# Total Synthesis of Junionone, a Natural Monoterpenoid from *Juniperus communis* L., and Determination of the Absolute Configuration of the Naturally Occurring Enantiomer by ROA Spectroscopy

by **Martin A. Lovchik***[a][1], **Georg Fráter**[a][b], **Andreas Goeke**[b][c], and **Werner Hug**[d]

[a]) *Givaudan UK Ltd*, Kennington Road, Ashford Kent TN24 0LT, UK (phone: +44-(0)1233-644923; e-mail: martin.lovchik@givaudan.com)
[b]) *Givaudan Schweiz AG*, Ueberlandstrasse 348, CH-8600 Duebendorf (phone: +41-44-824-2371; e-mail: georg.frater@givaudan.com)
[c]) *Shanghai Givaudan Ltd.*, 298 Li Shi Zhen Road, PuDong Zhang Jiang High-Tech Park, 201203 Shanghai, China (phone: +86-21-289-31101, e-mail: andreas.goeke@givaudan.com)
[d]) University of Fribourg, Pérolles, CH-1700 Fribourg (phone: +41-26-300-8713, e-mail: werner.hug@unifr.ch)

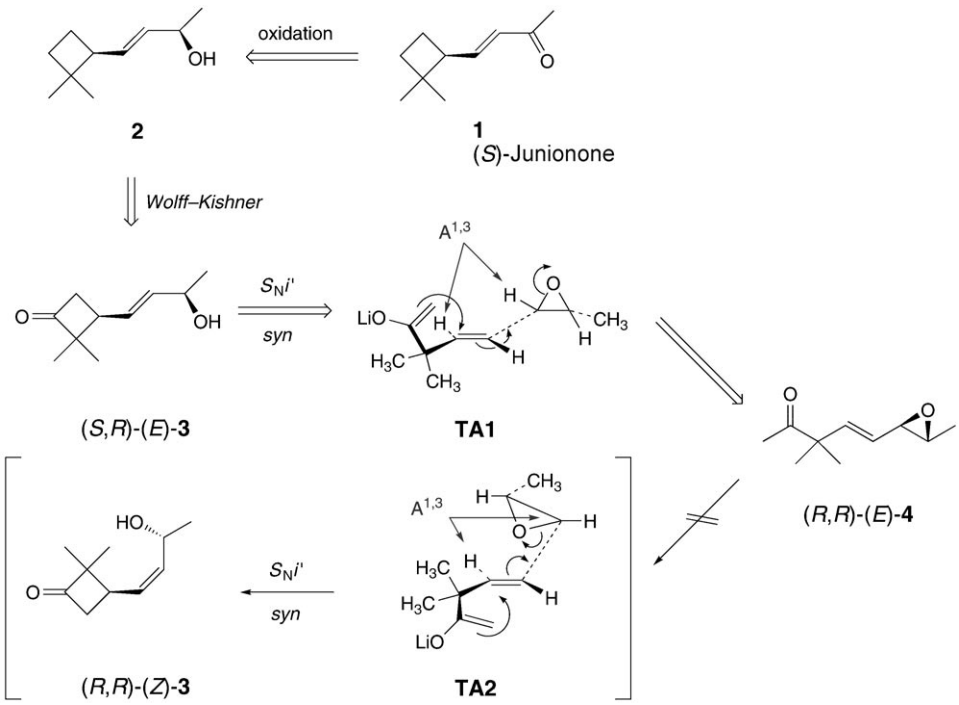
Recently, we reported a novel access to 2,2-diethyl-3-[(*E*/*Z*)-prop-1-en-1-yl]cyclobutanone by an intramolecular nucleophilic substitution with allylic rearrangement ($S_Ni'$) of (*E*)-6-chloro-3,3-diethylhept-4-en-2-one. The ring closure reaction was found to proceed with selective *syn*-displacement of the leaving group. This method was now applied to the total synthesis of junionone, an olfactorily interesting cyclobutane monoterpenoid isolated from *Juniperus communis*, L. $S_Ni'$ Ring closure of the ketone enolate of (*E*)-3,3-dimethyl-5-[(2*R*,3*R*)-3-methyloxiran-2-yl]pent-4-en-2-one (*R*,*R*)-(*E*)-**4′** proceeded only after the epoxide moiety had been activated by *Lewis* acid and led to the junionone precursors (3*R*)- and (3*S*)-3-[(1*E*,3*R*)-3-hydroxybut-1-en-1-yl]-2,2-dimethylcyclobutanone (*S*/*R*,*R*)-(*E*)-**3**. The ratio of *syn*- and *anti*-conformers in the transitory molecular arrangement was found to depend on the nature of the *Lewis* acid. The absolute configuration of both the synthetic as well as the natural junionone, isolated from juniper berry oil, was determined by *Raman* Optical Activity (ROA) spectroscopy. Our experiments led to a novel synthetic route to both (+)- and (−)-junionone, the first determination of the absolute configuration of natural junionone, and to the development of a practical ROA procedure for measuring milligram quantities of volatile liquids.

**Introduction.** – Junionone, a natural cyclobutane monoterpenoid with interesting olfactory properties, was first isolated from the oil of the fruit of *Juniperus communis*, L. by *Thomas* and *Ozainne* in 1973 [1]. The authors proposed structure **1** and synthesized optically active (−)-(*S*)-junionone ((*S*)-**1**) from (−)-caryophyllene. Although the structure of junionone was established by this synthesis, the insufficient amount of natural product did not allow to correlate its absolute configuration with that of (−)-caryophyllene. This fact prompted us to develop a stereoselective synthesis of (*S*)-**1** and to determine the absolute configuration of natural junionone by means of modern GC on chiral phase and *Raman* Optical Activity (ROA), both not available at the time junionone had been first discovered. Based on the information obtained during our studies on the $S_Ni'$ ring closure to cyclobutanones [2], we reckoned that the C-skeleton

[1]) Present address: Waidlistrasse 7, CH-8810 Horgen.

of junionone **1** can be constructed by a 4-*exo-trig* ring closure of the epoxy ketone **4** (*Scheme 1*) (see also in analogy [3]). *Wolff–Kishner* reduction of the resulting cyclobutanone **3**, followed by oxidation of the allylic alcohol **2**, would lead to junionone **1**. The C=C bond in **4** must possess (*E*)-configuration to prevent the 6-*exo-tet* mechanism to take place, which would lead to a six-membered ring by an $S_Ni$ reaction. In analogy to our earlier results [2], we expected the reaction to take place with *syn*-geometry relative to the leaving group and to proceed through two transitory arrangements **TA1** and **TA2** leading to either (*Z*)- or (*E*)-configuration of the C=C bond in product **3** (*Scheme 1*) [2]. The conformation adopted in **TA2** is strongly disfavored due to the more pronounced $A^{1,3}$ strain. Consequently, $S_Ni'$ reaction of (*R*,*R*)-(*E*)-**4**, proceeding through **TA1**, leads to (*S*)-junionone (*S*)-**1** with defined absolute configuration at C(1′). As the absolute configuration of natural junionone was not known, an enriched sample was isolated from juniper berry oil and compared to (+)-junionone, synthesized by the $S_Ni'$ method, using GC on chiral phase and ROA spectroscopy. The results allowed the determination of the distribution of the enantiomers in the sample and the absolute configuration of junionone found in nature.

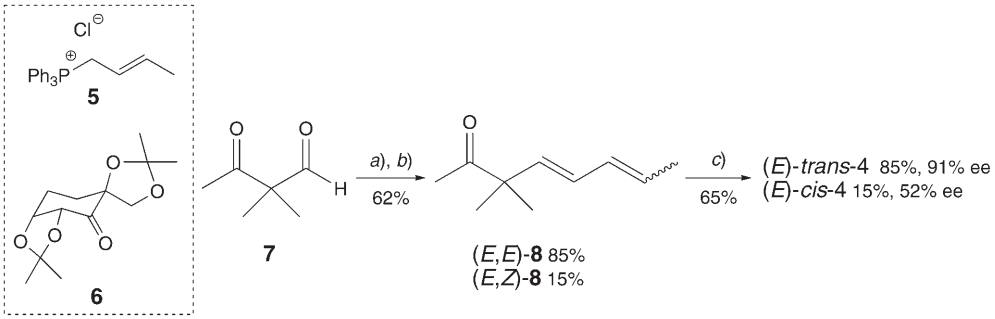
*Scheme 1*




**Results and Discussion.** – The starting material for the synthesis of the optically active key intermediate **4** is the oxo/aldehyde **7** (*Scheme 2*) which was synthesized according to a convenient protocol involving $BF_3 \cdot Et_2O$ induced rearrangement of 3,4-

epoxy-4-methylpentan-2-one [4], readily prepared on a large scale by action of alkaline $H_2O_2$ on mesityl oxide [5]. Chemoselective *Wittig* reaction of **7** with **5** led to a mixture of four isomers of **8** in a ratio of 4.3 : 1.2 : 2.5 : 1 [6]. This number of isomers was reduced by treating the mixture with a catalytic amount of $I_2$ in MeOH at room temperature to give 85% of (*E*,*E*)-**8** and 15% of (*E*,*Z*)-**8**. The configuration of the two isomers was determined by $^{13}$C-NMR spectroscopy. Regio- and enantioselective mono-epoxidation was performed according to the protocol of *Shi* and co-workers [7]. Catalyst **6** for the oxidation with $KHSO_5$ is not commercially available and has to be prepared by acetalization of D-fructose with acetone, followed by oxidation of the resulting diacetal with pyridinium chlorochromate (PCC) [8]. The *cis*/*trans* ratio and enantiomeric excess of the epoxide moiety in **4** was determined by $^1$H-NMR experiments with optically active shift reagents and found to be 85% (*E*)-*trans*-**4** (91% ee) and 15% (*E*)-*cis*-**4** (52% ee).

*Scheme 2*

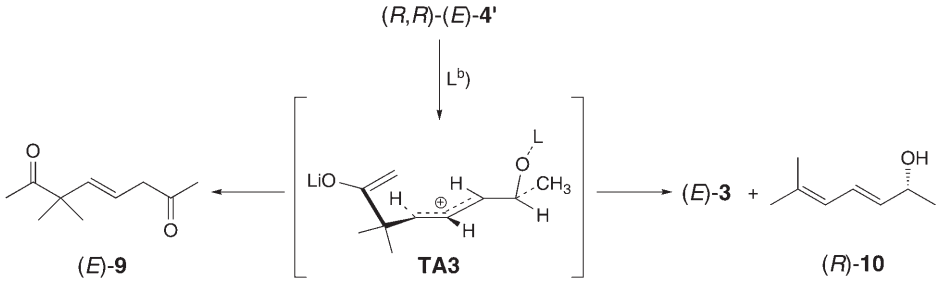



*a*) **5**, BuLi, benzene, 5°, 30 min. *b*) $I_2$, MeOH, r.t., 48 h. *c*) **8**, Oxone ($KHSO_5$), $K_2CO_3$, buffer, −10°.

ROA Spectroscopy presents a powerful tool for determining the absolute configuration of epoxides. To obtain a clean ROA spectrum, the (*E*)- and (*Z*)-isomers of **8** were separated by chromatography over silica gel impregnated with $AgNO_3$. A sample of pure (*E*,*E*)-**8** was converted to the mono-epoxide (*E*)-*trans*-**4** and then submitted to ROA spectroscopy. On the basis of the spectroscopic data and Gaussian 03 calculations, it was possible to unambiguously determine the (*R*,*R*)-configuration of **4** [9]. First attempts to perform the $S_Ni'$ reaction on **4** with $^t$BuOK in THF according to the procedure of *Fráter et al.* failed [10]. When the $S_Ni'$ reaction was attempted with lithium hexamethyldisilazane (LiHMDS) at −68°, elimination product **10** and only small amounts of the desired product **3** were isolated by preparative TLC. A strong C=O band at 1775 cm$^{-1}$ in the IR spectrum of **3** indicated the presence of a cyclobutanone structure [10]. These results showed that the epoxide must be activated to promote the 4-*exo*-*trig* ring closure and to inhibit formal 'ketene' elimination. $BF_3 \cdot Et_2O$ has been reported to be a good *Lewis* acid to increase the electrophilicity of epoxides [11]. The reaction was carried out by preparing the lithium enolate **4′** of **4** with LiHMDS at low temperatures and then adding 1 equiv. of $BF_3 \cdot Et_2O$ to the reaction mixture. Although the yield could be improved significantly, the $BF_3 \cdot Et_2O$-assisted cyclization of **4′** was accompanied by severe loss of stereoselectivity leading to (−)-(*E*)-

**3** with only 11% ee at C(3) of the cyclobutanone ring. The results led to the conclusion that the reaction proceeds at least partially *via* the ionic (*E*)-transitory arrangement **TA3** (*Table*). Although the experimental results indicate that cyclobutanone **3** can be synthesized by the reaction illustrated in *Scheme 1*, there were still two major problems to solve. The reaction proceeds with low yield (50%), mostly due to the competing hydride shift affording (*E*)-**9**. The low enantioselectivity observed was due to the loss of facial selectivity of the intermediate allyl cation **TA3**. To improve the stereoselectivity of the cyclization, it was desirable to find a 'softer' *Lewis* acid that would coordinate to the epoxide O-atom and weaken the C–O bond, without actually breaking it, therefore, allowing a $S_Ni'$ reaction to take place. The results obtained with different *Lewis* acids are summarized in the *Table.*

Table. *Cyclization Experiments of (*R,R*)-(*E*)-***4'*** with Different* Lewis *Acids*[a])

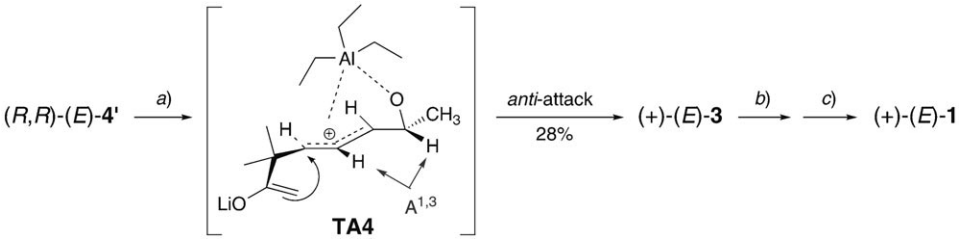



| *Lewis* acid (L) | Major product | Yield [%] (% ee)[c]) | Minor product | Yield [%] (% ee) | Ref. |
|---|---|---|---|---|---|
| None | (*R*)-**10** | 80 | (–)-(*E*)-**3** | 13 (16) | – |
| $BF_3 \cdot Et_2O$ | (–)-(*E*)-**3** | 50 (16) | (*R*)-**10** | 20 | [11] |
| $ZnCl_2 \cdot Et_2O$ | (*R*)-**10**+SM | 30 | – | – | [12] |
| $LiClO_4$ | (*R*)-**10**+SM | 50 | – | – | [13] |
| $Y(OTf)_3$[d]) | (*R*)-**10** | quant. | – | – | [14] |
| $Sc(OTf)_3$[d]) | (*R*)-**10** | 10 | intractable mat. | – | [15] |
| $Et_3Al$ | (+)-(*E*)-**3** | 28 (43) | (*E*)-**9**+(*R*)-**10** | – | – |
| $Me_3SiOTf$ | (–)-(*E*)-**3** | 69 (10) | – | – | [16] |

[a]) (*R,R*)-(*E*)-**4** and LiHMDS (1.2 equiv.), THF, –60°. [b]) *Lewis* acid (1.2 equiv.), –60°. [c]) The indicated ee value refers to C(3) on the cyclobutanone ring. [d]) Reaction carried out in toluene.

We found that the use of $Me_3SiOTf$ resulted in the highest yield (69%) although leading to significant loss of stereoselectivity. The best result in terms of enantioselectivity was obtained with $Et_3Al$ (43% ee), albeit the yield was rather low (28%). It was interesting to observe the change of sign of the optical rotation of the product, indicating that a different reaction mechanism was in effect in the $Et_3Al$-mediated reaction. It is imaginable that $Et_3Al$ coordinates simultaneously to the epoxide O-atom, and the forming allyl cation, thereby shielding the *si*-face of the molecule, forcing the enolate to attack *anti* to the epoxide. The selective formation of an (*E*)-double bond in (+)-junionone (+)-(*E*)-**1** indicates that the transitory arrangement **TA4** may be in effect, thereby minimizing the unfavorable $A^{1,3}$ strain (*Scheme 3*).

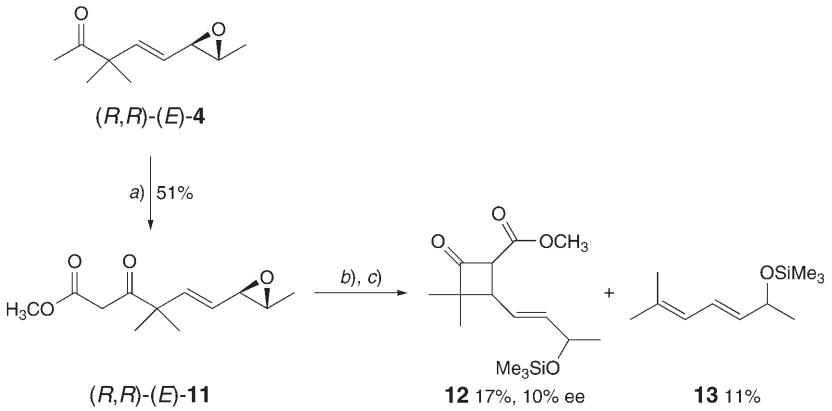
*Scheme 3*




*a*) Lithium hexamethylsilazane (LiHMDS), THF, $Et_3Al$, $-60°$, 30 min. *b*) $(HOC_2H_4)_2O$, $NH_2NH_2$, KOH, 190°. *c*) Pyridinium chlorochromate (PCC), molecular sieves (4 Å).

*Toromanoff et al.* performed a $S_Ni'$ reaction leading to cyclopentanone in the key step of the prostaglandin synthesis. In analogy to that procedure, **11** was prepared from **4** and methyl cyanoformate (*Scheme 4*) [3]. Deprotonation with LiHMDS and treatment with $Me_3SiOTf$ led to cyclobutanone **12** in 17% yield and *ca.* 10% ee, together with the fragmentation product **13** (11%) and intractable material. Attempts to convert **11** to the pyrrolidine enamine following the example by *Toromanoff et al.* failed, the apparent difference being the fully substituted 4-position of **11** in our case.

*Scheme 4*




*a*) LiHMDS, methyl cyanoformate, $-60°$, 30 min. *b*) LiHMDS, 0°, 30 min. *c*) $Me_3SiOTf$, $-60°$, 30 min.

Ring closure of **4′** using both $Me_3SiOTf$ and $Et_3Al$, followed by *Wolff–Kishner* reduction of the cyclobutanone carbonyl and oxidation of the allylic alcohol with pyridine chlorochromate, led to (−)- and (+)-**1** in 10% and 43% ee respectively. The olefinic H-atoms showed a coupling constant of 16.1 Hz in the $^1$H-NMR (500 MHz, $CDCl_3$, 5.99 and 6.83 ppm) spectrum indicating the presence of a (*E*)-configured C=C bond. According to GC/MS analysis, juniper berry oil contains at least 224 different compounds. The concentration of junionone was found to be *ca.* 0.01%, terpenes and more complex polycyclic hydrocarbons constitute the bulk of the compounds (*ca.* 90%) in the mixture. To obtain credible results, an enriched sample of natural junionone was

isolated from 1 kg of natural juniper berry oil. The hydrocarbons were removed by column chromatography over silica gel with hexane as an initial solvent. The polarity of the solvent was increased by adding *tert*-butyl methyl ether (*t*-BuOMe), and the eluate was collected in fractions and analyzed by GC and GC/MS. A colorless oil (250 mg) containing 7% of natural junionone was isolated and further purified by preparative HPLC, leading to 32 mg of colorless oil containing 55% natural junionone. Examination by GC on chiral phase revealed an enantiomeric excess of 43%. During the isolation process from natural juniper berry oil, the compounds were adsorbed on silica gel for extended periods of time. A stability test with optically active junionone on silica gel showed no sign of racemization even after several weeks. It can, therefore, be concluded that the junionone did not racemize in our hands during the isolation process[2]).

Synthetic (+)-junionone ((+)-(*E*)-**1**), prepared by $Et_3Al$ activation of the epoxide in **4′**, was analyzed by GC on chiral phase (*Fig. 1*). Coincidentally, the distribution of enantiomers of our synthetic (+)-junionone (43% ee) corresponds precisely to that of the natural junionone.

To unambiguously determine the absolute configuration, samples of the synthetic junionone (+)-(*E*)-**1** and the junionone isolated from juniper berry oil were subjected to *Raman* Optical Activity (ROA) spectroscopy. Based on *ab initio* computations [19], the absolute configuration of (+)-(*E*)-**1** was assigned as (*R*). *Fig. 2* shows the comparison of the *Raman* and ROA spectra, recorded in scattered circular polarization (SCP) backscattering. The general agreement of the ROA spectra leaves no doubt about the (*R*)-configuration of natural junionone, despite the presence of bands due to impurities, and despite a small positive offset for the natural sample. We have marked by asterisks the two most prominent ROA bands that are present in the natural sample and have no correspondence in the synthetic one. They correlate well with bands that are present in the *Raman* spectrum of the natural sample, and that do not appear in the synthetic one. The presence of many additional *Raman* bands, devoid of measurable ROA, visible in the *Raman* spectrum of the natural sample indicates that some of the impurities are achiral. The data demonstrate the decisive advantage which the presence of the numerous vibrational transitions, as compared to the much sparser electronic transitions in electronic spectroscopy, imparts to vibrational optical activity, when the absolute configuration of an impure compound needs to be safely assigned.

We have normalized the scattering intensities by dividing the number of electrons registered on the CCD detector, per element of its spectral resolution of 2.4 $cm^{-1}$, by the exciting energy of the laser passed through the sample. For measurements performed, on the same instrument with identical sample cells, the scattering intensities can be compared. One finds that differences between neighboring ROA signals with opposite signs for natural junionone, in those spectral regions where contributions from optically active impurities appear small, amount to 50–65% of the signals observed for synthetic junionone. From GC on chiral phase, we know that the ee values of both

---

[2]) Our result does not necessarily reflect the actual distribution of enantiomers of junionone in nature, for the values can differ depending on the geographic origin of the plant material [17]. In addition, we are not familiar with the conditions by which the oil was manufactured [18].

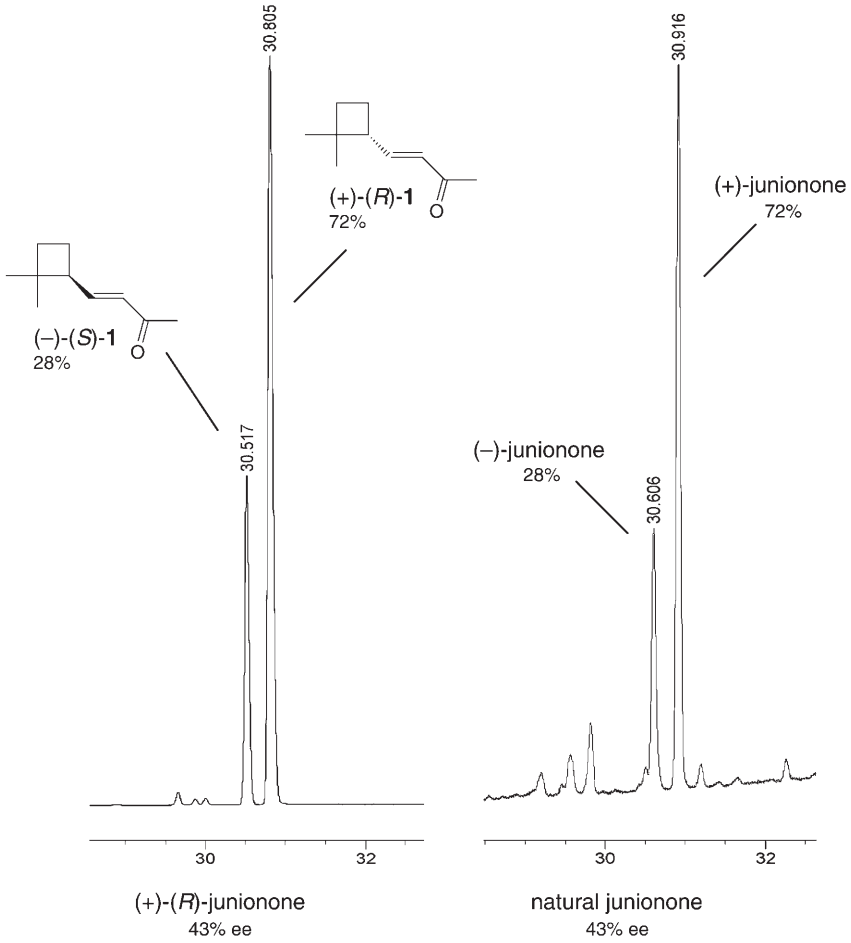



Fig. 1. *GC on chiral phase of synthetic (+)-junionone* vs. *natural junionone*

samples are the same (43%), and the relative size of the ROA signals thus is consistent with the presence of 55% junionone in the natural sample as determined by GC.

The computations [19] show that four conformers are present in more than 10% abundance. The vibrational energy representation of vibration 42 of the most prominent conformer is depicted in *Fig. 3*, with the corresponding ROA band marked in the experimental spectrum in *Fig. 2*. This vibration was chosen because of its typical spectral range, and because its computed ROA has the same sign for all conformers. Like some related vibrations in its vicinity, vibration 42 has a substantial wagging component from one of the $CH_2$ groups of the cyclobutane ring.

As the ROA measurements were undertaken after all other analytical tests had been performed, less than 1 mg of sample remained available. This is less than would have been required for mechanical purification, and we attribute the slight, positive offset in the measured ROA spectrum of the natural sample to the presence of dust.

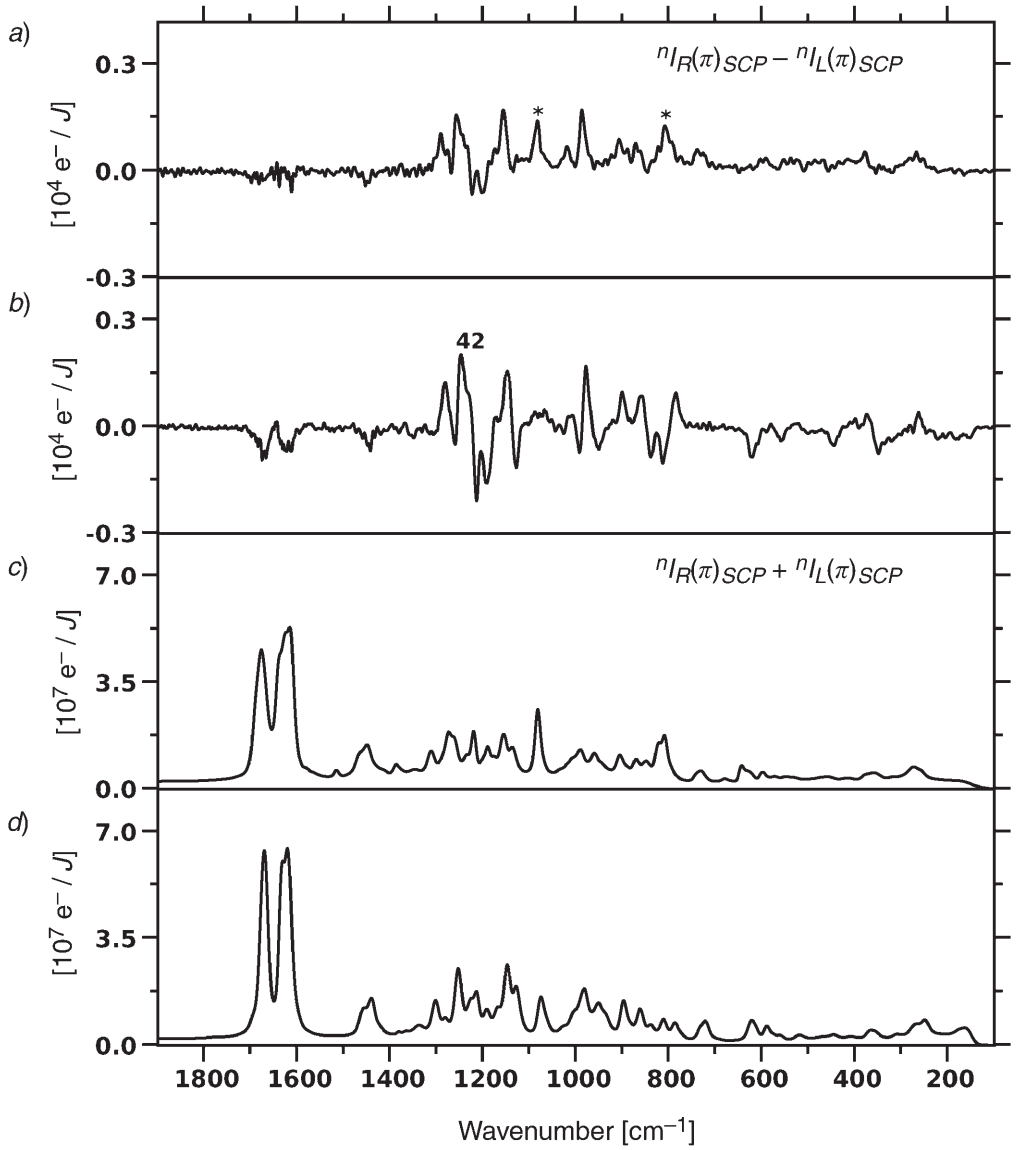



Fig. 2. Raman *and ROA SCP backscattering spectra of the sample of natural junionone* (curves *a* and *c*) *and of the synthetic (+)-(*R*)-(*E*)-junionone* (curves *b* and *d*). Measurement times and laser powers at the sample: curves *a* and *c*, 45 min and 300 mW; curves *b* and *d*, 60 min and 200 mW. Exciting wavelength: 532 nm. Resolution: 7 cm$^{-1}$. Sample sizes: columns of 4 mm of substance in 0.557-mm inner-diameter micro-capillaries corresponding to 1 µl. The vertical scale represents numbers of detected electrons per joule per column of the CCD detector, with one column covering 2.4 cm$^{-1}$ of spectral width. Onset of cut-off of the optical filters is *ca.* 160 cm$^{-1}$. The curves are slightly smoothed with a third-order five-points *Savitzky–Golay* procedure. The two major bands due to impurities are marked by asterisks, see text.

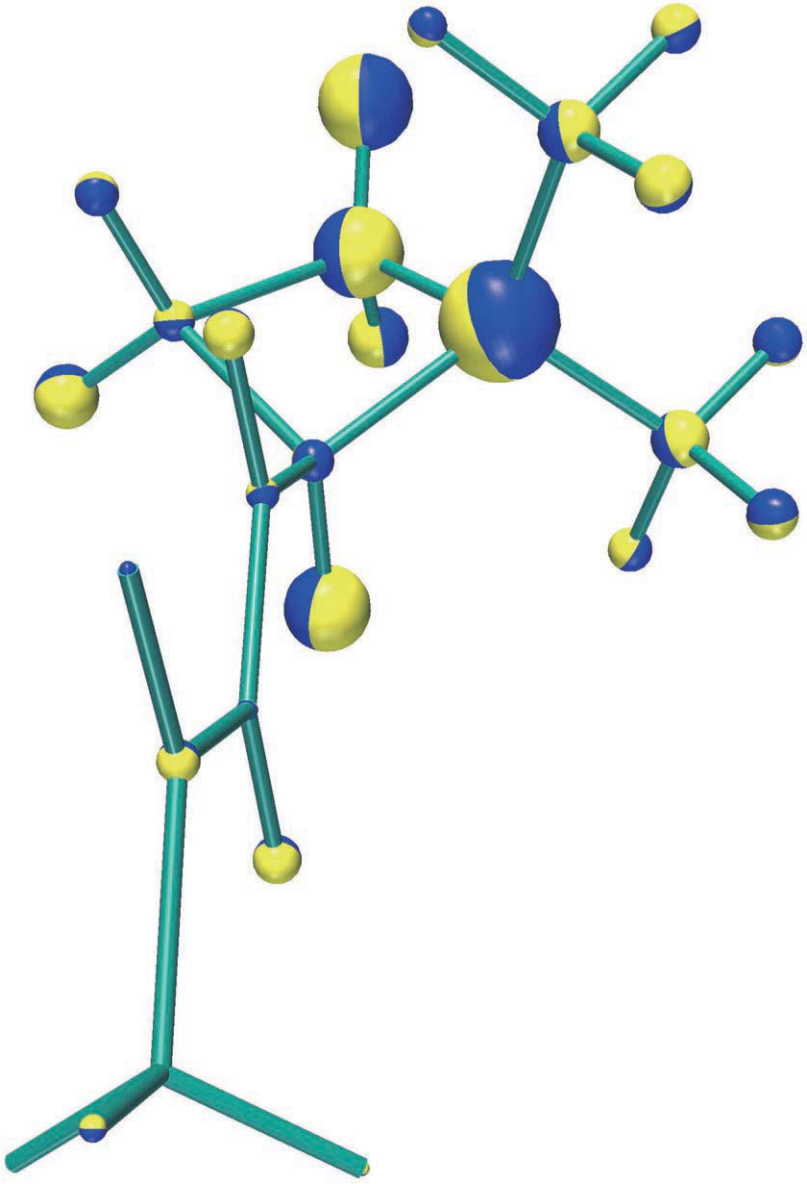


Fig. 3. *Vibrational energy representation of vibration 42 of the most abundant* (43%) *conformer of (+)-(*R*)-(*E*)-junionone.* The volume of the spheres is proportional to the vibrational energy of the nuclei, with the direction of motion perpendicular to the surface separating the two halves of the spheres depicted in different colors. Computational parameters: density functional theory with the B97-1 functional and the rr-pc-2 basis set [20].

Due to the small amount of substance available, we were required to use capillaries with a 0.557-mm inner diameter thus being far smaller than what has up to now been

thought possible for ROA backscattering measurements. While small diameter capillaries do not lead to problems in right angle scattering [21], we did, at the outset, not expect them to yield reliable ROA data in a backscattering arrangement. With the present results at hand, it is obvious that the optical correction scheme [22] of our instrument permits the elimination of deterministic offsets also for small capillaries. We believe, moreover, that the substantial reduction in scattering intensities observed in the present work can be compensated for in part by the use of faster than the employed *f*/1.1 light collection optics.

**Conclusions.** – Our findings offer a new stereoselective route to (+)-(*R*)- and (−)-(*S*)-junionone, an olfactorily interesting natural cyclobutane monoterpenoid isolated from *Juniperus communis* L. Based on our results obtained from the stereoselective $S_Ni'$ ring closure leading to cyclobutanones [2], (+)- and (−)-junionone were prepared from (*R*,*R*)-(*E*)-**4′**, followed by reduction of the cyclobutanone **3** and oxidation of the allylic alcohol **2**. The epoxide moiety in (*R*,*R*)-(*E*)-**4′** was not reactive enough to enable nucleophilic attack of the ketone enolate and had to be activated with a *Lewis* acid. $BF_3 \cdot Et_2O$ and $(CH_3)_3SiOTf$ were suitable, leading to the desired cyclobutanone (−)-(*E*)-**3** in 50 and 69% yield, respectively. Under these reaction conditions, significant loss of stereochemical integrity was observed at C(3) of the intermediate cyclobutanone **3**. A competing reaction mechanism involving an allyl cation intermediate was considered to be in effect. The observed (*E*)-configuration of the C=C bond in the product led to the conclusion that (*R*,*R*)-(*E*)-**4′** must adapt a *trans*-conformation in the transitory molecular arrangement, and loss of stereoselectivity results from the lack of *syn*/*anti* preference of the allyl cation. Extensive experimental research on the effect of different *Lewis* acids on the yield and stereoselective outcome of the reaction showed that epoxide activation with $Et_3Al$ results in enrichment of the opposite enantiomer leading to (+)-junionone (+)-(*R*)-(*E*)-**1** in 43% ee, after *Wolff–Kishner* reduction and oxidation with pyridinium chlorochromate (PCC).

A sample of enriched natural junionone was isolated from juniper berry oil and compared with synthetic (+)-junionone by GC on chiral phase and ROA spectroscopy. It was demonstrated, for the first time, that ROA backscattering spectra can be obtained from 1 mg of sample in capillaries with a 0.557-mm inner diameter. The results led to the conclusion that junionone, isolated from a natural source, occurs predominantly as the (+)-(*R*)-enantiomer.

Funding by *Givaudan* is gratefully acknowledged. *M. L.* thanks Prof. Dr. *Heinz Heimgartner* and his group from the University of Zurich for many valuable discussions. We are grateful to Dr. *Gerhard Brunner* from *Givaudan* for his help with various NMR related problems and to *Katarina Grman* from *Givaudan* for performing the GC on chiral phase, as well as to Dr. *Roman Kaiser* for his advice and support for the isolation of the natural junionone.

## Experimental Part

*General.* Column chromatography (CC): silica gel *Chemie Uetikon ZEOCHEM C-Gel C-560*, particle size 40–63 μm, eluant hexane and *t*-BuOMe. TLC: commercial *60*-mesh-silica gel plates, visualization with short-wavelength UV light (254 nm) and $KMnO_4$ staining reagent. Standard GC: *HP 5890* instrument with *HP 3396A* integrator and a *DB5* 30-m, 0.53-mm column. GC on chiral phase: *Fisons 8560* instrument; column: *Beta-Dex-110* (*Supelco*), 60 m, I.D. 0.25 mm, df 0.25 μm; carrier gas: $H_2$,

3.0 ml/min; sample amount: 0.1 µl ($c = 1.0$, MeOH). IR Spectra: were recorded on *Spectrum One FT-IR*- and *Bruker Vector 22 FT-IR* spectrometers. $^1$H- and $^{13}$C-NMR spectra: *Bruker AC-300*, *Bruker ARX-300* (both 300 MHz), or *Bruker Avance DPX-500* spectrometer; $\delta$ in ppm (relative to internal TMS), $J$ in Hz; $CDCl_3$ and $C_6D_6$ as solvents. The ee values of all chiral intermediates were determined by NMR experiments using 1-(anthracen-9-yl)-2,2,2-trifluoroethanol (*Pirkle*'s reagent) as chiral shift reagent in $C_6D_6$. In $^{13}$C-NMR spectra, the solvent itself served as the internal standard: $CDCl_3$ ($\delta$(C) = 77.00 ppm, *t*, $J$(C,D) = 31.5 Hz). The multiplicity is designated *q* (quadruplet) for $CH_3$, *t* (triplet) for $CH_2$, *d* (doublet) for CH, and *s* (singlet) for fully substituted C-atoms. MS in electron impact (EI) mode at 70 eV, with a source temp. of 200°, an acceleration voltage of 5 kV, and a resolution of 10000. GC/MS: *HP MSD 5973* instrument with a 30-m *HP5*/*MS* or *Varian VF5ms* column. High-resolution MS (HR-MS): *Finnigan MAT 95*. The *Raman* optical activity measurements were performed on a newly constructed instrument at the University of Fribourg, with a design derived from the instrument described in [22]. The two instruments have recently been shown to yield virtually identical ROA data [23]. Most products were short path distilled by the '*Kugelrohr*'-method. The vacuum was provided either by a rotary slide pump (0.05 mbar) or by a water-jet vacuum pump (10 mbar). Natural junionone was isolated from juniper berry oil of *Juniperus communis* L. from *Biolandes*/France.

*(4*E*,6*E/Z*)-3,3-Dimethylocta-4,6-dien-2-one* ((*E*,*E*/*Z*)-**8**). The allylic phosphonium salt **5** (11.00 g, 30.00 mmol, (*E*)/(*Z*) 4:1) was suspended in benzene (40.0 ml) and cooled to 5°. BuLi (18.75 ml, 30.00 mmol, 1.6M in hexane) was added dropwise to the stirred suspension over 20 min. The mixture was stirred at 5° for 30 min and then placed in a standard ultrasonic laboratory cleaning bath for 10 min. The deep red soln. was removed from the ultrasonic bath and cooled to 5° while stirring. *2,2-Dimethyl-3-oxobutanoic acid* (**7**) (3.42 g, 30.00 mmol) was added dropwise as a soln. in benzene (10.0 ml), and stirring was continued for 30 min. The mixture was diluted with hexane (100.0 ml) and filtered over a pad of silica gel (hexane/*t*-BuOMe 8:2). After short-path distillation (0.05 mbar, 70°), **8** (3.45 g, 76%) was isolated as a colorless liquid, tentatively consisting of a mixture of the four possible (*E*)/(*Z*) isomers in a ratio of 4.3:1.2:2.5:1, as determined by GC.

The mixture of C=C bond isomers of **8** was dissolved in MeOH (100.0 ml), and $I_2$ (0.50 g, 4.00 mmol) was added in several small portions during 48 h. The black mixture was treated with several drops of NaOH (30%) until the soln. discolored to a pale yellow liquid. The mixture was poured into $H_2O$ (200.0 ml) and extracted with *t*-BuOMe. The *t*-BuOMe layers were washed with $H_2O$ and brine, and concentrated. Purification of the residue over silica gel (hexane/*t*-BuOMe 9:1), followed by short-path distillation (0.05 mbar, 70°), furnished **8** (2.14 g, 62%). Colorless oil. The (*E*)/(*Z*)-ratio of the C(6)=C(7) bond (85:15) was determined by integrating the $^{13}$C-NMR signals (75 MHz, $CDCl_3$) of C(8) at $\delta$ 18.1 for (*E*,*E*)-**8** and 15.2 for (*E*,*Z*)-**8**. IR (neat): 2973*m*, 1707v*s*, 1466*w*, 1353*m*, 1232*w*, 1123*m*, 989*s*, 953*w*, 925*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.10–5.90 (*m*, 2 H); 5.69 (*dd*, $J$ = 13.8, 7.0, 1 H); 5.34 (*d*, $J$ = 10.2, 1 H); 2.13 (*s*, 3 H); 1.73 (*d*, $J$ = 6.2, 3 H); 1.27 (*s*, 6 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 212.5 (*s*); 132.8, 132.7, 130.9, 126.3 (4*d*); 65.8 (*s*); 49.5, 26.3 (85%), 25.8 (15%) (3*q*); 18.1 (85%), 15.2 (15%) (1*q*). GC/EI-MS: 152 (9, $M^{+\bullet}$), 109 (100), 91 (15), 81 (39), 79 (23), 77 (21), 67 (88), 55 (23), 43 (48). Anal. calc. for $C_{10}H_{16}O$ (152.12): C 78.90, H 10.59; found: C 78.13, H 10.06.

*(4*E*)-3,3-Dimethyl-5-[(2*R*,3*R*)-3-methyloxiran-2-yl]pent-4-en-2-one* ((*R*,*R*)-(*E*)-**4**). A mixture of dimethoxymethane (130.0 ml) and MeCN (70.0 ml) was placed in a reactor (1.5 l), and (*E*,*E*/*Z*)-**8** (2.00 g, 13.16 mmol, 85:15) was added. $Bu_4NHSO_4$ (380 mg, 1.00 mmol), buffer soln. (250.0 ml, 0.05M $Na_2B_2O_4 \cdot 10\ H_2O$ in aq. $4 \cdot 10^{-4}$ M ethylenediaminetetraacetic acid (EDTA)) and *Shi* catalyst **6** (1.60 g, 6.27 mmol) were added, and the soln. was cooled to $-10°$ by means of an ice/NaCl bath. A soln. of oxone ($KHSO_5$; 152 ml, 17.25 g, 28.25 mmol in aq. $4 \cdot 10^{-4}$ M EDTA) and a soln. of $K_2CO_3$ (152 ml, 17.25 g, 124.73 mmol in aq. $4 \cdot 10^{-4}$ M EDTA) were added simultaneously from two dropping funnels over 1.5 h. After the addition of the oxone and $K_2CO_3$ solns., the mixture was stirred for 1 h at $-10°$. The reaction was quenched by addition of hexane (1.0 l). The layers were separated, and the aq. layer was extracted with hexane. The combined org. layers were washed with $H_2O$ and brine, dried, and concentrated. Chromatography over silica gel (hexane/*t*-BuOMe 8:2) and short-path distillation (0.05 mbar, 110°) afforded (*R*,*R*)-(*E*)-**4** (1.17 g, 53%). Colorless oil. $[\alpha]_D^{25} = +44.88$ ($c$ = 1.050, MeOH). IR (neat): 2972*m*, 1707*s*, 1446*m*, 1354*m*, 1239*w*, 1123*m*, 1010*m*, 971*m*, 929*m*, 867*m*, 812*m*, 740*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 5.99 (15%) (*d*, $J$ = 15.8, 1 H); 5.96 (85%) (*d*, $J$ = 15.8, 1 H); 5.42 (15%) (*dd*, $J$ = 15.8, 7.2, 1 H);

5.26 (85%) (*dd*, *J* = 15.8, 7.8, 1 H); 3.39 (15%) (*dd*, *J* = 7.2, 4.3, 1 H); 3.18–13.20 (15%) (*m*, 1 H); 3.05 (85%) (*dd*, *J* = 7.8, 2.1, 1 H); 2.87–2.91 (85%) (*m*, 1 H); 2.11 (15%) (*s*, 3 H); 2.10 (85%) (*s*, 3 H); 1.31 (*d*, *J* = 5.2, 3 H); 1.21 (*d*, *J* = 3.1, 6 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 210.5 (*s*); 140.6 (15%), 139.2 (85%), 127.4 (2*d*); 59.2, 56.7 (85%), 56.3 (85%) (2*d*); 50.1 (*s*); 25.4, 23.82 (15%), 23.74 (85%), 23.68 (15%), 23.56 (85%), 17.3 (85%), 13.15 (15%) (4*q*). GC/EI-MS: 168 (11, $M^{+\cdot}$), 150 (13), 125 (33), 124 (57), 110 (43), 108 (100), 92 (53), 90 (51), 80 (48), 78 (54), 76 (54), 66 (67), 64 (64), 54 (76). Anal. calc. for $C_{10}H_{16}O_2$ (168.12): C 71.39, H 9.59; found: C 71.44, H 9.47.

*Methyl (5*E*)-4,4-Dimethyl-6-[(2*R,*3*R*)-3-methyloxiran-2-yl]-3-oxohex-5-enoate* ((*R*,*R*)-(*E*)-**11**). Hexamethyldisilazane (HMDS; 1.21 g, 7.02 mmol) was dissolved in THF (20.0 ml), and the soln. was cooled to $-10°$. BuLi (4.70 ml, 7.50 mmol, 1.6M in hexane) was added dropwise, and the mixture was stirred for 15 min. A soln. of (*R*,*R*)-(*E*)-**4** (1.18 g, 7.02 mmol) in THF (4.0 ml) was added dropwise. After stirring for 20 min, the mixture was cooled to $-60°$ by means of an acetone/$CO_2$ bath. Methyl cyanoformate (0.84 ml, 10.52 mmol) was added in 5 min, and the mixture was stirred at $-60°$ for 30 min. The mixture was poured into $H_2O$ and extracted with *t*-BuOMe. The combined *t*-BuOMe layers were washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated. Chromatography over silica gel (hexane/*t*-BuOMe 8:2), followed by short path distillation (0.05 mbar, 100°), afforded (*R*,*R*)-(*E*)-**11** (810 mg, 51%). Colorless oil. $[\alpha]_D^{25} = +36.30$ (*c* = 1.485, MeOH). IR (neat): 2973*m*, 1707*s*, 1467*w*, 1354*m*, 1238*w*, 1123*m*, 1010*m*, 971*m*, 929*m*, 867*m*, 812*m*, 740*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.12 (*d*, *J* = 16.4, 1 H); 5.52 (*dd*, *J* = 16.0, 7.6, 1 H); 3.89 (*s*, 3 H); 3.70 (*s*, 2 H); 3.25 (*d*, *J* = 7.6, 2.3, 1 H); 3.07–3.11 (*m*, 1 H); 1.52 (*d*, *J* = 5.0, 3 H); 1.43 (*d*, *J* = 2.3, 6 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 204.5, 167.7 (2*s*); 137.8, 128.6, 58.9, 56.3 (4*d*); 52.1 (*q*); 50.4 (*s*); 44.2 (*t*); 23.4, 23.3, 17.3 (3*q*). GC/EI-MS: 226 (1, $M^{+\cdot}$), 208 (1 $[M-H_2O]^+$), 195 (2), 183 (6), 167 (17), 125 (23), 108 (24), 101 (35), 93 (19), 83 (40), 69 (21), 55 (30) 43 (100).

*General Procedure for the Cyclization of (*R,R*)-(*E*)-***4*** and (*R,R*)-(*E*)-***11*** with* Lewis *Acids.* A soln. of HMDS (230 mg, 1.43 mmol) in THF (4.0 ml) was cooled by means of an ice/$H_2O$ bath, and BuLi (0.89 ml, 1.43 mmol, 1.6M in hexane) was added dropwise keeping the temp. between 5° and 10°. The soln. was stirred for 15 min and then cooled to $-60°$ by means of a $CO_2$/acetone bath. A soln. of the epoxide (1.19 mmol) in THF (1.0 ml) was added dropwise. The mixture was stirred for 15 min, and then the corresponding *Lewis* acid (1.43 mmol) was added by syringe. The reaction was monitored by TLC analysis (hexane/*t*-BuOMe 1:1). The mixture was poured into $H_2O$ and extracted with *t*-BuOMe. The org. layers were combined, washed with $H_2O$ and brine, and concentrated. The resulting cyclobutanone was isolated by chromatography over silica gel (hexane/*t*-BuOMe 1:1) and short-path distillation (0.05 mbar, 60°).

*(3*S*)-3-[(1*E*,3*R*)-3-Hydroxybut-1-en-1-yl]-2,2-dimethylcyclobutanone* ((*S*,*R*)-(*E*)-**3**). The reaction was performed according to the general procedure with $Me_3SiOTf$ as the *Lewis* acid. The crude product was dissolved in THF (5.0 ml), and $Bu_4NF$ (200 mg) was added. The mixture was stirred for 1 h to remove the $Me_3Si$ group from the allylic alcohol. Purification gave (*S*,*R*)-(*E*)-**3** (140 mg, 69%, 10% ee). Colorless oil. $[\alpha]_D^{25} = -2.14$ (*c* = 1.260, MeOH). IR (neat): 3435*m*, 2963*m*, 1775*s*, 1462*w*, 1365*w*, 1251*m*, 1143*m*, 1062*s*, 972*m*, 840*s*, 753*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 5.79–5.60 (*m*, 2 H); 4.31–438 (*m*, 1 H); 3.22–3.11 (*m*, 1 H); 2.98 (*dd*, *J* = 17.5, 7.6, 1 H); 2.68–2.72 (*m*, 1 H); 1.90 (*s*, 1 H); 1.29 (*d*, *J* = 6.1, 3 H); 1.20 (*d*, *J* = 0.8, 3 H); 1.05 (*d*, *J* = 1.1, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 213.9 (*s*); 136.6, 128.3, 128.2, 68.3 (3*d*); 63.0 (*s*); 47.6, 47.5 (1*t*); 38.5, 38.4 (1*d*); 23.5, 22.8, 18.2 (3*q*). GC/EI-MS: 168 (1, $M^{+\cdot}$), 150 (2), 135 (2), 126 (27), 111 (59), 108 (79), 93 (35), 81 (38), 70 (100), 55 (32), 43 (71). EI-HR-MS: 168.1147 ($M^+$, $C_{10}H_{16}O_2^+$; calc. 168.1150).

*(3*R*)-3-[(1*E*,3*R*)-3-Hydroxybut-1-en-1-yl]-2,2-dimethylcyclobutanone* ((*R*,*R*)-(*E*)-**3**). The reaction was performed according to the general procedure with $Et_3Al$ as the *Lewis* acid. Purification yielded (*R*,*R*)-(*E*)-**3** (56 mg, 28%, 43% ee). Colorless oil. $[\alpha]_D^{25} = +10.90$ (*c* = 1.050, MeOH).

*Methyl 3,3-Dimethyl-4-oxo-2-[(1*E*)-3-(trimethylsilyloxy)but-1-en-1-yl]cyclobutanecarboxylate* (**12**). The reaction was performed according to the general procedure starting from (*R*,*R*)-(*E*)-**11** (100 mg, 0.44 mmol) with $Me_3SiOTf$ as the *Lewis* acid. After purification by chromatography over silica gel (hexane/*t*-BuOMe 9:1), **12** (44 mg, 17%, 10% ee) and *2-methyl-6-(trimethylsilylyoxy)hepta-2,4-diene* (**13**; 18 mg, 11%) were obtained.

*Data of* **12**. $^1$H-NMR (300 MHz, $CDCl_3$): 5.50–5.59 (*m*, 2 H); 4.18–4.22 (*m*, 1 H); 3.94–4.03 (*m*, 1 H); 3.63 (*d*, *J* = 1.5, 3 H); 2.95–3.02 (*m*, 1 H); 1.09–1.13 (*m*, 6 H); 0.99 (*s*, 3 H); 0.00 (*s*, 9 H). $^{13}$C-NMR

(75 MHz, $CDCl_3$): 204.9, 166.8 (2*s*); 138.4, 124.6, 124.3, 68.5, 68.2, 64.1, 64.0 (4*d*); 62.4 (*s*); 52.2 (*q*); 41.5 (*d*); 24.3, 22.0, 18.6 (3*q*); 0.0 (3*q*).

*Data of* **13**. $^1$H-NMR (300 MHz, $CDCl_3$): 6.18–6.22 (*m*, 1 H); 5.65–5.69 (*m*, 1 H); 5.43 (*dd*, *J* = 15.3, 6.5, 1 H); 4.19–4.24 (*m*, 1 H); 1.64 (*d*, *J* = 6.1, 6 H); 1.12 (*d*, *J* = 6.1, 3 H); 0.00 (*s*, 9 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 134.8 (*s*); 134.7, 124.9, 124.2, 69.0 (4*d*); 25.7, 24.3, 17.9 (3*d*); 0.0 (3*q*).

*(3*E*)-4-[(1*S*)-2,2-Dimethylcyclobutyl]but-3-en-2-one* ((*S*)-(*E*)-**1**). A mixture of (*S*,*R*)-(*E*)-**3** (100 mg, 0.60 mmol), diethylene glycol (1.0 ml), $NH_2NH_2$ (80 µl, 2.20 mmol, 85% ) and one pellet of solid KOH (112 mg, 2.00 mmol) was heated to 100–120°. When the soln. became clear and homogeneous, the temp. was raised to reflux (125°) for 30 min. The condenser was removed, and the volatiles were removed by a constant stream of $N_2$. Heating was continued until the interior temp. reached 185–190°. Stirring was continued at this temp. for 2 h. After cooling to r.t., the mixture was poured into $H_2O$, and the mixture was extracted with *t*-BuOMe. The org. layers were combined, washed, dried, and concentrated. The crude product was purified by short-path distillation (0.05 mbar, 120°) and added to a suspension of powdered molecular sieves (4 Å; 0.10 g) and PCC (100 mg, 0.46 mmol) in $CH_2Cl_2$ (5.0 ml). The mixture was stirred at r.t. for 1 h. Hexane was added to the mixture under vigorous stirring until a black granular solid formed that settled rapidly. The solids were removed by filtration, and the clear filtrate was concentrated. The product was purified by short-path distillation (10 mbar, 80°). *(−)-Junionone* ((*S*)-(*E*)-**1**) was obtained as colorless oil (48 mg, 99%, 10% ee). $[\alpha]_D^{25} = -3.92$ (*c* = 0.605, $CHCl_3$). IR (neat): 2952*m*, 2863*w*, 1696*w*, 1671*s*, 1620*m*, 1462*w*, 1360*m*, 1253*s*, 1151*w*, 981*m*. $^1$H-NMR (500 MHz, $CDCl_3$): 6.83 (*dd*, *J* = 16.1, 7.3, 1 H); 5.99 (*dd*, *J* = 16.1, 1.6, 1 H); 2.72–2.76 (*m*, 1 H); 2.26 (*s*, 3 H); 1.99–2.03 (*m*, 1 H); 1.90–1.94 (*m*, 1 H); 1.76–1.80 (*m*, 1 H); 1.61–1.65 (*m*, 1 H); 1.13 (*s*, 3 H); 1.01 (*s*, 3 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 198.6 (*s*); 149.0, 130.6, 47.0 (3*d*); 40.8 (*s*); 32.6 (*t*); 30.0, 26.9, 23.4 (3*q*); 20.8 (*t*). GC/EI-MS: 152 (3, $M^{+\bullet}$), 137 (13, $[M-CH_3]^+$), 108 (80), 96 (100), 94 (49), 93 (45), 81 (46), 80 (88), 78 (49), 68 (37), 66 (41), 55 (54), 52 (55). EI-HR-MS: 152.1202 ($M^+$, $C_{10}H_{16}O^+$; calc. 152.1201).

*(3*E*)-4-[(1*R*)-2,2-Dimethylcyclobutyl]but-3-en-2-one* ((*R*)-(*E*)-**1**). The reduction/oxidation of (*R*,*R*)-(*E*)-**3** was performed according to the same procedure reported for (*S*,*R*)-(*E*)-**3**. (+)-Junionone (*R*)-(*E*)-**4** was obtained as a colorless oil (48 mg, 99%, 43% ee). $[\alpha]_D^{25} = +10.86$ (*c* = 1.010, $CHCl_3$).

## REFERENCES


[1] A. F. Thomas, M. Ozainne, *J. Chem. Soc., Chem. Commun.* **1973**, *19*, 746; see also: A. F. Thomas, to *Firmenich SA*, CH Pat. 559517 19750314; A. Ghosh, U. K. Banerjee, R. V. Venkateswaran, *Tetrahedron* **1990**, *46*, 3077; Y. Gaoni, A. Tomazic, *J. Org. Chem.* **1985**, *50*, 2948.

[2] M. A. Lovchik, Ph.D. Thesis, University of Zurich, 2006; M. A. Lovchik, A. Goeke, G. Fráter, *J. Org. Chem.* **2007**, *72*, 2427.

[3] E. Toromanoff, J. Martel, J. Mathieu, G. Nomine, *Tetrahedron Lett.* **1972**, *15*, 1491.

[4] H. O. House, R. L. Wasson, *J. Am. Chem. Soc.* **1956**, *78*, 4394.

[5] E. Weitz, A. Scheffer, *Ber. Dtsch. Chem. Ges.* **1921**, *54B*, 2327.

[6] C. M. R. Low, *Synlett* **1991**, 123.

[7] M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 2948.

[8] J. Herscovici, K. Antonakis, *J. Chem. Soc., Chem. Commun.* **1980**, 561.

[9] J. Haesler, M. A. Lovchik, W. Hug, in preparation.

[10] G. Fráter, U. Müller, W. Günther, *Tetrahedron* **1984**, *40*, 1269.

[11] M. Yamaguchi, K. Shibato, I. Hirao, *Tetrahedron Lett.* **1984**, *25*, 1159; M. Yamaguchi, I. Hirao, *Chem. Lett.* **1985**, 337; S. G. Davies, P. Warner, *Tetrahedron Lett.* **1985**, *26*, 4815.

[12] H. H. Wasserman, S. Wolff, T. Oku, *Tetrahedron Lett.* **1986**, *27*, 4909.

[13] M. Chini, P. Crotti, L. Favero, M. Pineschi, *Tetrahedron Lett.* **1991**, *32*, 7583.

[14] P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, M. Pineschi, *Tetrahedron Lett.* **1994**, *35*, 6537.

[15] P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, M. Pineschi, *J. Org. Chem.* **1996**, *61*, 9548; P. Crotti, F. Badalassi, V. Di Bussolo, L. Favero, M. Pineschi, *Tetrahedron* **2001**, *57*, 8559.

[16] M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1993**, *115*, 12208.

[17] M. L. Ruiz del Castillo, M. M. Caja, G. P. Blanch, M. Herraiz, *J. Food Prot.* **2003**, *66*, 1448.
[18] B. Weinreich, S. Nitz, *Technologie der Lebensmittel* **1992**, *14*, 117.
[19] D. Dudenko, W. Hug, to be published.
[20] W. Hug, M. Fedorovsky, *Theor. Chem. Acc.*; http://dx.doi.org/10.1007/s00214-006-0185-2.
[21] W. Hug, *Appl. Spectrosc.* **1981**, *35*, 115.
[22] W. Hug, *Appl. Spectrosc.* **2003**, *57*, 1.
[23] W. Hug, J. Haesler, S. I. Kozhushkov, A. de Meijere, *ChemPhysChem* **2007**, *8*, 1161.