Enantioselectivity in Odor Perception: Synthesis and Olfactory Properties of Iso-β-Bisabolol, a New Natural Product

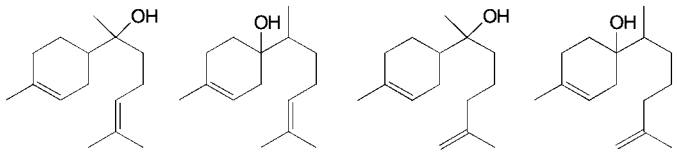
by **Norbert A. Braun***, **Manfred Meier**, **Gerhard Schmaus**, **Bernd Hölscher,** and **Wilhelm Pickenhagen***

Symrise GmbH & Co. KG[1]), Research & Development, D-37603 Holzminden
(phone: +49-5531-90-3832, e-mail: norbert.braun@symrise.com; phone: +49-5531-90-3270,
e-mail: wilhelm.pickenhagen@symrise.com)

The odorous trace constituent iso-β-bisabolol (**4**) was isolated from East Indian and Western Australian sandalwood oil and synthesized by using the (*E*/*Z*)-triene **12** (iso-γ-bisabolene) as a key intermediate. Only one of four stereoisomeric forms of **4**, (6*R*,7*R*)-**4a**, is odor active, having a strong floral, *muguet*-like, very pleasant scent.

Introduction. – Odor perception is initiated by an interaction of a volatile stimulant with a proteinaceous receptor [1]. Different diastereoisomers and enantiomers of the same molecular structure can elicit different odor impressions, both qualitative and quantitative [2]. In our continuous search for new natural trace constituents with high odor impact, we analyzed sandalwood oils of East Indian as well as Western Australian origin [3]. The oils are obtained from wood, trunk butt, or roots of *Santalum album* L. and *Santalum spicatum* (R. Br.) A. DC. by different extraction and/or distillation techniques [4].

Among a broad range of compounds, the odorless sesquiterpene alcohols α-bisabolol (**1**) and β-bisabolol (**2**) were detected by GC-MS analysis in both *Santalum* species [3a][3b]. The corresponding iso-α-bisabolol (**3**)[2]) and iso-β-bisabolol (**4**), however, have, to the best of our knowledge, neither been found in nature nor synthesized so far.



1 **2** **3** **4**

Here, we report the isolation, total synthesis, and olfactory properties of a new, odor-active trace constituent of East Indian and Western Australian sandalwood oil – iso-β-bisabolol (**4**).

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[1]) Former company name: *DRAGOCO Gerberding & Co. AG.*

[2]) Iso-α-bisabolol (**3**) was detected together with **1** in a distillate of Candeia oil (*Vanillosmopsis erythropappa* SCHULTZ-BIP.) by GC/MS in a ratio **1**/**3** 99.2:0.8 (*N. A. Braun*, *B. Kohlenberg*, unpublished results from our laboratory).

Results and Discussion. – Gas chromatographic (GC) olfactometry [5] of East Indian and Western Australian sandalwood oil led to the detection of a trace component (<0.001%) with a strong floral, *muguet*-like, very pleasant odor. The compound, which turned out to be **4**, was enriched up to 0.8% by fractional distillation, followed by repeated column chromatography and preparative two-dimensional GC. Its mass spectrum showed at *m/z* 222 and 204 the M^+ and $[M-H_2O]^+$ signals, respectively, very similar to that of β-bisabolol (**2**). Compound **4** was accompanied by alcohol **2** during the entire isolation process and displayed similar retention indices (RI) on two GC columns: *DBWax* (**2**: 2160; **4**: 2134) and *HP5* (**2**: 1670; **4**: 1651). This pointed to a sesquiterpene alcohol closely related to β-bisabolol (**2**).

During our investigations, we obtained a distillation fraction from the acid-catalyzed cyclization of nerolidol (**5**) [6], having an odor that was very reminiscent of **4**. We could not only detect, but also isolate alcohol **4** from this mixture. The mass spectrum and gas chromatogram (co-injection on two different GC-columns) strongly suggested that this compound was, indeed, identical to the one isolated from East Indian and Western Australian sandalwood oil.

The GC-FTIR spectrum of **4** showed a characteristic OH absorption band at 3629 cm^{-1}, and two bands at 3079 and 1646 cm^{-1}, respectively, pointing to an exocyclic double bond. Also, the corresponding ^{1}H- and the ^{13}C-NMR spectra clearly indicated the presence of the diastereomeric pairs **4a** *vs.* **4b** (*Fig. 1*).

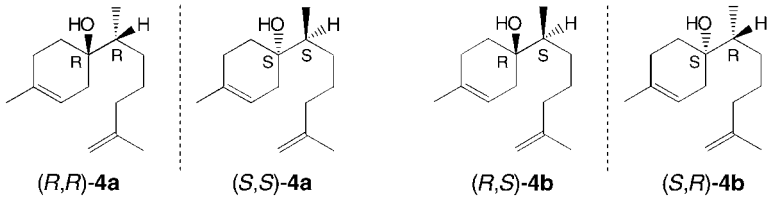
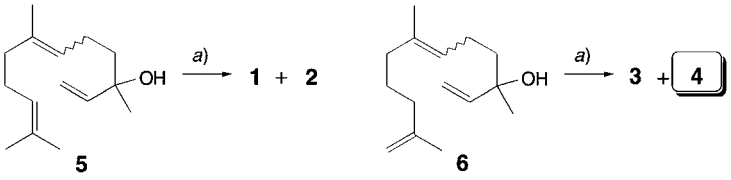


Fig. 1. *The four possible stereoisomers of iso-β-bisabolol* (**4**; stereoid-type numbering). Dashed lines indicate mirror planes of racemic couples.

The ^{1}H- and ^{13}C-NMR spectra of separated **4a** and **4b** were very similar. The ^{13}C-NMR spectra of **4a** and **4b** respectively, showed a tertiary alcohol function (*s* at 72.2 ppm), one *exo*-CH_2 group (109.7 (*t*) and 146.0 (*s*)), and a trisubstituted double bond (118.4 (*d*), 133.9 (*s*)). The ^{1}H-NMR spectra showed three down-field-shifted olefinic H-atoms at 4.67 (*m*, 1 H, $=CH_2$), 4.69 (*m*, 1 H, $=CH_2$), and 5.30 (*m*, H−C(3)), and three Me groups, two located at the double bonds (1.69 (*s*) and 1.71 (*s*)), and one at a secondary C-atom (**4a**: 0.91 (*d*); **4b**: 0.95 (*d*)).

The structure of iso-β-bisabolol (**4**) was further corroborated by synthesis. Although compound **4** was isolated from a fraction of the acid-catalyzed cyclization of nerolidol (= 3,7,11-trimethyl-dodeca-1,6,10-trien-3-ol; **5**), it seemed more obvious from a chemical point of view to use isonerolidol (**6**) [7] as a starting material. Cyclization of alcohol **6** led, indeed, to the formation of iso-α-bisabolol (**3**) and iso-β-bisabolol (**4**) in a ratio of **1**/**2** and **3**/**4** of 96:4 each (*Scheme 1*).

Scheme 1. *Acid-Catalyzed Cyclization of Nerolidol* (**5**) *and Isonerolidol* (**6**)

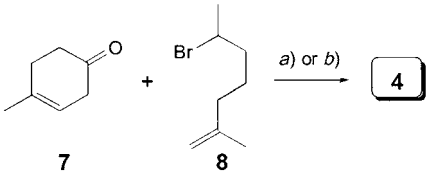


a) HCOOH, hexane, 43% (**1**/**2** and **3**/**4** 96:4).

Our results indicated that **4** was probably formed from impurities of isonerolidol (**6**) present in commercially available nerolidol (**5**). However, we could not completely rule out that **4** could also be formed directly from **5**, either by isomerization or *via* an unknown intermediate.

Unfortunately, the cyclization of isonerolidol (**6**) led to only trace amounts of iso-β-bisabolol (**4**). We, thus, tried a *Grignard*-type coupling of cyclic ketone **7** [8] with bromo compound **8** [9]. However, the reaction of **7** with the Mg reagent of **8** [10] or with the corresponding lithiated compound [11] afforded **4** in very low yields only (*Scheme 2*).

Scheme 2. *Synthesis of Iso-β-bisabolol* (**4**) via Grignard-*Type Reactions*



a) Mg, Et_2O, $<2\%$; *b*) Li, THF, 11%.

Next, we tested iso-γ-bisabolene ((*E*/*Z*)-**12**) as a starting material for the synthesis of **4** (*Scheme 3*). (*E*/*Z*)-**12** was prepared *via* a two-step procedure: allyl rearrangement of 1-isopropenyl-4-methylcyclohex-3-en-1-ol (**9**) [12] led to acetate **10** ((*E*/*Z*) 60:40), which was coupled with the Cu reagent of 4-bromo-2-methylbut-1-ene (**11**) [13] to yield (*E*/*Z*)-**12**[3]) in 12% overall yield [14]. Alternatively, (*E*/*Z*)-**12** was synthesized analogously to the procedure of *Faulkner* and co-workers from acid **14** [15] and ketone **15** [16]. Aldol reaction of the dianion of **14** with ketone **15** led to β-hydroxy acid **16**. The best yield (76%) was obtained in a 4:1 mixture of THF and TMEDA (= *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine) [17]. Compound **16** was transformed to (*E*/*Z*)-**12** (64% overall yield) *via* β-lactone **17**, followed by thermal decarboxylation. The configuration of **12** was determined as described by *Negishi et al.* for (*E*/*Z*)-γ-bisabolene [18].

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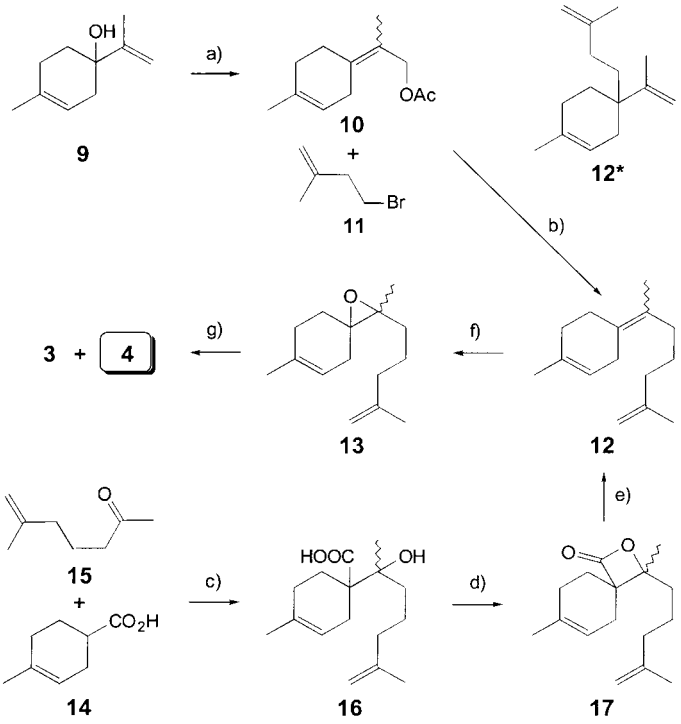
[3]) A side product of this reaction is the S_N1-type product **12**** formed at temperatures $\geq 0°$.

Scheme 3. *Synthesis of Iso-β-bisabolol* (**4**) via *(*E/Z*)-Triene* **12**. For abbreviations, see text.



a) Ac_2O, AcONa, H_2WO_4, 25%; *b*) Mg, $Li_2[CuCl_4]$, Et_2O/THF, 48%; *c*) BuLi, THF/TMEDA, 76%; *d*) TsCl, pyridine, CH_2Cl_2, 89%; *e*) Δ, 95%; *f*) MCPBA, CH_2Cl_2, 81%; *g*) $LiALH_4$, THF, 22% (**3**), 70% (**4**), ratio: **4**/**3** 76 : 24.

Compound (*E*/*Z*)-**12** was converted immediately after purification, due to its sensitivity to polymerization, to the epoxide **13** by means of 3-chloroperbenzoic acid (MCPBA). Reductive opening of the epoxide with $LiAlH_4$ [19] gave iso-β-bisabolol (**4**) together with iso-α-bisabolol (**3**) in a ratio of 76 : 24 in good yield. Synthetic **4** was, in all respects (^{1}H- and ^{13}C-NMR, GC/FTIR, and GC/MS), identical to the natural product.

It is known that diastereoisomers and even enantiomers can have different olfactory properties [2][20]. Having established the structure of **4**, we used a chiral GC column (2,3-di-*O*-acetyl-6-*O*-(*tert*-butyl)dimethylsilyl-β-cyclodextrin [3b][21]) to determine the olfactory properties of **4a** and **4b**. The gas chromatogram of synthetic **4** showed three peaks in a ratio of 2 : 1 : 1, the first corresponding to a strong floral, *muguet*-like, very pleasant odor (the others were odorless; *Fig. 2*, *a*). Separation of the diastereoisomers by HPLC showed that the first peak contained **4a** and **4b**, only the former being odor-active (*Fig. 2*, *b vs. 2*, *c*).

The relative configurations of **4a** and **4b** at C(6) and C(7) were determined by ^{1}H-NMR analogously to the stereochemical assignment of β-bisabolol (**2**): the Me group (*d*) at C(7) had a chemical shift δ of 0.91 ppm for (6*S**,7*S**)-**2** and 0.95 ppm for the corresponding diastereoisomeric (6*R**,7*S**)-**2** [22]. Similar shifts were observed for

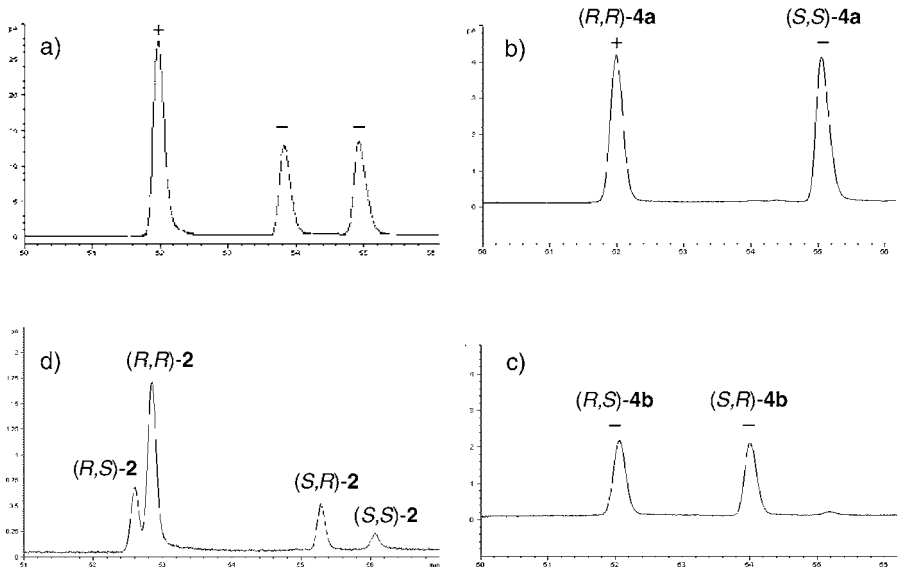


Fig. 2. *Gas chromatograms of synthetic and natural samples of* **4**. Odorous substances are marked with a plus (+), odorless ones with a minus (−). *a*) *Synthetic probe* (before HPLC separation); *b*) *racemic* **4a** (after HPLC); *c*) *racemic* **4b** (after HPLC); *d*) *natural probe from* Santalum album *L*.

(6*S**,7*S**)-**4a** and (6*S**,7*R**)-**4b**: 0.91 and 0.95 ppm, respectively. The odor-active compound **4a** showed a signal at 0.91 ppm, pointing to a (6*S**,7*S**) configuration. To determine the absolute configuration of **4a**, one could envisage several methods, *e.g.*, enantioselective synthesis starting from (*E*)-**12** and using enantioselective epoxidation or separation of the racemic mixture of **4a** by chiral HPLC [23], followed by derivatization and X-ray diffractometry. However, all attempts were, so far, unsuccessful. Therefore, we compared the retention times of racemic **4a** on two chiral GC columns (2,3-di-*O*-acetyl-6-*O*-(*tert*-butyl)dimethylsilyl-β-cyclodextrine and 2,3-di-*O*-acetyl-6-*O*-(*tert*-butyl)dimethylsilyl-β-cyclodextrine, resp.) with those of the corresponding racemic β-bisabolol (**2a**). The retention order of **2a** was determined by using enantiomerically pure β-bisabolol samples as references [3b][22]: (6*R*,7*R*)-**2a** was followed by (6*S*,7*S*)-**2a**. Assuming that the retention order is identical for iso-β-bisabolol (**4a**), the odor-active enantiomer of **4a** has the (6*R*,7*R*)-configuration.

One could envisage from a biogenetic point of view that β-bisabolol (**2**) could be transformed into iso-β-bisabolol (**4**) with the help of a double-bond isomerase. Although more iso-β-bisabolol (**4**) is present in *S. spicatum*, the odor impression is weaker than in *S. album*, pointing to a higher concentration of the odor-active (6*R*,7*R*)-isomer in *S. album*. This assumption is supported by the observation that only in *S. album* the main isomer of **2** has (6*R*,7*R*)-configuration (see *Fig. 2*, *d*), while in *S. spicatum* the (6*R*,7*S*)-isomer of **2** is dominant. Moreover, different ratios of the corresponding β-bisabolol isomers **2** are present in both *Santalum* species: (6*R*,7*S*)/(6*R*,7*R*)/(6*S*,7*R*)/(6*S*,7*S*) 21:55:19:5 in *S. album vs.* 61:19:5:15 in *S. spicatum*,

respectively [3a][3b]. It seems likely, that natural **4** from *S. album* and *S. spicatum* also consists of all four possible stereoisomers.

Finally, the odor-detection threshold [24] of **4a** in H_2O (0.785 μg/l) and air (0.081 μg/l) was measured. It seems noteworthy that some people in the test panels showed an anosmia for alcohol **4a**.

Conclusions. – Iso-β-bisabolol (**4**) was isolated for the first time from Western Australian and East Indian sandalwood oil and synthesized in five steps with an overall yield of 36%. Of the four possible stereoisomer of **4**, only the (6*R*,7*R*)-isomer **4a** is odor active. This is in contrast to other powerful chiral odorants (*e.g.*, *Hedione*® [25], (*Z*)-methyl jasmonate [26]), where at least two stereoisomeric forms are active [20a]. Apart from the steroid androstenone, a pig pheromone [27], iso-β-bisabolol (**4**) is, to the best of our knowledge, the first rigorously diastereo- as well as enantiospecific odorant, *i.e.*, only one isomer elicits a strong odor, whereas the other three are odorless. Stereoselective synthesis of alcohols **4a**–**d** will have to corroborate our results. Moreover, the chiral fragrant **4** nicely confirms the enantioselectivity of odor perception put forward by *Kraft* and *Fráter* [28].

Experimental Part

1. *General*. All reagents and solvents were commercial products (*Fluka*, *Aldrich*, or *Lancaster*) and used as received. All reactions were performed under N_2, monitored by TLC. East Indian sandalwood oil was purchased from *Frey & Lau GmbH* (Henstedt, Germany) and Australian sandalwood oil from *Mt. Romance Australia Pty. Ltd.* (Albany, Australia) [3a][3b]. Column chromatography (CC): *Merck* silica gel *60* (63–200 μm). HPLC: *Knauer HPLC-pump 64* (column: *Eurospher 100 Si*, 5 μm, 250 × 20 mm; flow rate: 10 ml/min; detection: λ = 220 nm). Two-dimensional preparative GC: *Hewlett-Packard 6890* with *Gerstel* trapping unit (I: *DB-1*, 15 m × 0.53 mm × 1.2 μm; II: *DB-Wax:* 27 m × 0.53 mm × 2 μm; 120°–220° at 4°/min; He]. Chiral GC: *Hewlett-Packard 6890* with FID and GC-sniffing-port (column: *Ivadex-3* = 2,3-di-*O*-acetyl-6-*O*-[(*tert*-butyl)dimethylsilyl]-β-cyclodextrine (30%) and *PS 086* (70%): 25 m × 0.25 mm × 0.15 μm; 80–150° with 1°/min, He). GC/FTIR: *Hewlett-Packard 5890B* with *Hewlett-Packard 5965B* IR detector (*DB-Wax* column: 60 m × 0.32 mm × 0.50 μm; 60–240° at 4°/min; He); ν in cm^{-1}. NMR: *Varian VXR-300* (^{1}H: 300 MHz; ^{13}C: 75.45 MHz) or *Varian Mercury Plus AS-400* (^{1}H-NMR: 400 MHz; ^{13}C-NMR: 100.70 MHz), unless otherwise noted, in $CDCl_3$ with TMS as internal standard; chemical shift (δ) in ppm, coupling constants (J) in Hz. GC-MS: *Hewlett-Packard 5973N* (*DB-Wax* column: 60 m × 0.25 mm × 0.25 μm; 60–240° at 4°/min; carrier gas: He), EI mode (70 eV); data in *m*/*z* (%). LC-MS: *Bruker Esquire-LCMS* (injection with syringe pump; flow rate 240 μl/h), ESI mode (negative or positive). HR-MS: EI mode (70 eV), Institut für Organische Chemie, Georg-August-Universität Göttingen.

2. *Enrichment of Iso-β-bisabolol* (**4**) *from* S. album *and* S. spicatum. East Indian sandalwood oil (2 kg) was rectified via *Sulzer* distillation under reduced pressure [3a]. During the isolation process, fractions were combined according to their composition as assessed by GC olfactometry; alternatively, alcohol **2** was used as a GC marker substance. Alcohol **4** was enriched by repeated CC of a *Sulzer* fraction: *a*) SiO_2, hexane/Et_2O 100:0 in 1%-steps to 85:15; *b*) SiO_2 containing 15% $AgNO_3$ [29], hexane/Et_2O 80:20. Further separation was carried out by two-dimensional preparative GC, leading to an enriched fraction of **4** (0.2%) used for GC-MS and a pure fraction of β-bisabolol (**2**). The same procedure was used to enrich alcohol **4** (0.8%) from Australian sandalwood oil (1.5 kg).

(1S/R)-1-[(1S/R)-1,5-Dimethylhex-4-enyl]-4-methylcyclohex-3-en-1-ol (= β-Bisabolol; **2**) [3b]. Colorless, highly viscous oil, odorless. GC/RI: 2160 (*DBWax*), 1670 (*HP5*). ^{1}H-NMR (300 MHz): 0.91, 0.95 (*d*, *J* = 6.8, Me–C(1′)); 1.06 (*m*, 1 H); 1.45 (*m*, 1 H); 1.55–1.63 (*m*, 3 H); 1.56 (*s*, Me(6′)); 1.68 (*s*, Me–C(4) and Me–C(5′)); 1.76 (*s*, OH); 1.85–1.97 (*m*, 3 H); 2.04–2.24 (*m*, 3 H); 5.11 (*m*, H–C(4′)); 5.28 (*m*, H–C(3)). ^{13}C-NMR (75 MHz): 13.4 (2*q*, *Me*–C(1′)); 17.5 (*q*, Me–C(6′)); 23.1 (2*q*, C(4)); 25.5 (*q*, Me–C(5′)); 26.4, 26.5 (*t*, C(6)); 26.8, 26.9 (*t*, C(2′)), 30.6, 30.7 (*t*, C(5)); 30.8 (2*t*, C(3′)); 34.0, 34.6 (*t*, C(2)); 41.6, 41.9 (*d*, C(1′)); 71.8, 71.9 (*s*, C(1)); 118.3 (*d*, C(3)); 124.6, 124.7 (*d*, C(4′)); 131.0 (2*s*, C(5′)); 133.6, 133.7 (*s*, C(4)). GC-MS: 222 (1),

207 (1), 204 (25), 189 (2), 161 (11), 154 (4), 140 (9), 139 (6), 126 (2), 121 (36), 119 (37), 111 (46), 107 (14), 93 (69), 83 (34), 82 (100), 72 (33), 69 (44), 67 (41), 57 (23), 55 (43), 43 (39), 41 (69).

(1S/R)-1-[(1S/R)-1,5-Dimethylhex-5-enyl]-4-methylcyclohex-3-en-1-ol (= Iso-β-bisabolol; **4**): GC/RI: 2134 (*DBWax*), 1651 (HP5). GC-MS: 222 (4, M^+), 207 (1), 204 (8), 189 (1), 161 (5), 154 (10), 153 (9), 140 (22), 139 (24), 126 (5), 121 (23), 119 (31), 111 (100), 93 (67), 83 (50), 82 (93), 72 (50), 69 (68), 55 (57), 43 (34), 41 (35).

3. *Isolation of Iso-β-bisabolol* (**4**) *from a Distillation Fraction of the Acid Catalyzed Nerolidol Cyclization*. The isolation started from a forerun fraction (10 kg) of a production-scale distillation, which was rectified *via Sulzer* distillation under reduced pressure. Fractions were combined according to their composition, as assessed by GC olfactometry or GC. Alcohol **4** was further enriched from a *Sulzer* fraction by repeated CC as described in *Sect. 2* and purified by two-dimensional prep. GC. Colorless, highly viscous oil, **4a**/**4b** 1:1. GC/FT-IR: 3629, 3079, 2972, 2932, 1646, 1449, 1379, 889. GC-MS: 222 (4, M^+), 207 (1), 204 (8), 189 (1), 161 (5), 154 (10), 153 (9), 140 (22), 139 (24), 126 (5), 121 (23), 119 (31), 111 (100), 93 (67), 83 (50), 82 (93), 72 (50), 69 (68), 55(57), 43 (34), 41 (35). ^{1}H-NMR (300 MHz): 0.91, 0.95 (*d*, J = 6.9, Me–C(1′)); 1.02 (*m*, 1 H); 1.33 (*m*, 1 H); 1.36 (*s*, OH); 1.46 (*m*, 1 H); 1.53–1.65 (*m*, 4 H); 1.69 (*s*, Me–C(4)); 1.71 (*s*, Me–C(5′)); 1.80–2.07 (*m*, 4 H); 2.12–2.24 (*m*, 2 H); 4.67, 4.69 (*m*, 1 H, CH_2(6′)); 5.30 (*m*, H–C(3)). ^{13}C-NMR (300 MHz): 13.6, 13.7 (*q*, *Me*–C(1′)); 22.3 (2*q*, *Me*–C(5′)); 23.2, 23.3 (*q*, *Me*–C(4)); 26.2, 26.3 (*t*, C(6)); 27.0 (2*t*, C(2′)); 30.3 (*t*, C(3′)); 30.6, 30.9 (*t*, C(5)); 34.2, 34.8 (*t*, C(2)); 38.0 (*t*, C(4′)); 42.1, 42.4 (*d*, C(1′)); 72.2 (2*s*, C(1)); 109.7 (2*t*, C(6′)); 118.4 (2*d*, C(3)); 133.8, 133.9 (*s*, C(4)); 146.0 (2*s*, C(5′)). HR-MS: 222.1983 ($C_{15}H_{26}O$).

4. *Synthesis of* **4** via *Li*-Grignard-*Reaction of Ketone* **7** *and bromide* **8**. *4-Methylcyclohex-3-en-1-one* (**7**) was synthesized from terpinolene in three steps in 60% overall yield according to [8]. Colorless oil. ^{1}H-NMR (300 MHz): 1.78 (*m*, Me–C(4)); 2.38–2.42 (*m*, CH_2(5)); 2.47–2.52 (*m*, CH_2(6)); 2.81–2.84 (*m*, CH_2(2)); 5.44 (*m*, H–C(3)). ^{13}C-NMR (75 MHz): 22.6 (*q*, Me); 29.9 (*t*, C(5)); 38.0 (*t*, C(2)); 39.1 (*t*, C(2)); 117.8 (*d*, C(3)); 134.2 (*s*, C(4)); 210.4 (*s*, C(1)).

6-Bromo-2-methyl-hept-1-ene (**8**) was prepared from ethyl 3-oxobutanoate in five steps according to [9] (overall yield: 35%). Colorless oil. ^{1}H-NMR (300 MHz): 1.49–1.59 (*m*, 2 H); 1.70 (*d*, J = 6.6, Me(7)); 1.71 (*s*, Me(2)); 1.72–1.83 (*m*, 2 H); 2.02 (*tq*, J = 0.7, 7.2, 2 H); 4.13 (*m*, H–C(6)); 4.68, 4.70 (*m*, J = 0.7, 2 × 1 H, H_2C(1)). ^{13}C-NMR (75 MHz): 22.1 (*q*, Me–C(2)); 25.5 (*t*, C(4)); 26.4 (*q*, C(7)); 36.9 (*t*, C(5)); 40.5 (*t*, C(3)); 51.3 (*d*, C(6)); 110.3 (*t*, C(1)); 144.9 (*s*, C(2)).

(1S/R)-1-[(1S/R)-1,5-Dimethylhex-5-enyl]-4-methylcyclohex-3-en-1-ol (= Iso-β-bisabolol; **4**). To a suspension of Li pellets (0.15 g, 22 mmol) in THF (10 ml) was slowly added a mixture of **7** (1.21 g, 11 mmol) and **8** (1.91 g, 10 mmol) in THF (10 ml) at $-10°$. Stirring was continued for 30 min at that temp., then the mixture was warmed to r.t. over 2 h and stirred for 8 h. The suspension was carefully hydrolyzed with aq. NH_4Cl soln. (10 ml) and extracted with Et_2O (4 × 15 ml). The org. layers were dried (Na_2SO_4), concentrated, and the residue was purified by *a*) CC (SiO_2, hexane/Et_2O 100:0 → 85:15 in 1%-steps, then 80:20, 75:25), *b*) prep. TLC (SiO_2, hexane/Et_2O 8:2) to yield 0.24 g (11%) of alcohol **4**. Colorless oil, **4a**/**4b** 1:1. The synthetic material was identical in all respects (TLC, GC, IR, NMR, MS) to the natural product. HR-MS ($C_{15}H_{26}O$, 220.1984, calc.: 222.1984).

5. *Synthesis of* **4** via *Cu*-Grignard-*Reaction of Acetate* **10** *and Bromide* **11**. *4-Bromo-2-methylbut-1-ene* (**11**) was prepared from commercial 3-methylbut-3-en-1-ol in 2 steps according to [13] (overall yield: 87%). Pale yellow oil. ^{1}H-NMR (300 MHz): 1.74 (*d*, J = 0.9, Me–C(2)); 2.57 (*tt*, J = 1.6, 7.4, H_2C(3)); 3.47 (*t*, J = 7.4, H_2C(4)); 4.77 (*q*, J = 0.9, H–C(1)); 4.85 (*t*, J = 1.6, H–C(1)). ^{13}C-NMR (75 MHz): 21.8 (*q*, *Me*–C(2)); 30.6 (*t*, C(4)); 40.8 (*t*, C(3)); 112.5 (*t*, C(1)); 142.2 (*s*, C(2)).

2-[(E/Z)-4-Methylcyclohex-3-en-1-ylidene]propyl Acetate (**10**). Ac_2O (61.0 g, 0.6 mmol), AcONa (3.0 g, 36 mmol), and H_2WO_4 (1.25 g, 5 mmol) was placed in a 500-ml 3-necked round-bottom flask equipped with a thermometer, reflux condenser, and dropping funnel. The mixture was heated to 130–140°. Then, *4-methyl-1-isopropenylcyclohex-3-en-1-ol* (= *p*-mentha-1,8-dien-4-ol; **9**) (90.0 g, 0.5 mol) was added dropwise over 30 min, and heating was continued for 1 h. The mixture was cooled to 80°, H_2O (100 ml) was added, and stirring was continued for 30 min at 80°. After cooling, the mixture was extracted with Et_2O (3 × 50 ml). The org. layers were washed with H_2O (3 × 40 ml), dried (Na_2SO_4), evaporated, and the residue was purified by fractional distillation to afford 24.06 g (25%) of **10**. Pale yellow liquid. (*E*)/(*Z*) 60:40. B.p. 115°/5 mbar [30]. ^{1}H-NMR (300 MHz): 1.66 (*d*, J = 1.3, Me–C(4)); 1.72, 1.75 (*s*, Me); 1.99–2.08 (*m*, H_2C(5)); 2.05 (*s*, 3 H, Ac); 2.36 (*t*, J = 6.4, 2 H, H_2C(6)) and 2.41 (*dt*, J = 1.0, 6.3, 2 H, H_2C(6)); 2.77, 2.83 (*m*, H_2C(2)); 4.60, 4.64 (*s*, CH_2O); 5.34 (*m*, H–C(3)). ^{13}C-NMR (75 MHz): 15.9, 16.6 (*q*, Me); 20.8, 20.9 (*q*, *Me*CO); 23.1 (*q*, *Me*–C(4)); 26.7, 27.0 (*t*, C(6)); 29.1, 29.8 (*t*, C(5)); 30.9, 31.5 (*t*, C(2)); 65.0, 65.1 (*t*, CH_2O); 119.7, 119.9 (*d*, C(3)); 120.6, 120.8 (*s*, C(1)); 134.0, 134.2 (*s*, C(4)); 135.4, 136.0 (*s*, =C); 171.1 (*s*, COO). GC-MS ((*E*)-isomer): 151 (0.1, $[M - C_2H_3O]^+$), 134 (100, $[M - C_2H_4O_2]^+$), 119 (65), 105 (30), 93 (31), 92 (21), 91 (38), 79 (21), 77 (16), 43 (33), 41

(10). GC/MS ((*Z*)-isomer): 151 (0.1, $[M-C_2H_3O]^+$), 134 (100, $[M-C_2H_4O_2]^+$), 119 (72), 105 (27), 93 (26), 92 (18), 91 (37), 79 (19), 77 (15), 43 (30), 41 (10).

*4-[(*E*/*Z*)-1,5-Dimethylhex-5-enylidene]-1-methylcyclohex-1-ene* (= Iso-γ-bisabolene; **12**). Bromide **11** (2.24 g, 15 mmol) was slowly added to Mg metal shavings (0.40 g, 16.5 mmol) in Et_2O (15 ml) and THF (5 ml). The suspension was refluxed for 30 min and then cooled to −20°. A 0.1M soln. of $Li_2[CuCl_4]$ (5 ml, 0.5 mmol) in THF was slowly added, and stirring was continued for 30 min at −20°. Then, acetate **10** (1.94 g, 10 mmol) in THF (5 ml) was added dropwise at a temp. below −10° to avoid formation of **12***. The mixture was stirred for 2 h at −20°, then slowly warmed to 0°, and carefully quenched with H_2O (10 ml), followed by 1M H_2SO_4 (15 ml). Once extracted with Et_2O (3 × 40 ml), the org. layers were washed with brine (10 ml), dried (Na_2SO_4), and purified by CC (SiO_2, hexane) to afford 0.98 g (48%) of **12**. Colorless oil. (*E*)/(*Z*) 60:40. GC-FT-IR: 3080, 2974, 2935, 2915, 2869, 1648, 1451, 1380, 890. ^{1}H-NMR (300 MHz): 1.44–1.54 (*m*, 2 H); 1.65 (*m*, Me–C(4), Me–C(1′)); 1.72 (*s*, Me–C(5′)); 1.96–2.09 (*m*, 6 H); 2.31 (*t*, *J* = 6.3, H_2C(6)); 2.73 (*s*, H_2C(2)); 4.67, 4.69 (*m*, 2 × 1 H, H_2C(6′)); 5.36 (*m*, H–C(3)). ^{13}C-NMR (75 MHz): 17.7, 18.3 (*q*, *Me*–C(1′)); 22.5 (*q*, *Me*–C(5′)); 23.4 (*q*, *Me*–C(4)); 26.1, 26.5 (*t*, C(6)); 26.7, 26.9 (*t*, C(2′)); 29.3, 29.7 (*t*, C(5)); 31.6, 31.8 (*t*, C(3′)); 33.6, 33.9 (*t*, C(2)); 37.8 (*t*, C(4′)); 109.6 (*t*, C(6′)); 120.7, 120.8 (*d*, C(3)); 125.8, 126.0 (*s*, C(1)); 128.21 (*s*, C(1′)); 134.2 (*s*, C(4)); 146.1 (*s*, C(5′)). GC/MS ((*Z*)-isomer): 204 (39), 189 (9), 161 (18), 148 (12), 147 (17), 134 (38), 133 (49), 121 (85), 119 (100), 109 (10), 107 (33), 106 (29), 105 (57), 93 (75), 91 (60), 79 (39), 77 (32), 55 (19), 41 (23). GC-MS ((*E*)-isomer): 204 (27), 189 (10), 161 (14), 148 (28), 147 (12), 134 (23), 133 (52), 121 (100), 119 (94), 109 (16), 107 (40), 106 (42), 105 (64), 93 (91), 91 (70), 79 (47), 77 (38), 55 (27), 41 (32). HR-MS: calc.: 204.1878 ($C_{15}H_+^{24}$).

4-Isopropenyl-1-methyl-4-(3-methylbut-3-enyl)cyclohex-1-ene (**12***). Colorless oil. GC/FT-IR: 3081, 2973, 2937, 1639, 1451, 1379, 892. ^{1}H-NMR (300 MHz): 1.33 (*m*, 1 H); 1.56–1.68 (*m*, 2 H); 1.62 (*s*, Me); 1.69–1.71 (*m*, 6 H, Me–C(4), Me–C(3′)); 1.76–2.04 (*m*, 6 H); 2.16 (*m*, 1 H); 4.64–4.68 (*m*, CH_2(4′), H–C=); 4.86 (*m*, H–C=); 5.30 (*m*, H–C(3)). ^{13}C-NMR (75 MHz): 18.9 (*q*, *Me*–C(1)); 22.8 (*q*, Me–C(3′)); 23.3 (*q*, Me); 27.7 (*t*, C(5)); 31.1 (*t*, C(1′)); 32.1 (*t*, C(6)); 35.4 (*t*, C(3)); 35.5 (*t*, C(2′)); 40.2 (*s*, C(4)); 109.0 (*t*, =CH_2); 111.3 (*t*, C(4′)); 119.3 (*d*, C(2)); 133.0 (*s*, C(1)); 146.9 (*s*, C=); 148.5 (*s*, C(3′)). GC-MS: 204 (6), 189 (28), 176 (18), 175 (11), 161 (8), 148 (14), 133 (28), 121 (69), 119 (25), 108 (40), 107 (93), 105 (42), 93 (100), 91 (46), 81 (25), 79 (65), 77 (31), 67 (23), 55 (33), 53 (22), 41 (48), 39 (22).

2,6-Dimethyl-2-(4-methylpent-4-enyl)-1-oxaspiro[2.5]oct-5-ene (**13**). A soln. of (*E*/*Z*)-**12** (0.31 g, 1.5 mmol) in CH_2Cl_2 (15 ml) was cooled to 0°, and 70% MCPBA (0.41 g, 1.65 mmol) was added. The mixture was slowly warmed to r.t., stirred for 8 h, and filtered under suction. The remaining solid was rinsed with CH_2Cl_2 (20 ml). The organic layers were successively washed with solns. of 10% $NaHSO_3$ (10 ml), sat. K_2CO_3 (10 ml), and brine (10 ml), dried (Na_2SO_4), and purified by CC (SiO_2, hexane/Et_2O 3:1) to yield 0.22 g (81%) of **13**. Colorless oil. Two diastereoisomers [(*S**,*S**)/(*S**,*R**) = 60:40]. ^{1}H-NMR (300 MHz): 1.30, 1.34 (*s*, Me–C(2)); 1.43–1.65 (*m*, 4 H); 1.69 (*m*, Me–C(6)); 1.71 (*s*, Me–C(4′)); 1.70–1.89 (*m*, 2 H); 1.94–2.10 (*m*, 3 H); 2.12–2.30 (*m*, 2 H); 2.35 (*m*, *J* = 17.6, 1 H); 4.66, 4.70 (*m*, 3 × 1 H, CH_2(5′)); 5.33 (*m*, 1 H, CH_2(5)). ^{13}C-NMR (75 MHz): 17.9, 18.3 (*q*, *Me*–C(2)); 22.2 (2*q*, *Me*–C(4′)); 23.1, 23.2 (*q*, *Me*–C(6)); 23.3, 23.6 (*t*, C(8)); 26.5, 27.3 (*t*, C(1′)); 28.6, 29.1 (*t*, C(2′)); 30.5, 31.1 (*t*, C(7)); 34.0, 34.3 (*t*, C(4)); 37.8 (2*t*, C(3′)); 64.0, 64.3 (*s*, C(2)); 64.6, 64.7 (*s*, C(3)); 109.9 (2*t*, C(5′)); 118.9, 119.0 (*d*, C(5)); 133.9 (2*s*, C(6)); 144.8 (*s*, C(4′)). GC/MS ((*S**,*R**)-isomer): 220 (2), 205 (6), 202 (4), 187 (3), 159 (3), 152 (5), 151 (4), 147 (5), 138 (10), 137 (14), 132 (8), 119 (10), 111 (14), 110 (43), 109 (17), 107 (7), 105 (10), 95 (100), 94 (25), 93 (28), 91 (22), 81 (17), 79 (63), 77 (24), 69 (14), 68 (16), 67 (22), 55 (23), 43 (19), 41 (19). GC/MS ((*S**,*S**)-isomer): 220 (1), 205 (4), 202 (4), 187 (2), 159 (3), 152 (6), 147 (5), 138 (9), 137 (13), 132 (7), 119 (9), 111 (16), 110 (47), 109 (16), 107 (6), 105 (9), 95 (100), 94 (25), 93 (27), 91 (19), 81 (18), 79 (64), 77 (22), 69 (14), 68 (16), 67 (22), 55 (24), 43 (20), 41 (21). HR-MS: 220.1826 ($C_{15}H_{24}O$; calc. 220.1827).

Mixture of **4** *and 6-Methyl-2-(4-methylcyclohex-3-enyl)hept-6-en-2-ol* (= Iso-α-bisabolol; **3**). $LiAlH_4$ (0.12 g, 3 mmol) was added slowly to a soln. of **13** (0.44 g, 2.0 mmol) in anh. THF (15 ml), and the mixture was heated under reflux for 2 h. The suspension was cooled to 0°, and H_2O (2 ml) was carefully added. The mixture was filtered over glass wool, the residue was rinsed with Et_2O (40 ml), and the org. layers were washed with brine (10 ml), dried (Na_2SO_4) and evaporated. CC (SiO_2, hexane/Et_2O 8:2) afforded 311.6 mg (70%) of **4** and 98.4 mg (22%) of **3** in a ratio of 76:24. *Iso-β-bisabolol* (**4**), a colorless oil, ((*S**,*S**)/(*S**,*R**) 60:40) matched the natural product in all respects.

Iso-α-bisabolol (**3**): Colorless oil, odorless. Diastereoisomer ratio: (*S**,*S**)/(*S**,*R**) 60:40. GC/FT-IR: 3641, 3080, 2972, 2930, 1648, 1453, 1379, 891. ^{1}H-NMR (300 MHz): 1.11, 1.14 (*s*, Me(1)); 1.20–1.36 (*m*, 2 H); 1.40–1.61 (*m*, 5 H); 1.44 (*s*, OH); 1.62 (*s*, *Me*–C(4′)); 1.72 (*s*, *Me*–C(6)); 1.75–1.94 (*m*, 2 H); 1.95–2.05 (*m*, 4 H); 4.69, 4.71 (*s*, 1 H, CH_2(7)); 5.39 (*m*, H–C(3′)). ^{13}C-NMR (75 MHz): 21.1, 21.4 (*t*, C(4)); 22.3 (*q*, C(1)); 23.2

(*t*, C(6′)); 23.3 (2*q*, *Me*–C(6)); 23.8 (*t*, C(6′)); 24.0 (*q*, *Me*–C(4′)); 26.0, 26.8 (*t*, C(3)); 30.9, 31.0 (*t*, C(5′)); 38.2 (2*t*, C(2′)); 39.0, 39.8 (*t*, C(5)); 42.8, 43.1 (*d*, C(1′)); 74.2 (2*s*, C(2)); 109.9 (*t*, C(7)); 120.5, 120.7 (*d*, C(3′)); 133.7, 134.0 (*s*, C(2′)); 145.6 (*s*, C(6)). GC-MS: 222 (0.2, M^+), 207 (0.4), 204 (10), 189 (4), 161 (5), 139 (19), 133 (7), 121 (36), 119 (81), 109 (100), 105 (11), 95 (26), 94 (24), 93 (40), 81 (29), 71 (35), 69 (60), 55 (17), 43 (63), 41 (22). HR-MS: 222.1984 ($C_{15}H_{26}O$; calc. 222.1984).

6. *Synthesis of* **4** via *Nucleophilic Addition of* **14** *to* **15**. *4-Methyl-cyclohex-3-encarboxylic Acid* (**14**) was prepared in 71% overall yield according to [15]. Colorless crystals. M.p. 97–99°. ^{1}H-NMR (400 MHz): 1.65 (*d*, *J* = 0.7, Me–C(4)); 1.72 (*m*, 1 H); 1.97–2.06 (*m*, 3 H); 2.18–2.25 (*m*, 2 H); 2.52 (*m*, 1 H); 5.37 (*m*, H–C(3)); 11.24 (*m*, COOH). ^{13}C-NMR (100 MHz): 23.4 (*q*, *Me*–C(4)); 25.2 (*t*, C(6)); 27.4 (*t*, C(5)); 29.1 (*t*, C(2)); 39.1 (*d*, C(1)); 118.8 (*d*, C(3)); 133.5 (*s*, C(4)); 182.4 (*s*, COO).

6-Methyl-hept-6-en-2-one (**15**) was prepared in an overall yield of 42% according to [9a]. Colorless oil. B.p. 63°/18 mbar. ^{1}H-NMR (300 MHz): 1.67–1.77 (*m*, CH_2(4)); 1.71 (*m*, *Me*–C(6)); 2.01 (*t*, *J* = 7.4, CH_2(5)); 2.14 (*s*, Me(1)); 2.42 (*t*, *J* = 7.4, CH_2(3)); 4.67, 4.73 (*m*, 2 × 1 H, CH_2(7)). ^{13}C-NMR (300 MHz): 21.4 (*t*, C(4)); 22.1 (*q*, *Me*–C(6)); 29.9 (*q*, C(1)); 36.9 (*t*, C(5)); 42.9 (*t*, C(3)); 110.5 (*t*, C(7)); 144.9 (*s*, C(6)); 208.9 (*s*, C(2)).

1-(1-Hydroxy-1,5-dimethylhex-5-enyl)-4-methylcyclohex-3-enecarboxylic Acid (**16**). To a soln. of (i-Pr)NH (6.02 g, 60 mmol) in anh. THF (120 ml) and TMEDA (30 ml) was added a 1.83M soln. of BuLi in hexane (32.7 ml, 60 mmol) at −40°. After stirring for 30 min, a soln. of **14** (4.2 g, 30 mmol) in THF (20 ml) was added dropwise at a temp. below −20°. The mixture was stirred for 15 min at −20° and then heated to 50° for 3 h. The soln. was cooled to −40°, and **15** (3.78 g, 30 mmol) was slowly added. Stirring was continued for 3 h at −40°, the mixture was poured onto ice and extracted with Et_2O (3 × 50 ml). The org. layers were discarded. The aq. layer was acidified with 1.5M H_2SO_4 to pH ≤ 3 and extracted with Et_2O (4 × 75 ml). The org. layers were dried (Na_2SO_4), and the solvent was removed to yield 6.10 g (76%) of **16**. Highly viscous colorless oil (solidifies upon standing). Diastereoisomer ratio: 1:1. ^{1}H-NMR (400 MHz): 1.18, 1.20 (*s*, Me–C(1′)); 1.40–1.58 (*m*, 3 H); 1.64 (*m*, Me–C(4)); 1.60–1.72 (*m*, 2 H); 1.70 (*s*, Me–C(5′)); 1.92–2.02 (*m*, 3 H); 2.03–2.22 (*m*, 3 H); 2.49 (*m*, 1 H); 4.66, 4.69 (*m*, 2 × 1 H, H_2C(6′)); 5.37 (*m*, H–C(3)). ^{13}C-NMR (100 MHz): 21.1 (*q*, *Me*–C(1′)); 21.3, 21.5 (*t*, C(3′)); 21.5 (*q*, *Me*–C(1′)); 22.3 (2*q*, *Me*–C(5′)); 23.2 (*q*, *Me*–C(4)); 25.3, 25.4 (*t*, C(2′)); 28.1, 28.2 (*t*, C(6)); 28.6, 28.7 (*t*, C(5)); 36.6, 37.1 (*t*, C(2)); 38.1, 38.2 (*t*, C(4′)); 53.7 (2*s*, C(1)); 75.5, 75.6 (*s*, C(1′)); 109.8, 109.9 (*t*, C(6′)); 119.1, 119.3 (*d*, C(3)); 132.8, 133.1 (*s*, C(4)); 145.2 (*s*, C(5′)); 180.2, 180.3 (*s*, COO). ^{1}H-NMR (400 MHz, (D_6)acetone): 1.19, 1.20 (*s*, Me–C(1′)); 1.45–1.57 (*m*, 3 H); 1.58 (*m*, Me–C(4)); 1.62–1.72 (*m*, 2 H); 1.69 (*s*, Me–C(5′)); 1.90 (*m*, 1 H); 1.98–2.03 (*m*, 2 H); 2.09–2.23 (*m*, 3 H); 2.51 (*m*, 1 H); 4.66 (*m*, H_2C(6′)); 5.34 (*m*, H–C(3)). ^{13}C-NMR (100 MHz, (D_6) acetone): 21.7, 22.1 (*q*, *Me*–C(1′)); 22.2, 22.3 (*t*, C(3′)); 22.4 (*q*, Me–C(5′)); 23.3 (*q*, Me–C(4)); 25.8, 25.9 (*t*, C(2′)); 28.8, 28.9 (*t*, C(6)); 29.1, 29.4 (*t*, C(5)); 37.3, 37.6 (*t*, C(2)); 38.9 (2*t*, C(4′)); 54.1, 54.2 (*s*, C(1)); 74.9, 75.1 (*s*, C(1′)); 110.0 (*t*, C(6′)); 120.7 (2*d*, C(3)); 132.9, 133.0 (*s*, C(4)); 146.2 (2*s*, C(5′)); 176.6, 176.7 (*s*, COO). LC-MS (neg.): 265 (100, $[M-H]^-$), 139 (15, $[C_8H_{11}O_2]^-$). LC-MS (pos.): 305 (19, $[M+K]^+$), 289 (100, $[M+Na]^+$). HR-MS: 248.1776 ($C_{16}H_{26}O_3$; $[M-H_2O]^+$; calc. for M^+: 266.1882).

3,7-Dimethyl-3-(4-methylpent-4-enyl)-2-oxa-spiro[3.5]non-6-en-1-one (**17**). Hydroxy acid **16** (5.32 g, 20 mmol) was dissolved in anh. pyridine (80 ml) and CH_2Cl_2 (80 ml). After cooling to −5°, *p*-toluenesulfonyl chloride (11.43 g, 60 mmol) was added with stirring. The mixture was stirred at 0° for 18 h, then poured on ice, and extracted with Et_2O (4 × 50 ml). The org. layers were washed with 10% H_2SO_4 (2 × 30 ml), neutralized with aq. $NaHCO_3$ soln. (4 × 50 ml), and dried (Na_2SO_4) to yield 4.43 g (89%) of **17**, which was used without further purification. Colorless oil. Diastereoisomer ratio: 1:1. ^{1}H-NMR (400 MHz): 1.45, 1.51 (*s*, Me–C(3)); 1.48–1.60 (*m*, 3 H); 1.67 (*m*, Me–C(7)); 1.70, 1.71 (*s*, Me–C(5′)); 1.69–1.93 (*m*, 2 H); 1.96–2.12 (*m*, 3 H); 2.14–2.44 (*m*, 4 H); 4.67, 4.71 (*m*, H_2C(5′)); 5.33 (*m*, 1 H, CH_2(6)). ^{13}C-NMR (100 MHz): 19.6, 19.7 (*q*, *Me*–C(3)); 21.8, 21.9 (*t*, C(2′)); 22.1 (*q*, *Me*–C(4′)); 23.0 (2*q*, *Me*–C(7)); 24.2, 24.9 (*t*, C(1′)); 26.9, 27.0 (*t*, C(9)); 27.5, 28.1 (*t*, C(8)); 35.1, 35.5 (*t*, C(5)); 37.7 (2*t*, C(3′)); 56.5, 56.7 (*s*, C(4)); 84.7, 85.2 (*s*, C(3)); 110.2 (2*t*, C(5′)); 116.5, 116.8 (*d*, C(6)); 133.7, 134.0 (*s*, C(7)); 144.4 (2*s*, C(4′)); 174.1, 174.3 (*s*, C(1)). HR-MS: 248.1776 ($C_{16}H_{24}O_2$; calc.: 248.1776).

Decarboxylation of **17** *to give* **12**. The crude β-lactone **17** (3.72 g, 15 mmol) was heated to 150–160° under N_2 for 2 h (evolution of CO_2) and then cooled. The crude brown oil was distilled in a bulb-to-bulb apparatus under reduced pressure and further purified by CC (SiO_2, hexane) to obtain 2.92 g (95%) of (*E*/*Z*)-**12**. Colorless oil. Diastereomer ratio: 1:1. This material had properties identical to those of another sample of iso-γ-bisabolene prepared synthetically (*cf. Sect. 5* of the *Exper. Part*).

7. *Separation of Iso-β-bisabolol Isomers* (**4a**,**b**). The mixture of **4a**,**b** was separated *via* HPLC (hexane/Et_2O 9:1, injection: 150 µl of a 25% solution) to obtain two fractions.

(1S)-1-[(1S*)-1,5-Dimethyl-hex-5-enyl]-4-methylcyclohex-3-en-1-ol* (**4a**). Colorless oil, strong floral, *muguet*-like, very pleasant odor. ^{1}H-NMR (300 MHz): 0.91 (*d*, *J* = 6.9, Me–C(1′)); 1.02 (*m*, 1 H); 1.26 (*s*, OH); 1.33 (*m*, 1 H); 1.46 (*m*, 1 H); 1.53–1.65 (*m*, 4 H); 1.69 (*s*, Me–C(4)); 1.71 (*s*, Me–C(5′)); 1.80–1.98 (*m*, 2 H); 1.98–2.06 (*m*, 2 H); 2.12–2.24 (*m*, 2 H); 4.67, 4.69 (*m*, H_2C(6′)); 5.30 (*m*, H–C(3). ^{13}C-NMR (75 MHz): 13.7 (*q*, *Me*–C(1′)); 22.3 (*q*, *Me*–C(5′)); 23.3 (*q*, *Me*–C(4)); 26.3 (*t*, C(6)); 27.0 (*t*, C(2′)); 30.3 (*t*, C(3′)); 30.9 (*t*, C(5)); 34.2 (*t*, C(2)); 38.0 (*t*, C(4′)); 42.4 (*d*, C(1′)); 72.2 (*s*, C(1)); 109.7 (*t*, C(6′)); 118.4 (*d*, C(3)); 133.8 (*s*, C(4)); 146.0 (*s*, C(5′)).

(1S)-1-[(1R*)-1,5-Dimethylhex-5-enyl]-4-methylcyclohex-3-en-1-ol* (**4b**). Colorless oil. Odorless. ^{1}H-NMR (300 MHz): 0.95 (*d*, *J* = 6.9, Me–C(1′)); 1.03 (*m*, 1 H); 1.34 (*s*, OH); 1.35 (*m*, 1 H); 1.43–1.63 (*m*, 5 H); 1.69 (*s*, Me–C(4)); 1.71 (*s*, *Me*–C(5′)); 1.83–2.05 (*m*, 4 H); 2.13–2.24 (*m*, 2 H); 4.67 (*m*, 1 H); 4.69 (*m*, 1 H); 5.29 (*m*, 1 H). ^{13}C-NMR (75 MHz): 13.6 (*q*, *Me*–C(1′)); 22.3 (*q*, *Me*–C(5′)); 23.2 (*q*, *Me*–C(4)); 26.2 (*t*, C(6)); 27.0 (*t*, C(2′)); 30.3 (*t*, C(3′)); 30.6 (*t*, C(5)); 34.8 (*t*, C(2)); 38.0 (*t*, C(4′)), 42.1 (*d*, C(1′)); 72.2 (*s*, C(1)); 109.7 (*t*, C(6′)); 118.4 (*d*, C(3)); 133.9 (*s*, C(4)); 146.0 (*s*, C(5′)).

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