Gas-Phase Structures

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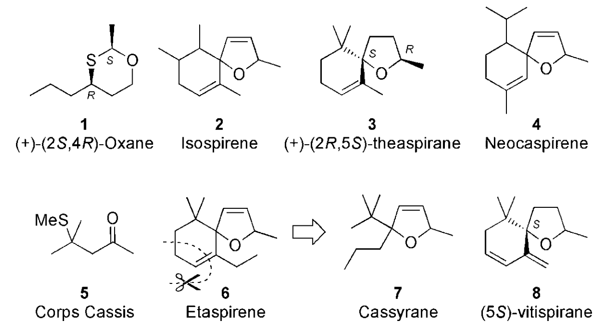
Cassis Odor through Microwave Eyes: Olfactory Properties and Gas-Phase Structures of all the Cassyrane Stereoisomers and its Dihydro Derivatives**

Halima Mouhib, Wolfgang Stahl, Monique Lüthy, Michelle Büchel, and Philip Kraft**

Dedicated to Urs Müller

Blackcurrant is arguably the most sophisticated and elegant fruity top note in perfumery,[1] with an extreme 18% of "Cassis base 345B" in "Le monde est beau" (Kenzo, 1997) by Daniela Andrier and 2.2% in "DKNY Be Delicious" (Donna Karan, 2004) by Maurice Roucel, in the latter perfume juxtaposed to 7.7% undecavertol.[1] "Cassis base 345B" contains the 1,3-oxathiane Oxane, the odor of which is due mainly to the (+)-2*S*,4*R* stereoisomer **1**[2] and Isospirene (**2**), a less-volatile synthetic theaspirane derivative. Theaspiranes occur in different enantiomeric ratios in a variety of natural products, but the blackcurrant odor originates predominantly from the (+)-2*R*,5*S* stereoisomer **3**.[3] More potent derivatives such as Isospirene (**2**), Neocaspirene (**4**), and Etaspirene (**6**) have been introduced to perfumery, but these are less volatile and diffusive than **3**. For top notes, only the sulfur-containing *rac*-**1** and Corps Cassis (**5**) were available, until the recent introduction of Cassyrane (**7**),[4] which can be regarded as a *seco*-Etaspirene (Scheme 1) and is devoid of sulfur off-odors.



Scheme 1. Important blackcurrant and theaspirane odorants.

For the related vitispiranes, such as the 5*S*-configured diastereomers **8** that occur in vanilla oleoresin,[5] the more intense *cis* compounds possess a green chrysanthemum note, while the *trans* isomers resemble exotic flowers with earthy-woody undertones.[6] Since the cassis odor of **1** and **3** was also critically dependent upon the stereochemistry, it was highly interesting to investigate the olfactory properties of the stereoisomers of Cassyrane (**7**) and its dihydro derivatives. A combination of microwave spectroscopy and quantum chemistry seemed ideal to determine the relative stereochemistry and their gas-phase structures, since microwave spectroscopy has recently been applied to solving the structures of sizeable molecules where energy differences are small and conformational distinction is not possible by quantum chemical calculations alone.[7] Here we report on the gas-phase structures of the Cassyrane stereoisomers **7** and its dihydro derivatives **15** calculated by quantum chemical methods and validated by molecular beam Fourier transform microwave (MB-FTMW) spectroscopy.

The synthesis of the stereoisomers **7** and its dihydro derivatives **15** started with the commercially available (*R*)- and (*S*)-butynol **9** ($\geq$ 99% *ee*), as shown in Scheme 2 for the 5*R*-configured isomers. In analogy to the preparation of the racemic material,[4] (*S*)-alkyne **9** was transformed into its Grignard reagent and treated with ketone **10** in the presence of cerium(III) chloride to afford diol **11** as a 5*R*/5*S* diastereoisomeric mixture of 56:44. Lindlar reduction, acetylation, and chromatographic separation furnished the acetates **13a** and **14a** in good overall yield and with retained absolute stereochemistry (99% *ee*). The most apparent strategy would have been hydrolysis of the acetates and subsequent cyclization of the diols **13b** and **14b** via the corresponding tosylates or mesylates. However, under a variety of conditions, 1–10% of the C-5 epimers (5*S*)-**7** were formed, together with other side products. Diol **14b** was more prone to side reactions than **13b**, and experiments with the latter indicated that mesylation/cyclization at various temperatures was inferior to tosylation/cyclization (94.8% *de* versus 98.2% *de*, see the Supporting Information). Therefore, a cyclization route in which the acetate function was used as a leaving group was envisaged. Treatment of **14a** with 1.5 equivalents of NaH in THF at reflux indeed furnished (2*S*,5*R*)-**7** in 73% yield (85%

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[*] Dipl.-Chem. H. Mouhib, Prof. Dr. W. Stahl
Institute of Physical Chemistry, RWTH Aachen University
52056 Aachen (Germany)
Fax: (+49) 241-80-92365
E-mail: w.stahl@rwth-aachen.de
Dr. M. Lüthy, M. Büchel, Dr. P. Kraft
Givaudan Schweiz AG, Fragrance Research
Überlandstrasse 138, 8600 Dübendorf (Switzerland)
Fax: (+41) 44-824-2926
E-mail: philip.kraft@givaudan.com

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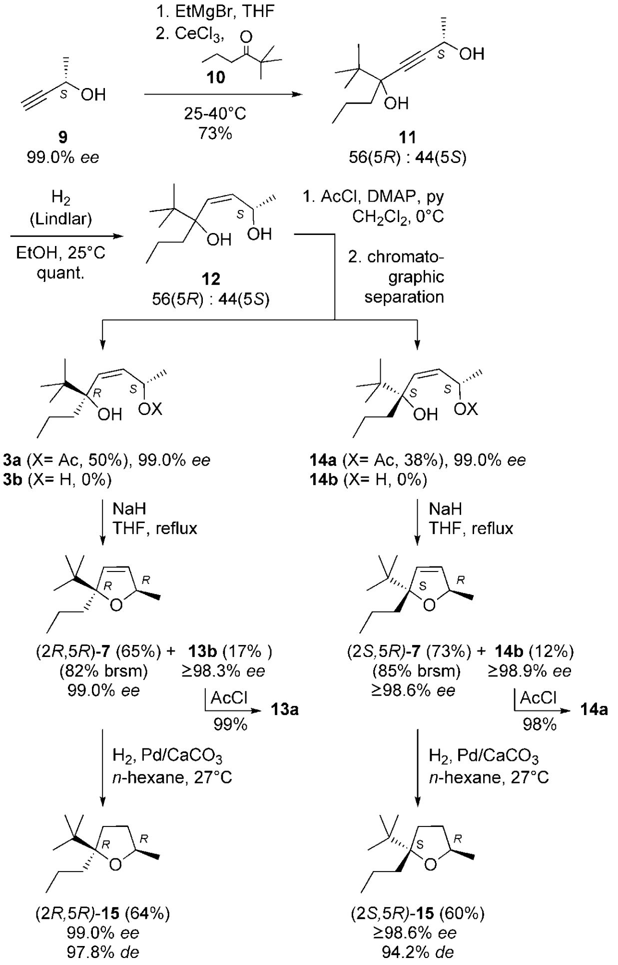


Scheme 2. Synthetic route to the 5*R*-configured enantiomers of Cassyrane (5*R*)-**7** and its dihydro derivatives (5*R*)-**15**. brsm = based on recovered starting material, DMAP = 4-dimethylaminopyridine, py = pyridine.

based on recovered **14a**), accompanied by 12% of **14b**. This allowed the utilization of the acetate group required for separation of the diastereomers as a leaving group in a clean S_N2 reaction. The desired products (2*R*,5*R*)- and (2*S*,5*R*)-**7** were each obtained as a single diastereoisomer (chirospecific gas chromatography), and their conformations were determined by microwave spectroscopy.

Highly accurate rotational constants were obtained using a MB-FTMW spectrometer, and compared with the rotational constants of several conformers obtained from ab initio calculations at the MP2/6-311++G(d,p) level using the Gaussian03 program package.[8] Additionally, quantum chemical calculations were carried out at the B3LYP/6-311++G(d,p) level, where harmonic frequency calculations were used to verify the nature of the stationary points. First, the racemic diastereomeric mixture **7** was measured, then samples of the pure stereoisomers (2*S*,5*S*)-, (2*R*,5*S*)-, (2*S*,5*R*)-, and (2*R*,5*R*)-**7** were used to confirm the assignments. In the range of 9–15 GHz, 115 lines were measured for **7**, of which 59 lines were assigned to the *like*-configured Cassyrane (*like*-**7**) diastereomer, and 42 lines to the *unlike*-Cassyrane (*unlike*-**7**). All the lines seemed to be slightly broadened, but only in a few cases were they split because of internal rotation of the methyl groups or magnetic coupling effects of the protons. The remaining 14 lines were quite weak and remained unassigned. They might be attributed to vibrationally excited states or a huge number of isotopologues.

The microwave spectroscopic data and quantum chemical constants of the observed stereoisomers of **7** are given in Table 1. The calculated coordinates are considered correct, since the rotational constants obtained at the MP2/6-311++G(d,p) level agreed with the experimental values within less than 1%. The deviations between the experimental constants and those obtained by DFT calculations at the B3LYP/6-311++G(d,p) level are slightly larger, but still below 1.5%. This relative stereochemistry is also in accord with NOESY NMR experiments.

As the isomeric mixture of the dihydro derivatives **15** also possesses a cassis note,[4] the Cassyrane stereoisomers (2*R*,5*R*)-**7** (99.0% *ee*) and (2*S*,5*R*)-**7** (≥ 98.6% *ee*) were subjected to hydrogenation experiments in the presence of either Pd/C or Pt/C. Tetrahydrofurans **15** were obtained in high yield, although the C-5 epimers (5*S*)-**15** were formed in

Table 1: Microwave spectroscopic data and quantum chemical constants of the stereoisomers of Cassyrane (**7**).[a]

Constant	Unit	(2*S*,5*S*)-Cassyrane [(2*S*,5*S*)-**7**]			(2*S*,5*R*)-Cassyrane [(2*S*,5*R*)-**7**]		
		experimental	MP2	B3LYP	experimental	MP2	B3LYP
A	GHz	0.85572511(55)	0.857 (−0.15%)	0.847 (1.02%)	0.87535362(95)	0.876 (−0.08%)	0.864 (1.30%)
B	GHz	0.74545173(20)	0.751 (−0.74%)	0.736 (1.27%)	0.73161093(26)	0.736 (−0.60%)	0.724 (1.05%)
C	GHz	0.50849730(33)	0.512 (−0.69%)	0.502 (1.28%)	0.50873267(57)	0.512 (−0.65%)	0.502 (1.33%)
Δ_J	kHz	0.0177(14)			0.0285(26)		
Δ_{JK}	kHz	0.0605(44)			−0.0494(72)		
Δ_K	kHz	−0.0273(37)			0.1331(54)		
δ_J	kHz	0.00589(57)			0.00582(78)		
δ_K	kHz	0.0268(17)			0		
σ	kHz	2.5			1.9		
κ		0.36			0.22		
N		59			42		

[a] The microwave data set was fitted using the program xiam.[9] A–C: Rotational constants; Δ_J, Δ_{JK}, Δ_K, δ_J, δ_K: centrifugal distortion constants (Watson's *A* reduction, I^r representation);[10] σ: standard deviation of the fit; κ: Ray's asymmetry parameter;[11] *N*: total number of fitted lines. δ_K was set to 0 for (2*S*,5*R*)-**7** because of a high correlation with other centrifugal distortion constants. The basis set 6-311++G(d,p) was used for both the MP2 and B3LYP calculations. The relative deviations in percent are given with respect to the experimental value. Errors of the experimental data given in parentheses are in units of the last digit.

Table 2: Microwave spectroscopic data and quantum chemical constants of the stereoisomers of dihydro-Cassyrane (**15**).[a]

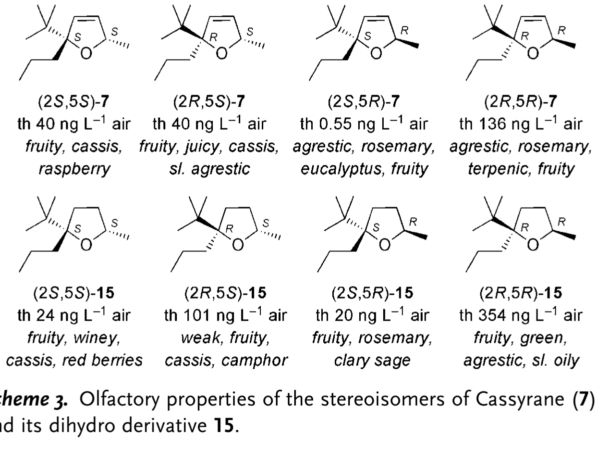
Constant	Unit	(2*S*,5*S*)-Dihydro-Cassyrane [(2*S*,5*S*)-**15**]			(2*S*,5*R*)-Dihydro-Cassyrane [(2*S*,5*R*)-**15**]		
		experimental	MP2	B3LYP	experimental	MP2	B3LYP
A	GHz	0.81225157(18)	0.816 (−0.47%)	0.802 (1.27%)	0.83285824(29)	0.838 (−0.62%)	0.822 (1.30%)
B	GHz	0.734234120(78)	0.739 (−0.65%)	0.727 (0.99%)	0.71904648(12)	0.723 (−0.55%)	0.713 (0.84%)
C	GHz	0.502004166(54)	0.505 (−0.60%)	0.496 (1.20%)	0.501751068(95)	0.505 (−0.65%)	0.496 (1.15%)
Δ_J	kHz	0.01727(48)			0.02241(70)		
Δ_{JK}	kHz	0.0494(22)			−0.0464(33)		
Δ_K	kHz	−0.0280(16)			0.1222(22)		
δ_J	kHz	0.00555(23)			0.00797(34)		
δ_K	kHz	0.02392(56)			−0.00925(87)		
σ	kHz	1.2			1.6		
κ		0.50			0.31		
N		75			65		

[a] See Table 1.

significant quantities via the corresponding 2,3-dihydrofurans. Homogeneous hydrogenation experiments or diimide reduction afforded, however, only traces of **15**. Further heterogeneous experiments revealed that (5*R*)-**7** could be hydrogenated with less than 3% epimerization to (2*R*,5*R*)-**15** and (2*S*,5*R*)-**15** by using $Pd/CaCO_3$ in *n*-hexane and continuous hydrogenation equipment (97.8% *de* and 94.2% *de*, respectively). In a conventional setup, the same catalyst was less reliable (3.5% epimerization for *cis*-**15** and 10% for *trans*-**15**; see the Supporting Information).

In an analogous manner, the 5*S*-configured enantiomers of Cassyrane (5*S*)-**7** and the corresponding tetrahydrofurans (5*S*)-**15** were prepared. The gas-phase structures of the dihydro Cassyrane stereoisomers **15** were determined in the same way as for Cassyrane (**7**). In the range of 9–14 GHz, 149 lines were measured for **15**, of which 75 lines were assigned to the *like*-configured dihydro Cassyrane (*like*-**15**) diastereomer, and 65 lines to the *unlike*-configured dihydro Cassyrane (*unlike*-**15**) diastereomer. Only 9 weak lines remained unassigned. The rotational constants obtained at the MP2/6-311++G(d,p) level agreed with the experimental values within less than 1%, those from the DFT calculations at the B3LYP/6-311++G(d,p) level are also below 1.5% (Table 2).

The olfactory properties and odor thresholds (th) of all the stereoisomers of Cassyrane (**7**) and its dihydro derivative **15** are shown in Scheme 3. Interestingly, rather than being fruity, the most intense (0.55 $\mathrm{ng\,L^{-1}}$ air) Cassyrane enantiomer (2*S*,5*R*)-**7** is foremost agrestic (reminiscent of Provencal herbs) in character with rosemary and eucalyptus aspects. The two (5*S*)-**7** enantiomers (40 $\mathrm{ng\,L^{-1}}$ each) possess an odor threshold about 70 times higher and a more pronounced fruity, juicy, cassis character. As the 2*S*,5*R* configuration of the most powerful enantiomer of Cassyrane (**7**) matches that of the most powerful theaspirane enantiomer **3**,[3] one might question whether **3** really is the most typical or only the strongest smelling isomer. The odor of the stereoisomers of theaspirane (**3**) may thus have to be reassessed.



(2*S*,5*S*)-**7**
th 40 ng L−1 air
fruity, cassis, raspberry

(2*R*,5*S*)-**7**
th 40 ng L−1 air
fruity, juicy, cassis, sl. agrestic

(2*S*,5*R*)-**7**
th 0.55 ng L−1 air
agrestic, rosemary, eucalyptus, fruity

(2*R*,5*R*)-**7**
th 136 ng L−1 air
agrestic, rosemary, terpenic, fruity

(2*S*,5*S*)-**15**
th 24 ng L−1 air
fruity, winey, cassis, red berries

(2*R*,5*S*)-**15**
th 101 ng L−1 air
weak, fruity, cassis, camphor

(2*S*,5*R*)-**15**
th 20 ng L−1 air
fruity, rosemary, clary sage

(2*R*,5*R*)-**15**
th 354 ng L−1 air
fruity, green, agrestic, sl. oily

Scheme 3. Olfactory properties of the stereoisomers of Cassyrane (**7**) and its dihydro derivative **15**.

A 5*R* configuration in both **7** and **15** elicits an agrestic character in the direction of rosemary, while the 5*S*-configured isomers smell fruity-cassis. However, the C2 stereocenter has an enormous influence on the intensity, as (2*S*,5*R*)-**7** is over 600 times more potent in terms of its threshold than (2*R*,5*R*)-**15**. With about 20% β-pinene and 2% Veloutone (2,2,5-trimethyl-5-pentylcyclopentanone) in "Cassis base 345B", agrestic aspects actually accentuate the cassis character, so also (2*S*,5*R*)-**7** boosts the fruity, juicy cassis note of the (5*S*)-**7** isomers.

The gas-phase structures of the most powerful and most fruity (2*S*)-**7** and (2*S*)-**15** stereoisomers are shown in Figure 1, and reveal that the puckering of the tetrahydrofuran ring in Figure 1 c,d flattens out the protruding methyl substituent from the ring plane, which seems to enhance the fruity, cassis character of (2*S*,5*S*)-**15**, while it raises its odor threshold compared to that of (2*S*,5*R*)-**7**.

The gas-phase structures thus obtained can directly be used for molecular modeling studies, as shown in Figure 2 with the superposition analysis of the pronounced fruity-cassis isomers (5*S*)-**7** on (+)-(2*S*,4*R*)-Oxane (**1**, 20% steric, 80% electrostatic field), in which the methyl groups only overlay well if C-5 center of Cassyrane (**7**) is *S* configured.

The C-2 substituents of Cassyrane (**7**) may be interchanged without much impact on the steric bulk of **1**, although the most fruity 2*S*,5*S* stereoisomer **7** superimposes best on the fruity (+)-2*S*,4*R* isomer of Oxane (**1**). The enantiomer *ent*-**1** of (+)-(2*S*,4*R*)-Oxane has been reported to possess only a sulfurous, linseed oil like odor.[4] Looking at the position of 2-methyl substituent in the superimposed (+)-(2*S*,4*R*)-Oxane (Figure 2), it makes sense that the flatter dihydro-Cassyrane isomer (2*S*,5*S*)-**15** is even more fruity and cassis-like than (2*S*,5*S*)-**7**. This demonstrates the immediate

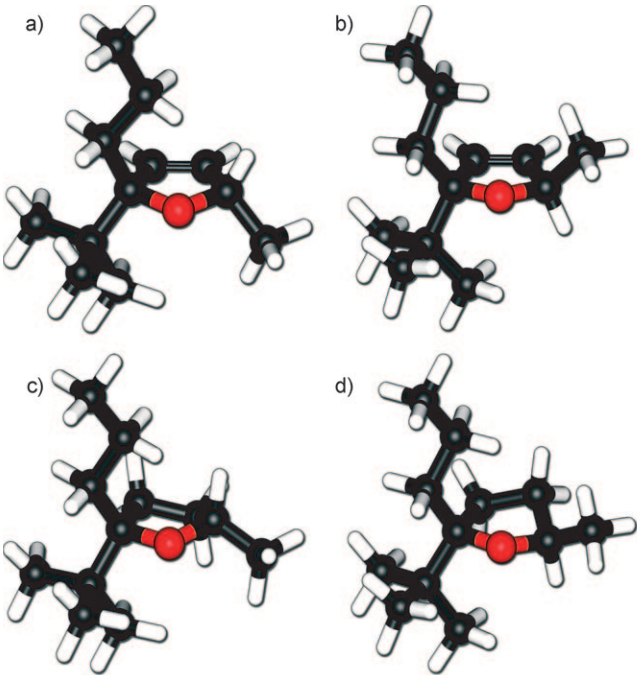


Figure 1. Gas-phase structures of a) the most fruity cassis odorant (2*S*,5*S*)-**7**, b) the most powerful Cassyrane stereoisomer (2*S*,5*R*)-**7**, c) the most fruity dihydro isomer (2*S*,5*S*)-**15**, and d) the most powerful dihydro derivative (2*S*,5*R*)-**15**.

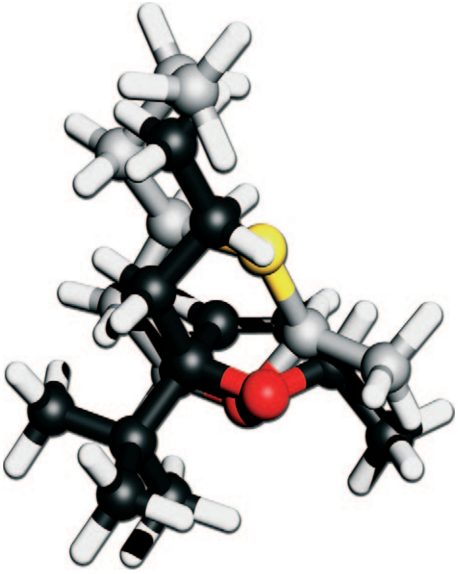


Figure 2. Superposition analysis of (+)-(2*S*,4*R*)-Oxane (**1**, silver) with rotatable bonds on the observed structure of the most fruity Cassyrane isomer (2*S*,5*S*)-**7** (black); 20% steric, 80% electrostatic field.[12] black/silver C, white H, red O, yellow S.

usefulness of gas-phase structures for structure–odor correlations, and as most odorants are noncrystalline, microwave spectroscopy is an interesting new tool for Fragrance Chemistry.

Experimental Section

The detailed experimental procedures, with assigned NMR spectra, tables for cyclization and hydrogenation experiments, microwave frequency lists for the observed conformers of **7** and **15**, as well as the Cartesian coordinates and the dipole moment components in the principal axes system at the MP2/6-311++G(d,p) and the B3LYP/6-311++G(d,p) level with the electronic energies, are given in the Supporting Information.

(2*S*,5*S*)-**7** (97.8% *de*, 99.0% *ee*): $[\alpha]_D^{22}=+126.9$ ($c=0.96$, EtOH). Odor description: Fruity, cassis, raspberry-type odor with slight herbaceous aspects reminiscent of rosemary. Odor threshold: 40 ng L^{-1} air.

(2*R*,5*S*)-**7** (≥98.9% *ee*): $[\alpha]_D^{22}=+85.8$ ($c=0.90$, EtOH). Odor description: Fruity-juicy cassis odor with slightly agrestic aspects and nuances of eucalyptus seed and dried leaves. Odor threshold: 40 ng L^{-1} air.

(2*S*,5*R*)-**7** (≥98.6% *ee*): $[\alpha]_D^{22}=-87.4$ ($c=1.00$, EtOH). Odor description: Agrestic odor in the direction of rosemary and eucalyptus with fruity, strawlike aspects, and slightly medicinal, terpenic, dry woody-resinous facets. Odor threshold: 0.55 ng L^{-1} air.

(2*R*,5*R*)-**7** (99.0% *ee*): $[\alpha]_D^{22}=-130.6$ ($c=0.98$, EtOH). Odor description: Agrestic, rosemary, terpenic-pine odor with fruity, eucalyptus-like and slightly resinous nuances. Odor threshold: 136 ng L^{-1} air.

(2*S*,5*S*)-**15** (91.8% *de*, 99.0% *ee*): $[\alpha]_D^{22}=+0.7$ ($c=0.99$, EtOH). Odor description: Fruity-winey, cassis odor with aspects of raspberry and strawberry, and a slightly fatty tonality. Odor threshold: 24 ng L^{-1} air.

(2*R*,5*S*)-**15** (79.2% *de*, ≥98.9% *ee*): $[\alpha]_D^{22}=+18.4$ ($c=0.94$, EtOH). Odor description: Weak, fruity, cassis-type odor with fresh, camphoraceous and slightly woody facets. Odor threshold: 101 ng L^{-1} air.

(2*S*,5*R*)-**15** (94.2% *de*, ≥98.6% *ee*): $[\alpha]_D^{22}=-20.9$ ($c=0.94$, EtOH). Odor description: Fruity, agrestic odor reminiscent of rosemary with a clary sage effect and terpenic-woody, somewhat fatty nuances. Odor threshold: 20 ng L^{-1} air.

(2*R*,5*R*)-**15** (97.8% *de*, 99.0% *ee*): $[\alpha]_D^{22}=-2.7$ ($c=1.02$, EtOH). Odor description: Fruity, green, agrestic odor with fresh, slightly oily rosy aspects. Odor threshold: 354 ng L^{-1} air.

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Keywords: enantiodiscrimination · fragrances · rotational spectroscopy · stereoisomers · structure–activity relationships

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