2O (350 ml) to afford, after distillation at 130–135°/11 mbar, (±)-4-methylpentane-1,3-diol ((±)-**22**; 12.9 g, 75%)[7]. Methylation of (±)-**22** (KH, MeI) as described in *Exper. 5.3* afforded (±)-**23** in 44.1% yield. ^{1}H-NMR: 3.65 (*dt*, *J* = 9.1, 5.2, 1 H–C(1)); 3.55 (*m*, 1 H–C(1), H–C(3)); 3.35 (*s*, MeO); 2.87 (*d*, *J* = 3.2, OH); 1.75–1.60 (*m*, 2 H–C(2), H–C(4)); 0.93, 0.91 (2 *d*, *J* = 7.1, 3 H–C(5), Me–C(4)). ^{13}C-NMR: 76.27 (*d*); 72.13 (*t*); 58.88 (*q*); 33.73 (*d*); 33.10 (*t*); 18.46 (*q*); 17.69 (*q*). MS: 133 (0.5, $[M+1]^+$), 100 (5, $[M-\text{MeOH}]^+$), 89 (64), 71 (14), 57 (16), 45 (100).

9.2. *(±)-*S*-[1-(2-Methoxyethyl)-2-methylpropyl] Ethanethioate* ((±)-**24**). Adapted from [16]: To a soln. of 1,3-dimethyl-2-fluoropyridinium 4-methylbenzenesulfonate (1.63 g, 5.5 mmol) in acetone/benzene 1 : 1 (12.5 ml), Et_3N (765 µl, 5.5 mmol) was added, followed by (±)-**23** (660 mg, 5.0 mmol). The clear soln. was stirred for 1 h. Thioacetic acid (390 µl, 5.5 mmol), and Et_3N (765 µl, 5.5 mmol) in acetone/benzene 1 : 1 (2.5 ml) were added. The mixture was heated at 75° for 3 h. Workup (Et_2O) and purification of the crude product by FC (cyclohexane/Et_2O 96 : 4 and 90 : 10) afforded, after distillation, (±)-**24** (520 mg, 54.7%). B.p. 90°/1 mbar. IR: 1708*s*, 1126*s*. ^{1}H-NMR: 3.61 (*dt*, *J* = 10.3, 4.1, 1 H of CH_2O); 3.50–3.34 (*m*, H–C(1), 1 H of CH_2O); 3.31 (*s*, MeO); 2.39 (*s*, MeCO); 1.93 (*m*, 2 H); 1.70 (*m*, 1 H); 0.94, 0.92 (2 *d*, *J* = 6.9, 3 H–C(3), Me–C(2)). ^{13}C-NMR: 95.68 (*s*); 70.58 (*t*); 58.70 (*q*); 47.70 (*d*); 32.50 (*t*); 32.44 (*d*); 30.82 (*q*); 19.87 (*q*); 18.69 (*q*). MS: 192 (0.5), 191 (3), 190 (8, M^+), 147 (43), 115 (20), 88 (24), 71 (47), 55 (50), 45 (100), 43 (98).

9.3. *(±)-1-Methoxy-4-methylpentane-3-thiol* ((±)-**4**). Reduction of (±)-**24** (600 mg, 3.15 mmol) with $LiAlH_4$ in Et_2O as described in *Exper. 5.5* yielded, after FC (pentane/Et_2O 96.5 : 3.5) and bulb-to-bulb distillation, (±)-**4** (300 mg, 64.3%). B.p. 75°/15 mbar. $I_{SPB\text{-}1}$1029, I_{SPWax}1345. IR: 1123*s*. ^{1}H-NMR: 3.55 (*m*, 2 H–C(1)); 3.35 (*s*, MeO); 2.90 (*m*, H–C(3)); 1.94, 1.85, 1.60 (3*m*, 2 H–C(2), H–C(4)); 1.18 (*d*, *J* = 7.9, SH); 0.99, 0.92 (2*d*, *J* = 6.7, 3 H–C(5), Me–C(4)). ^{13}C-NMR: 70.61 (*t*); 58.70 (*q*); 44.27 (*d*); 36.20 (*t*); 33.94 (*d*); 20.19 (*q*); 17.29 (*q*). MS: 150 (0.5, $[M+2]^+$), 149 (1, $[M+1]^+$), 148 (9, M^+), 116 (15), 114 (10), 101 (5), 88 (10), 83 (20), 71 (35), 67 (5), 58 (9), 55 (30), 47 (2), 45 (100), 41 (24).

9.4. *(±)-1-Methoxyheptane-3-thiol* ((±)-**3**). From **26**, in analogy to *Exper. 9.1–9.3*. B.p. 85°/15 mbar. 99.6% pure (GC). $I_{SPB\text{-}1}$1140, I_{SPWax}1458. IR: 1124*s*. ^{1}H-NMR: 3.54 (*m*, 2 H–C(1)); 3.34 (*s*, MeO); 2.93 (*m*, H–C(3)); 1.97 (*m*, 2 H); 1.65 (*m*, 2 H); 1.49 (*m*, 2 H); 1.38 (*d*, *J* = 7.8, SH); 1.33 (*m*, 2 H); 0.91 (*t*, *J* = 7.1, 3 H–C(7)). ^{13}C-NMR: 70.28 (*t*, C(1)); 58.71 (*q*, MeO); 39.02 (*t*); 38.82 (*t*); 37.83 (*d*, C(3)); 29.20 (*t*); 22.44 (*t*); 14.02 (*q*, C(7)). MS: 164 (0.5, $[M+2]^+$), 163 (1, $[M+1]^+$), 162 (11, M^+), 130 (10), 128 (9), 101 (9), 97 (15), 88 (62), 81 (15), 71 (55), 55 (49), 47 (5), 45 (100), 41 (35).

10. *Enantioselective Synthesis of (*R*)-***4**. 10.1. *Methyl (3*S*)-3-Hydroxy-4-methylpentanoate* ((*S*)-**25**). From **21** (15.0 g, 20.8 mmol) as described in *Exper. 5.1:* yield 4.30 g (28.3%). $[\alpha]_D = -40.9$ ($c = 1.00$, $CHCl_3$).

10.2. *(3*S*)-1-Methoxy-4-methylpentan-3-ol* ((*S*)-**23**). To a suspension of $LiAlH_4$ (0.99 g, 26 mmol) in anh. Et_2O (70 ml), (*S*)-**25** (3.8 g, 26 mmol) in Et_2O (25 ml) was added at 5°. The mixture was stirred overnight at r.t. (reduction complete as shown by GC), then hydrolyzed, and worked up as described in *Exper. 5.2:* (*S*)-**22** (2.48 g, 80.7%). $[\alpha]_D = -12.3$ ($c = 1.01$, $CHCl_3$); > 95% ee by anal. GC (*BetaDex*™*-225*).

(*S*)-**22** (2.20 g, 18.6 mmol) was methylated as described in *Exper. 5.3:* (*S*)-**23** (1.02 g, 41.5%). $[\alpha]_D = -0.69$ ($c = 1.01$, $CHCl_3$); > 95% ee by anal. GC (*BetaDex*™*-225*). NMR and MS: identical with those of (±)-**23**.

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[7] A one-step reduction of **21** with $LiAlH_4$ produced a complex mixture from which (±)-**22** was isolated in less than 25%.

10.3. S-*[(1*R*)-1-(2-Methoxyethyl)-2-methylpropyl] Ethanethioate* ((*R*)-**24**). From (*S*)-**23** (780 mg, 5.9 mmol) as described in *Exper. 5.4:* (*R*)-**24** (270 mg, 24.0%). $[\alpha]_D = +1.2$ ($c = 0.99$, $CHCl_3$). NMR and MS: identical with those of (±)-**24**.

10.4. *(3*R*)-1-Methoxy-4-methylpentane-3-thiol* ((*R*)-**4**). From (*R*)-**24** (200 mg, 10.5 mmol) as described in *Exper. 5.5:* (*R*)-**4** (100 mg, 64.1%). $[\alpha]_D = +23.0$ ($c = 1.03$, $CHCl_3$); >95% ee by anal. GC (*BetaDex*™*-225*). (*R*)-**4** corresponded to the first peak of (±)-**4** and co-eluted with natural **4**. NMR and MS: identical with those of (±)-**4**.

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