Synthesis and Structure Elucidation of a New Potent Sandalwood-Oil Substitute

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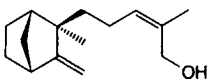
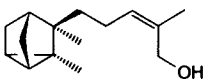
New derivatives of campholenaldehyde (= 2-(2,2,3-trimethylcyclopent-3-enyl)ethanal) bearing two cyclopropane moieties were synthesized, and the structure of the stereoisomer responsible for its exceptionally strong, diffusive, and natural sandalwood-oil scent, ((1*S*,2*S*)-1-methyl-2-{[(1*S*,3*R*,5*R*)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]methyl}cyclopropyl)methanol (**13a**), was elucidated.

Introduction. – The main constituents of sandalwood oils are unsaturated alcohols, aldehydes, and ketones consisting of a bulky bi- or tricycloheptane (or -octane) moiety separated from the functional group by an unsaturated *spacer* of 4–5 C-atoms (*e.g.*, **1**–**4**) [1]. The best synthetic substitutes of this noble perfumery raw material are (trimethylcyclopentyl) alkenols **5**–**8** [1–4] derived from campholenaldehyde. The structural resem-



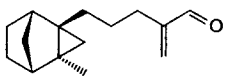
1
(–)-(*Z*)-*β*-Santalol

typical sandalwood, woody, milky, urinous



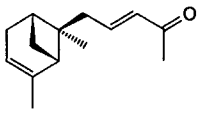
2
(+)-(*Z*)-*α*-Santalol

woody, cedarwood



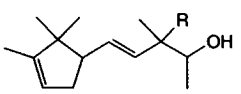
3

woody, ambergris, sandalwood

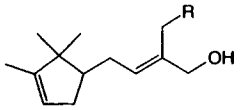


4
(–)-Nor-*α*-*trans*-bergamotenone

fatty, nutty, milky, sandalwood [1])



5 R = H
7 R = Me



6 R = H
8 R = Me

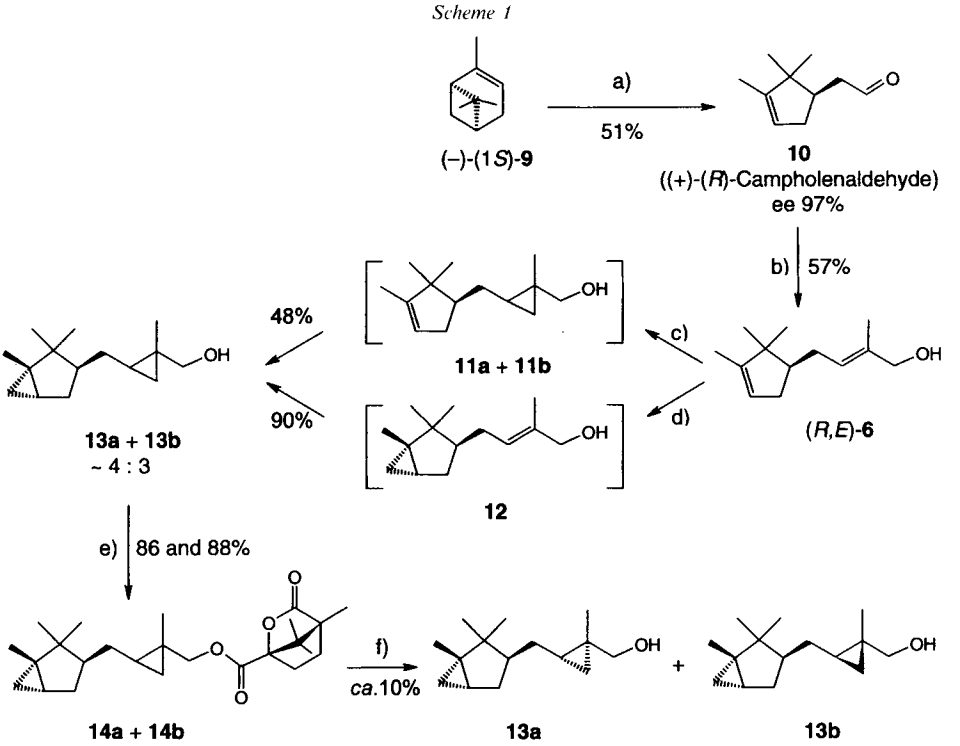
sandalwood type

[1]) The scent of this trace constituent of sandalwood oil, isolated by *Brunke* and *Schmaus* [1b][6] only in 1994, was reported to '*possess a powerful fatty, nutty scent, which reminds clearly to the smell of sandalwood itself*'. Recently, *Chapuis et al.* [7] established its absolute configuration *via* synthesis and found that its '*fatty, oily, organoleptic properties* (...) *allow its possible application for the reconstitution of sandalwood essential oil top notes, despite the fact that* (this molecule) *itself does not possess any woody, sandalwood-like character*'.

blance between these two groups of compounds is obvious. Already in 1979, the presence of a C=C bond or a cyclopropane ring in the lipophilic part of the sandalwood-smelling molecules was recognized as one of the conditions for the unique, woody milky lactonic and slightly urinous scent, typical of natural sandalwood oil [1][5]. To the best of our knowledge, the cyclopropane ring has never been introduced to the campholenaldehyde-derived sandalwood-oil substitutes.

Results and Discussion. – In the course of our studies on the structure-odor relationship in the woody/amber/sandalwood superfamily of odors and the search for the sandalwood *olfactophore(s)*, we replaced C=C bonds in a series of derivatives of α-, β-, and γ-campholenaldehydes by the isoelectronic cyclopropane ring [8]. One of the synthesized compounds, **13**, an analogue of **6** with two cyclopropane moieties, has an exceptionally *natural* sandalwood-odor profile and one of the lowest odor threshold among all the commercial odorants. Consequently, we wanted to know which of the stereoisomers represents the main odor vector. For this purpose, the syntheses starting from (−)-(1*S*)- and (+)-(1*R*)-α-pinenes, **9** and *ent*-**9**, respectively, of the highest commercially available ee of 97% were carried out (*Scheme 1*). The preparation of campholenaldehyde **10** *via*

Scheme 1



a) 1. AcO_2H, Na_2CO_3, ethylenediaminetetraacetic acid (EDTA); 2. $ZnBr_2$. *b*) 1. EtCHO, MeONa; 2. $NaBH_4$. *c*) CH_2Br_2, Zn, CuBr, AcBr, or ultrasound. *d*) CH_2I_2, Et_3Al. *e*) (−)-(1*S*)-Camphanoyl chloride, pyridine; from fractions enriched in one of the two diastereoisomers. *f*) 1. Diastereoisomer separation by sixfold recrystallization from pentane, hexane, and $EtOH/H_2O$ 20:1; 2. KOH/MeOH.

rearrangement of epoxy-pinanes, as well as the following aldol condensation and reduction, constitute a well-known industrial process.

As the cyclopropanation of the cyclopentene ring of (*E*)-**6** turned out to be highly stereoselective[2][3]), we disposed of two diastereoisomeric pairs **13a** + **13b** and **13c** + **13d** (*cf. Table*) that were olfactorily evaluated by the GC/sniff technique [11]. Perfumers detected one strong odorant in both pairs, but only one of them, obtained from the (*R*)-α-campholenaldehyde (**10**) had a strong, natural sandalwood odor. The main sandalwood odor vector had, therefore, to be either **13a** or **13b**. It was the major constituent of the diastereoisomeric couple. Conformational analysis of the precursor (*Fig. 1*) [12] allowed to assume that the major diastereoisomer resulted from the carbenoid addition to the less hindered face of the chain C=C bond that led to the structure **13a**.

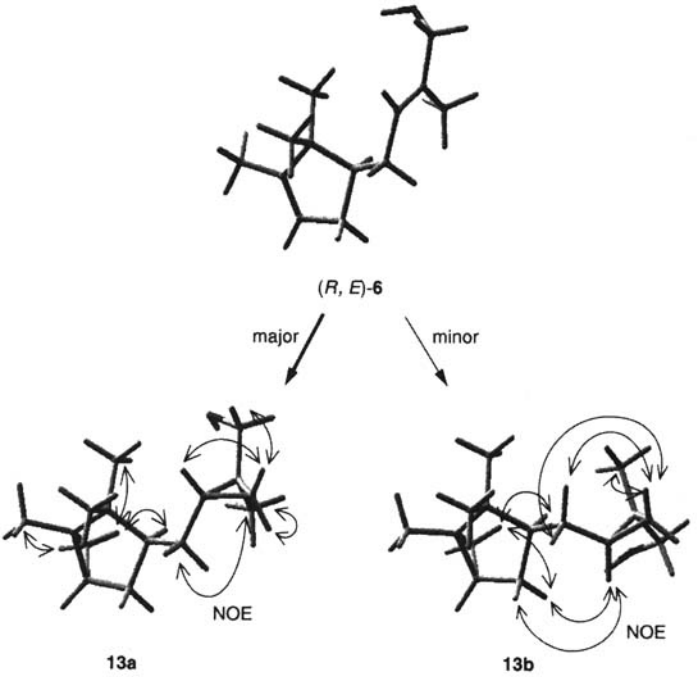


Fig. 1. *Lowest-energy conformers* [7] *of* **13a** *and* **13b** *and of their common precursor* (R,E)-**6**. Only selected NOEs are shown.

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[2]) No (*Z*)-diastereoisomer was found employing different variants of the *Simmons-Smith* reactions or when applying the trialkylaluminum method [9]; de values were > 95%. The main difference between these two methods consisted in the regioselectivity of the first cyclopropanation: the trialkylaluminum/CH_2I_2 preferred the isolated C=C bond of the cyclopentene ring, while the zinc carbenoid first attacked the electron rich allylic alcohol. The separation of monocyclopropanated intermediates **11** and **12** from the substrate **6** as well as from the bicyclopropanated product **13** was not straightforward. Their structures were established by comparison with independently prepared samples (*cf. Exper. Part*).

[3]) Cyclopropanation of protected (as dioxolane or 5,5-dimethyl-1,3-dioxane) α-campholenaldehyde was also diastereoselective: de ≥ 99%. Similarly, epoxidation of the dioxolane was reported to give exclusively (*E*)-diastereoisomer [10].

A NOESY experiment, carried out with the diastereoisomeric pair enriched (de 46%) in the minor constituent, correlated with the conformational analysis, seemed to corroborate this hypothesis (*cf. Fig. 1*). The final proof of the absolute configuration of all the constituents of the mixture came from the X-ray crystal-structure analysis of the corresponding camphanates[4]) **14a** and **14b**, separated by repeated fractional recrystallization (*Fig. 2*).

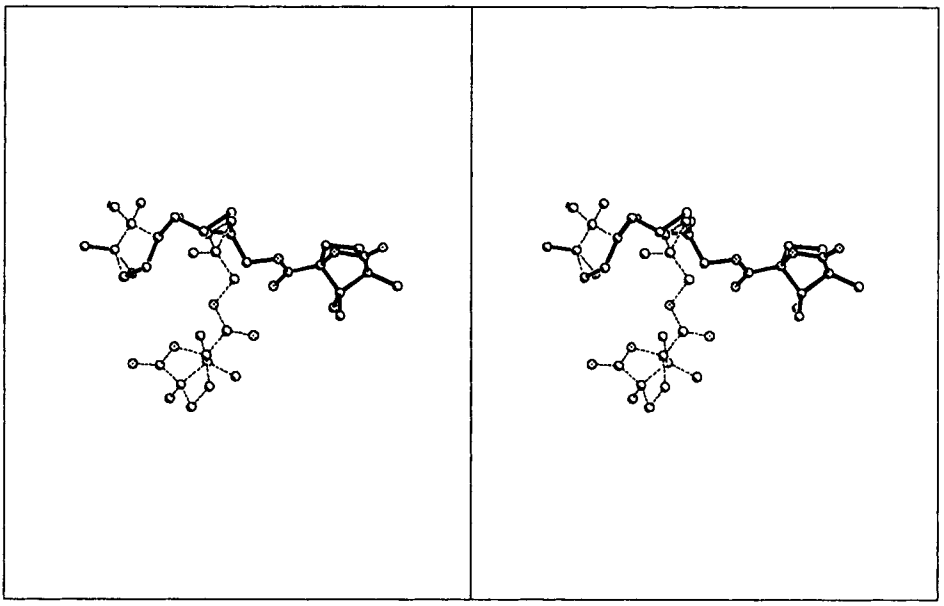


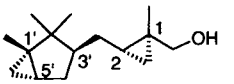
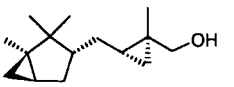
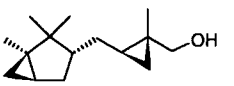
Fig. 2. *Stereoplot of X-ray structures of the camphanates* **14a** (dashed bonds) *and* **14b** *of the two stereoisomeric alcohols* **13a** *and* **13b**. The C-atoms of the trimethylbicyclohexane moieties are superimposed. H-Atoms were omitted for better clarity of the plot. C- and O-atoms are drawn as open and dotted circles, respectively.

Further confirmation of the structure was obtained from enrichment of the isomeric mixture in the active constituent *via* asymmetric cyclopropanation. Two recent modified *Simmons-Smith* procedures seemed best suited for this transformation. The method of *Denmark* and *O'Connor* [13], using (*R,R*)-*N,N'*-cyclohexane-1,2-diylbis[methanesulfonamide] as chiral promoter, gave only a small, nonsignificant diastereoisomeric enrichment, but the *Charette* procedure [14], which applies a chiral dioxaborolane ligand derived from (+)-(*R,R*)-*N,N,N',N'*-tetramethyltartaramide and butylboronic acid, ended up with an encouraging 71% de (13% non-optimized yield) of the desired (*cf.* the synthesis of (+)-bicyclohumulenone [14a]) diastereoisomer **13a**.

The odor thresholds of the stereoisomers of **13** (*Table*) depend critically on the absolute configuration of the *spacer* linking the *osmophoric* group to the lipophilic, bulky part of the molecule. Inversion of the (*S,S*)-configuration of the side-chain cyclopropane

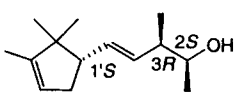
[4]) Crystallographic data for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-101410. Copies of the data can be obtained, free of charge, on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk).

Table. *Olfactory Properties of Single Stereoisomers of* **13**

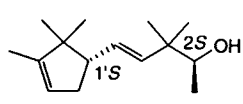
	Configuration		GC[a]) Odor threshold [ng][b])	Odor description[a])
13a	(1*S*,1'*S*,2*S*,3'*R*,5'*R*)		0.015	sandalwood, creamy, warm, strong
13b	(1*R*,1'*S*,2*R*,3'*R*,5'*R*)		≥ 15	lactonic
13c	(1*S*,1'*R*,2*S*,3'*S*,5'*S*)		0.51	floral, rosy, milky, sandalwood
13d	(1*R*,1'*R*,2*R*,3'*S*,5'*S*)		1.4[c]	lactonic, lily of the valley

[a]) Measured and evaluated by the GC/sniff technique with two diastereoisomeric couples **13a** + **13b** and **13c** + **13d** using a *DB-FFAP* 30 m × 0.32 mm/0.25 μm column; the GC OT values in ng correspond roughly to the olfactometer odor thresholds in ng/l. [b]) To be compared to 0.54, 7.4, 0.06, and 4.0 ng for **1**, **2**, (+)-(*R*,*E*)-**6** and (−)-(*S*,*E*)-**6**, respectively. [c]) Probably due to the contamination by *ca.* 1.5% of the strongly smelling enantiomer **13a**.

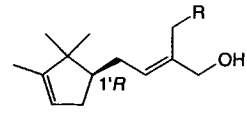
results in a dramatic decrease of the odor intensity (**13a** > **13c** >> **13b** and **13d**). According to our preliminary measurements, GC odor thresholds of both monocyclopropanated intermediates **11a** + **11b** + *ent*-**11a** + *ent*-**11b** and **12** + *ent*-**12**, prepared from **10**/*ent*-**10** 2:5, are at least 80 times higher than that of **13a**, the odor of the latter being significantly weaker and less sandalwood-like. These observations confirm the importance of the geometry of the immediate environment (*spacer*) of the *osmophoric* OH group for the intensity of sandalwood scent of the campholenaldehyde derivatives, already reported for **5a** [15], **7a** [16], and some other sandalwood-oil substitutes, **6a**–**8a**, **13a**, **15**, and **16**, of this family [1].



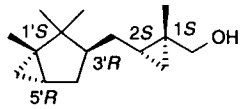
5a [15]
(1'*S*,2*S*,3*R*) > (1'*R*,2*S*,3*R*)



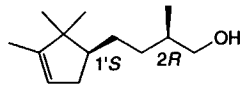
7a [16]
(1'*S*,2*S*) > (1'*R*,2*S*)



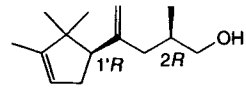
6a R = H [17][18]
8a R = Me [18][19]



13a [8a]
cf. this study



15a [20]
(1'*S*,2*R*) ≥ (1'*R*,2*R*)



16a [21]
(1'*R*,2*R*) > (1'*R*,2*S*)

Two contradictory structure-odor-correlation studies of **6** have been published during the preparation of this paper [17][18]. Our perfumers found that only the enantiomer (+)-(*R*)-**6** possesses a strong sandalwood-like odor, the evaluation being in agreement with that of *Aida et al.* [18]. The active enantiomer of **6** and of the *ca.* 4 times more powerful and more *natural* and *substantive* (long-lasting) sandalwood-odor vector **13a** have the same absolute configuration of the ring C-atoms linked to the *spacers*. The spatial orientation of the slightly different lipophilic parts *vs.* the *osmophoric* OH groups could, therefore, be very similar. Hopefully, these new structure-odor-relationship data will help to fine-tune models of the sandalwood *olfactophore(s)* [1][5][22] including all the steric and electronic requirements.

We are indebted to Dr. *G. Brunner* and Mr. *J. Märki* for NMR experiments, Ms. *A. Flückiger*, Dr. *J.-M. Decazes*, Mr. *A. Gaillard*, and Mr. *H. Koch* for olfactory evaluations and measurements, and Mr. *U. Müller* for skillful technical assistance.

Experimental Part

General. All reagents and solvents were commercially available and were used without any purification. (+)-(1*R*) and (−)-(1*S*)-α-pinenes of ee 97% were purchased from *Aldrich*. Their optical purity was confirmed by chiral GC (on *OV-1701*/octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin [23][5]) 1:1 stationary phase) of the intermediate campholenaldehydes **10** and *ent*-**10**. Not all reactions, carried out initially starting from **10**/*ent*-**10**[6]) (*Givaudan Roure*), were repeated with pure **10** and *ent*-**10**. The yields of isolated products were not optimized. TLC: *Merck* silica gel *60* F_{254} anal. plates. GC: *DB*^{TM}*-1701*, *DB*^{TM}*-WAX*, and *DB*^{TM}*-FFAP* columns. Flash chromatography (FC): *Merck* silica gel *60* (230–400 mesh). M.p.: *Büchi Melting Point B-545* apparatus, uncorrected. Optical rotation: *Perkin-Elmer 241*. IR Spectra: *Nicolet 510 FT-IR*; in cm^{-1}. NMR: *Bruker DPX-400*; ^1H at 400 and ^{13}C at 100 MHz; in $CDCl_3$ if not otherwise stated; chemical shifts (δ) in ppm downfield from TMS; *J* in Hz; NOESY, and GRASP COSY-DQF, HMBC, and HMQC experiments were performed with **12**, **13**, **13a**, and **13b**. MS and GC/MS: *Finnigan MAT 212* (EI, 70 eV); intensities (in brackets) in % rel. to the base peak.

Molecular Modeling. Conformational analyses were performed on *Silicon Graphics Indy R4400SC* workstation using Moloc 2.9 software package with MAB force field [12].

Crystallographic Analysis. All measurements were made at 183(2) K on a *Siemens P4* diffractometer with graphite-monochromated CuK_α radiation from a rotating anode generator. The structure was solved using direct methods (SHELXS-93) and refined against F^2 by full-matrix least-squares methods using SHELXL-93 [24].

Syntheses. *(+)-(E)-2-Methyl-4-[(1R)-2,2,3-trimethylcyclopent-3-enyl]but-2-en-1-ol* ((+)-(*R*)-**6**). Prepared according to [2][25], starting from (−)-(1*S*,5*S*)-α-pinene (**9**). $[\alpha]_D^{22} = +0.7$ (*c* = 1.00, EtOH) [17]. Odor: woody, sandalwood, strong, animal (urinous). The same procedure applied to (+)-(1*R*,5*R*)-α-pinene (*ent*-**9**) afforded (−)-(*S*)-**6**. $[\alpha]_D^{22} = -0.5$ (*c* = 1.06, EtOH) [17]. Odor: woody, terpenic, sandalwood, weak.

{1-Methyl-2-[(2,2,3-trimethylcyclopent-3-enyl)methyl]cyclopropyl}methanol (**11**)[7]). CH_2Br_2 (2.0 g, 12 mmol) and 3 drops of AcBr were added to a stirred suspension of Zn powder (9.8 g, 0.15 mol) and finely ground CuBr (1.5 g, 10 mmol) in 40 ml of anh. Et_2O. After 30 min stirring at r.t., a soln. of (*R*)-**6**/(*S*)-**6** (2:5; 9.7 g, 50 mmol) in 30 ml of the same solvent was added quickly and stirring at r.t. continued for further 7 h. During this period, more CH_2Br_2 (19.0 g, 0.11 mol) was added in 4 portions. The mixture was filtered and the filtrate washed successively with 1N HCl (100 ml) and H_2O (100 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give 7.4 g of yellow oil containing 44% of the starting material and 34% of **11**. MnO_2 (21.7 g, 0.25 mol) was added to oxidize the former. After 7 h stirring at r.t., the mixture was filtered over *Celite*, the filtrate concentrated *in vacuo*, and the residue purified by FC (hexane/*t*-BuOMe 4:1) to give **11a**/**11b**/*ent*-**11a**/*ent*-**11b** (8:6:20:15; 1.5 g, 14%). Colorless oil. R_f 0.23. IR (neat): 3346, 3034, 2953, 2928, 2865, 1693, 1463, 1447, 1382, 1395, 1030, 1013, 798. ^1H-NMR: major diastereoisomer: −0.05 (*dd*, *J* = 4.8, 4.4, 1 H); 0.53 (*dd*, *J* = 8.8, 4.4, 1 H); 0.58–0.68 (*m*, 1 H);

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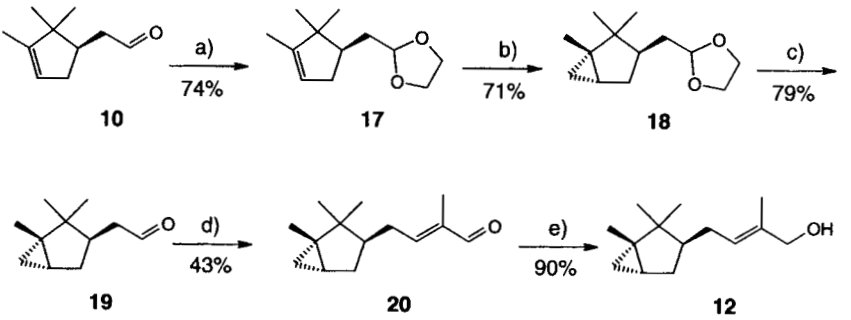
[5]) For enantiomer separation of α-campholene derivatives on similar phases, see [23b].

[6]) To limit the number of syntheses and, therefore, shorten the process of discovery of new interesting odorants.

[7]) Attempts to prepare **11** by the *Corey-Chaykovsky* reaction starting from the corresponding α,β-unsaturated aldehyde failed, despite good results obtained with the homologous methyl ketones [8].

0.75 (*s*, 3 H); 0.99 (*s*, 3 H); 1.16 (*s*, 3 H); 1.61 (*s*, 3 H); 2.31–2.43 (*m*, 1 H); 3.33 (*d*, J_{AB} = 10.9, 1 H); 3.37 (*d*, J_{AB} = 10.9, 1 H); 5.25 (br. *s*, 1 H); minor diastereoisomer: 0.03 (*dd*, *J* = 4.7, 4.2, 1 H); 0.55 (*dd*, *J* = 8.7, 4.2, 1 H); 0.58–0.68 (*m*, 1 H); 0.74 (*s*, 3 H); 0.98 (*s*, 3 H); 1.15 (*s*, 3 H); 1.61 (*s*, 3 H); 2.31–2.43 (*m*, 1 H); 3.33 (br. *s*, 1 H); 5.25 (br. *s*, 1 H). ^{13}C-NMR: major diastereoisomer: 12.48 (*q*); 15.59 (*q*); 16.33 (*t*); 19.47 (*q*); 20.98 (*d*); 22.39 (*s*); 25.60 (*q*); 28.64 (*t*); 35.48 (*t*); 46.42 (*s*); 50.70 (*d*); 72.10 (*t*); 121.64 (*d*); 148.46 (*s*); minor diastereoisomer: 12.45 (*q*); 15.03 (*q*); 16.91 (*t*); 19.39 (*q*); 20.64 (*d*); 21.46 (*s*); 25.52 (*q*); 29.16 (*t*); 35.45 (*t*); 46.62 (*s*); 51.06 (*d*); 72.19 (*t*); 121.74 (*d*); 148.41 (*s*). MS: 208 (0.4, M^+), 193 (1), 177 (2), 175 (3), 153 (7), 147 (4), 136 (21), 121 (35), 107 (39), 95 (43), 93 (100), 91 (35), 79 (43), 67 (42), 55 (41), 43 (69), 41 (64), 31 (5), 27 (16). Odor: creamy, lactonic, sandalwood.

Scheme 2



a) $HO(CH_2)_2OH$, TsOH. *b*) CH_2I_2, Et_2Zn. *c*) SiO_2/HCl. *d*) EtCHO, MeONa. *e*) $NaBH_4$.

(E)-2-Methyl-4-[(1S,3S,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]but-2-en-1-ol (**12**; cf. *Scheme 2*). $NaBH_4$ (0.5 g, 10 mmol) dissolved in 5 ml of H_2O was added portionwise to the soln. of **20** (5.0 g, 24 mmol) in 20 ml of EtOH maintained at 0°. Stirring was continued for 1 h at 0 – 5°, then acetone was added to destroy the excess of $NaBH_4$. The mixture was poured into H_2O (100 ml), extracted with Et_2O (2 × 100 ml), dried ($MgSO_4$), and evaporated *in vacuo*. Bulb-to-bulb distillation of the residue at 160°/0.1 Torr afforded **12** (4.5 g, 90%). Colorless oil, de ≥ 99%. R_f (hexane/Et_2O 4:1) 0.12. $[\alpha]_D^{22}$ = + 20.4 (*c* = 1.05, EtOH). IR (neat): 3320, 3059, 2998, 2952, 2927, 2858, 1463, 1451, 1386, 1362, 1298, 1076, 1013, 834. ^{1}H-NMR: 0.01 (*dd*, *J* = 7.8, 4.7, 1 H); 0.42 (*dd*, *J* = 4.7, 3.6, 1 H); 0.80 (*s*, 3 H); 0.91 (*s*, 3 H); 0.96 (*ddd*, *J* = 7.8, 4.2, 3.6, 1 H); 1.04 (*s*, 3 H); 1.12–1.2 (*m*, 1 H); 1.38 (*ddd*, *J* = 12.1, 11.4, 4.2, 1 H); 1.40–1.45 (*m*, 1 H); 1.65 (*s*, 3 H); 1.72 (*dd*, *J* = 12.1, 6.8, 1 H); 1.71–1.80 (*m*, 1 H); 1.97–2.05 (*m*, 1 H); 3.97 (br. *s*, 2 H); 5.36 (*ddddq*, *J* = 7.2, 7.2, 1.3, 1.3, 1.3, 1 H). ^{13}C-NMR: 13.63 (*q*); 13.83 (*t*); 17.34 (*q*); 19.66 (*q*); 22.43 (*d*); 22.89 (*q*); 28.15 (*t*); 31.29 (*s*); 32.38 (*t*); 41.19 (*s*); 44.62 (*d*); 69.02 (*t*); 126.16 (*d*); 134.29 (*s*). MS: 208 (0.5, M^+), 193 (19), 177 (5), 175 (11), 149 (8), 147 (4), 140 (7), 135 (13), 123 (55), 121 (61), 109 (57), 107 (60), 93 (35), 91 (31), 79 (43), 81 (100), 67 (40), 55 (50), 43 (72), 41 (71), 29 (18). Odor: woody, sandalwood, slightly camphor.

[1-Methyl-2-(1,2,2-trimethylbicyclo[3.1.0]hex-3-ylmethyl)cyclopropyl]methanol (**13**). a) *By the* Simmons-Smith *Cyclopropanation of* **6**. CH_2Br_2 (200 g, 1.15 mol) and AcBr (1 ml, 0.013 mol) were added successively to a suspension of Zn powder (85 g, 1.3 mol) and finely ground CuBr (12 g, 83 mmol) in anh. Et_2O (250 ml). The mixture was stirred until its color changed from gray to black (*ca.* 30 min). After addition of (*R*)-**6**/(*S*)-**6** (2:5; 50 g, 0.26 mol) dissolved in the same solvent (50 ml; during 10 min, smooth reflux, the exothermic reaction) and two drops of $TiCl_4$, the mixture was stirred at r.t. for further 7 h, then diluted with *t*-BuOMe (300 ml) and filtered through *Celite*. The filtrate was washed with ice-cold 0.1N HCl (200 ml) and brine (3 × 200 ml), dried ($MgSO_4$), concentrated *in vacuo*, and distilled rapidly (0.1 Torr) to give 39 g of **13** (55%, 81% pure). Further purification by distillation using a 15-cm *Vigreux* column (0.08 Torr) afforded **13** (27.4 g, 48%; colorless oil crystallizing slowly on standing) that consisted of 56% of **13a** + **13d** and 44% of **13b** + **13c**, the latter pair of enantiomers being first eluted on the *DB-FFAP* GC column. The activation of Zn by sonication, instead of AcBr, gave the same result. Odor: sandalwood, very natural, floral, creamy, powdery, very strong and long-lasting.

b) *By* Et_3Al*-Mediated Cyclopropanation of* **6**. A 15% soln. of Et_3Al in hexane (42 ml, 40 mmol) was added dropwise at 5° to (*R*)-**6**/(*S*)-**6** (2:5; 1.94 g, 10 mmol) and CH_2I_2 (10.8 g, 40 mmol) dissolved in hexane (50 ml). The mixture was stirred at r.t. for 2 h, then poured into 10% ice-cold aq. NaOH soln. (100 ml), and extracted with *t*-BuOMe (200 ml). The org. layer was washed with aq. NH_4Cl soln. (50 ml) and brine (3 × 50 ml), dried

($MgSO_4$), concentrated *in vacuo*, and purified by bulb-to-bulb distillation to give **13** (2.0 g, 90%; GC purity 80%, colorless oil, (**13a** + **13d**)/(**13b** + **13c**) ratio *ca.* 3:2). Odor: as above.

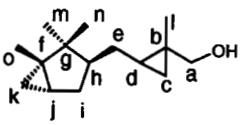
c) *By Hydrolysis of* **14**. A soln. of **14a** (140 mg, 0.35 mmol; synthesis, see later) and KOH (42 mg, 0.75 mmol) in MeOH (3.7 ml) was stirred at r.t. for 2 h, poured into 100 ml of ice-water and extracted with 100 ml of *t*-BuOMe. The org. layer was washed with 2 × 50 ml of H_2O, dried ($MgSO_4$), concentrated *in vacuo*, and purified by FC (hexane/*t*-BuOMe 4:1) to afford *((1S,2S)-1-Methyl-2-{[(1S,3R,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]-methyl}cyclopropyl)methanol* (**13a**; 50 mg, 65%). R_f 0.19. $[\alpha]_D^{22} = +46.4$ ($c = 1.01$, EtOH). IR (neat): 3338, 3058, 2951, 2925, 2867, 1463, 1450, 1385, 1362, 1028, 1014, 870. ^{1}H-NMR[8]): −0.11 (*dd*, $J = 4.9, 4.7$, 1 H–C(c)); 0.02 (*dd*, $J = 7.8, 4.7$, 1 H–C(k)); 0.45–0.50 (*m*, 1 H–C(c), 1 H–C(k)); 0.52–0.59 (*m*, H–C(d)); 0.75 (*s*, Me(n)); 0.89 (*s*, Me(m)); 0.97 (*ddd*, $J = 7.8, 4.2, 3.5$, H–C(j)); 1.04 (*s*, Me(o)); 1.12 (*s*, Me(l)); 1.13–1.23 (*m*, 2 H–C(e), H–C(h)); 1.36–1.45 (*m*, 1 H–C(i), OH); 1.81 (*dd*, $J = 12.0, 5.8$, 1 H–C(i)); 3.30 (*d*, $J_{AB} = 11.1$, 1 H–C(a)); 3.34 (*d*, $J_{AB} = 11.1$, 1 H–C(a)). ^{13}C-NMR[8]): 13.86 (C(k)); 15.65 (C(l)); 16.43 (C(c)); 17.38 (C(o)); 19.72 (C(n)); 21.46 (C(d)); 22.55 (C(j)); 22.71 (C(b)); 22.89 (C(m)); 28.96 (C(e)); 31.37 (C(f)); 32.42 (C(i)); 41.16 (C(g)); 44.77 (C(h)); 72.50 (C(a)). MS: 222 (0.1, M^+), 207 (4), 189 (6), 167 (5), 163 (5), 149 (11), 135 (23), 123 (32), 121 (46), 109 (34), 107 (76), 93 (61), 81 (100), 79 (54), 67 (59), 55 (72), 43 (88), 41 (91), 29 (24).

The same hydrolysis carried out with 260 mg of **14b** yielded *((1R,2R)-1-Methyl-2-{[(1S,3R,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]methyl}cyclopropyl)methanol* (**13b**; 90 mg, 63%). R_f 0.19. $[\alpha]_D^{22} = +8.5$ ($c = 1.02$, EtOH). IR (neat): 3338, 3058, 2951, 2926, 2857, 1463, 1451, 1385, 1362, 1028, 1014. ^{1}H-NMR: −0.03 (br. *s*, 1 H); 0.02 (*dd*, $J = 7.8, 4.7$, 1 H); 0.45 (*dd*, $J = 4.7, 3.5$, 1 H); 0.48–0.54 (*m*, 2 H); 0.74 (*s*, 3 H); 0.88 (*s*, 3 H); 0.94–1.02 (*m*, 2 H); 1.03 (*s*, 3 H); 1.11 (*s*, 3 H); 1.13–1.23 (*m*, 1 H); 1.30–1.44 (*m*, 3 H); 1.85 (*dd*, $J = 12.1, 6.7$, 1 H); 3.30 (br. *s*, 2 H). ^{13}C-NMR[8]): 13.95 (C(k)); 15.09 (C(l)); 17.05 (C(c)); 17.36 (C(o)); 19.60 (C(n)); 21.08 (C(d)); 21.75 (C(b)); 22.65 (C(j)); 22.87 (C(m)); 29.56 (C(e)); 31.28 (C(f)); 32.48 (C(i)); 41.39 (C(g)); 45.18 (C(h)); 72.57 (C(a)). MS: 222 (0.2, M^+), 207 (4), 189 (7), 161 (4), 149 (10), 135 (24), 123 (33), 121 (54), 107 (74), 93 (60), 81 (100), 79 (54), 55 (65), 43 (75), 41 (87), 29 (26).

d) *By Asymmetric Cyclopropanation of* **6**. CH_2I_2 (15.3 ml, 19 mmol) was added to a soln. of Et_2Zn (95 ml of 1M soln. in hexane), CH_2Cl_2 (50 ml), and freshly distilled 1,2-dimethoxyethane (DME, 10 ml, 96 mmol) at −15° during 20 min. The soln. of $Zn(CH_2I)_2 \cdot$ DME complex was added dropwise, during 20 min, to the mixture of (4*R*,5*R*)-2-butyl-*N*,*N*,*N*′,*N*′-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (5.6 g, 21 mmol), prepared from (+)-*N*,*N*,*N*′,*N*′-tetramethyl-L-tartaramide (*Fluka*) according to [14b], (*R*,*E*)-**6** (3.7 g, 19 mmol, 97% ee), and 4-Å molecular sieves (1 g) in 100 ml of CH_2Cl_2 maintained at −15°. The mixture was stirred at −10° for 2 h and then at r.t. for 18 h. As the GC indicated no further progress of the reaction (stopped at the **13**/**11** ratio 48:43), the mixture was poured into ice-cold NH_4Cl soln. (200 ml), and extracted with *t*-BuOMe (500 ml). The org. layer was then successively washed with 2N NaOH (100 ml), 2N HCl (100 ml), and brine (2 × 100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The completion of the cyclopropanation of the residue (3.3 g) was carried out using Zn powder (3.25 g, 50 mmol), CuBr (0.5 g, 3.5 mmol), and CH_2Br_2 (8.7 g, 50 mmol) to give **13a**/**13b** (85:15; 0.51 g, 13%). $[\alpha]_D^{22} = +39.5$ ($c = 1.01$, EtOH).

((1S,2S)-1-Methyl-2-{[(1S,3R,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]methyl}cyclopropyl)methyl (1S,4R)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**14a**). A soln. of (−)-(1*S*)-camphanoyl chloride (1.8 g, 8.3 mmol; *Fluka*, ee ≥ 99%) and an FC fraction of **13a** + **13b** (2:1; 1.8 g, 8.1 mmol) in pyridine (20 ml) was stirred at r.t. for 2 h, poured on ice-water (100 ml), and extracted with *t*-BuOMe (100 ml). The extract was washed with dil. HCl, $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by FC on silica gel (*t*-BuOMe/hexane 1:6) to give **14a** + **14b** (2.8 g, 86%). Fractional crystallization of this mixture from pentane (3×), hexane (2×), and EtOH/H_2O 20:1 afforded colorless crystals of **14a** (de with respect to the configuration of the side chain cyclopropane ≥ 99%). M.p. 80.5–81.5°. $[\alpha]_D^{22} = +18.0$ ($c = 1.05$, EtOH). IR (KBr): 3024, 2961, 2850, 1787, 1743, 1460, 1386, 1309, 1275, 1261, 1173, 1108, 1065, 1029, 935. ^{1}H-NMR: −0.01 (*dd*, $J = 4.9, 4.7$, 1 H); 0.02 (*dd*, $J = 7.8, 4.7$, 1 H); 0.45 (*dd*, $J = 4.7, 3.5$, 1 H); 0.58–0.68 (*m*, 2 H); 0.75 (*s*, 3 H); 0.88 (*s*, 3 H); 0.97 (*ddd*, $J = 7.8, 4.2, 3.5$, 1 H); 0.98 (*s*, 3 H); 1.04 (*s*, 3 H); 1.08 (*s*, 3 H); 1.12 (*s*, 3 H); 1.13 (*s*, 3 H); 1.14–1.20 (*m*, 3 H); 1.40 (*ddd*, $J = 11.9, 11.0, 4.2$, 1 H); 1.70 (*ddd*, $J = 13.2, 9.3, 4.2$, 1 H); 1.82 (*dd*, $J = 11.9, 5.8$, 1 H); 1.94 (*ddd*, $J = 13.2, 10.7, 4.6$, 1 H); 2.05 (*ddd*, $J = 13.5, 9.3, 4.6$, 1 H); 2.44 (*ddd*, $J = 13.5, 10.7, 4.2$, 1 H); 3.96 (*d*, $J_{AB} = 11.1$, 1 H); 3.99 (*d*, $J_{AB} = 11.1$, 1 H). ^{13}C-NMR: 9.68 (*q*); 13.81 (*t*); 16.15 (*q*); 16.72 (*q*); 16.76 (*q*);

[8]) For assignments:



17.09 (*t*); 17.33 (*q*); 19.60 (*s*); 19.68 (*q*); 22.14 (*d*); 22.44 (*d*); 22.84 (*q*); 28.73 (*t*); 28.93 (*t*); 30.53 (*t*); 31.29 (*s*); 32.35 (*t*); 41.12 (*s*); 44.64 (*d*); 53.98 (*s*); 54.71 (*s*); 74.82 (*t*); 91.27 (*s*); 167.51 (*s*); 178.15 (*s*). MS: 402 (2, M^+), 387 (5), 253 (10), 235 (79), 207 (89), 204 (20), 189 (36), 150 (100), 135 (68), 123 (49), 122 (40), 121 (64), 109 (38), 107 (87), 93 (50), 83 (58), 81 (58), 69 (39), 55 (70), 41 (60). *X-Ray crystal-structure analysis*: $C_{25}H_{38}O_4$ (402.55), colorless needle, $0.2 \times 0.2 \times 0.05$ mm, monoclinic, space group, $P2_1$, $a = 10.705(4)$, $b = 6.765(3)$, $c = 16.398(7)$ Å, $\beta = 101.65(2)°$, $Z = 2$, $\rho_{calc.} = 1.149$ g/cm^3, $\mu = 0.600$ mm^{-1}, $F(000) = 440$; the final residuals for 263 parameters (with anisotropic *B* factors) without restraints refined against 1352 unique data with $I > 2\sigma(I)$ were $R = 0.0779$ and $R_w = 0.1791$.

((1R,2R)-1-Methyl-2-{[(1S,3R,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]methyl}cyclopropyl)methyl (1S,4R)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (**14b**). An FC fraction of **13a** + **13b** (4:5; 2.0 g, 9.0 mmol) was transformed into **14a** + **14b** (3.2 g, 88%), and **14b** (colorless crystals, de with respect to the configuration of the side-chain cyclopropane ≥ 95%) separated by fractional crystallization as described above. M.p. 104.5 – 106°. $[\alpha]_D^{22} = +1.6$ (*c* = 1.03, EtOH). IR (KBr): 2997, 2972, 2926, 1783, 1725, 1456, 1396, 1342, 1318, 1170, 1098, 1057, 1024, 912. ^{1}H-NMR: −0.01–0.08 (*m*, 2 H); 0.44 (br. *s*, 1 H); 0.58–0.72 (*m*, 2 H); 0.74 (*s*, 3 H); 0.87 (*s*, 3 H); 0.98 (*s*, 3 H); 1.03 (*s*, 3 H); 0.95–1.28 (*m*, 3 H); 1.07 (*s*, 3 H); 1.11 (*s*, 3 H); 1.13 (*s*, 3 H); 1.27–1.33 (*m*, 1 H); 1.40 (*ddd*, *J* = 11.9, 11.3, 4.1, 1 H); 1.70 (*ddd*, *J* = 13.2, 9.3, 4.2, 1 H); 1.86 (*dd*, *J* = 11.9, 6.8, 1 H); 1.76–1.97 (*m*, 1 H); 2.04 (*ddd*, *J* = 13.6, 9.3, 4.3, 1 H); 2.44 (*ddd*, *J* = 13.6, 10.7, 4.2, 1 H); 3.90 (*d*, J_{AB} = 11.0, 1 H); 4.05 (*d*, J_{AB} = 11.0, 1 H). ^{13}C-NMR: 9.70 (*q*); 13.87 (*t*); 15.50 (*q*); 16.75 (*q*); 16.80 (*q*); 17.32 (*q*); 17.51 (*t*); 18.74 (*s*); 19.56 (*q*); 22.78 (*d*); 22.58 (*d*); 22.84 (*q*); 28.93 (*t*); 29.49 (*t*); 30.56 (*t*); 31.18 (*s*); 32.31 (*t*); 41.37 (*s*); 44.95 (*d*); 53.97 (*s*); 54.73 (*s*); 74.90 (*t*); 91.27 (*s*); 167.54 (*s*); 178.21 (*s*). MS: 402 (1, M^+), 387 (7), 279 (5), 253 (6), 204 (17), 189 (29), 150 (42), 135 (54), 123 (62), 122 (41), 121 (72), 109 (41), 107 (100), 93 (56), 81 (76), 55 (42). *X-Ray crystal-structure analysis* (final crystallization from MeOH/EtOH/H$_2$O 5:10:1): $C_{25}H_{38}O_4$ (402.55), colorless needle, $0.2 \times 0.05 \times 0.05$ mm, orthorhombic, space group $P2_12_12_1$, $a = 6.265(3)$, $b = 12.232(5)$, $c = 30.408(7)$ Å, $Z = 4$, $\rho_{calc.} = 1.147$ g/cm^3, $\mu = 0.599$ mm^{-1}, $F(000) = 880$; the final residuals for 263 parameters (with anisotropic *B* factors) without restraints refined against 1471 unique data with $I > 2\sigma(I)$ were $R = 0.0731$ and $R_w = 0.1860$.

2-{[(1S,3R,5R)-1,2,2-Trimethylbicyclo[3.1.0]hex-3-yl]methyl}-1,3-dioxolane (**18**). 1.0N soln. of Et_2Zn in hexane (150 ml, 0.15 mol), and CH_2I_2 (66 g, 0.23 mol) were successively added to 500 ml of $ClCH_2CH_2Cl$ under N_2 at 15–20° (ice bath), and the soln. was stirred at r.t. for 30 min. *(R)-2-[(2,2,3-trimethylcyclopent-3-enyl)methyl]-1,3-dioxolane* (**17**; $[\alpha]_D^{22} = -6.7$ (*c* = 1.03, EtOH) [10]; 20 g, 0.10 mmol) was added dropwise at 25° and the stirring continued for 3 h. The mixture was treated with 20% aq. K_2CO_3 soln. (100 ml), the org. layer separated, and the aq. layer extracted with Et_2O. The combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (22 g) was distilled at 95°/0.1 Torr to afford **18** (14.9 g, 71%, colorless oil) used in the next step without further purification. An anal. sample was purified by FC (hexane/Et_2O 9:1). R_f 0.33; de (NMR) ≥ 99%. $[\alpha]_D^{22} = +18.4$ (*c* = 1.00, EtOH). IR (neat): 3060, 2998, 2951, 2870, 1464, 1411, 1363, 1140, 1104, 1048, 1016, 945, 907, 772. ^{1}H-NMR: 0.02 (*dd*, *J* = 7.8, 4.8, 1 H); 0.47 (*dd*, *J* = 4.8, 3.5, 1 H); 0.77 (*s*, 3 H); 0.90 (*s*, 3 H); 0.98 (*ddd*, *J* = 7.8, 4.1, 3.5, 1 H); 1.04 (*s*, 3 H); 1.30–1.37 (*m*, 1 H); 1.39–1.48 (*m*, 2 H); 1.60 (*ddd*, *J* = 13.2, 6.2, 3.0, 1 H); 1.83 (*dd*, *J* = 12.0, 6.6, 1 H); 3.83 (*m*, 2 H); 3.95 (*m*, 2 H); 4.79 (*dd*, *J* = 6.2, 3.9, 1 H). ^{13}C-NMR: 13.85 (*t*); 17.39 (*q*); 19.72 (*q*); 22.60 (*q*); 22.74 (*d*); 30.85 (*s*); 32.36 (*t*); 34.60 (*t*); 39.88 (*d*); 41.52 (*s*); 64.58 (*t*); 64.77 (*t*); 104.43 (*d*). MS: 210 (0.1, M^+), 195 (0.4), 169 (2), 148 (2), 133 (4), 122 (18), 107 (19), 91 (7), 79 (7), 73 (100), 55 (9), 45 (23), 41 (16), 29 (6).

[(1S,3R,5R)-1,2,2-Trimethylbicyclo[3.1.0]hex-3-yl]ethanal (**19**). A mixture of **18** (11.0 g, 52 mmol), acetone (80 ml), H_2O (40 ml), conc. HCl (1.5 ml), and SiO_2 (10 g) was refluxed for 4 h. After filtration, the soln. was diluted with Et_2O (200 ml), washed with H_2O (2 × 200 ml), dried ($MgSO_4$), and evaporated *in vacuo*. Bulb-to-bulb distillation of the residue gave **19** (6.8 g, 79%). Colorless oil. R_f (hexane/*t*-BuOMe 10:1) 0.31. $[\alpha]_D^{22} = +14.0$ (*c* = 1.00, $CHCl_3$). IR (neat): 3061, 3000, 2956, 2929, 2869, 2717, 1726, 1711, 1464, 1453, 1388, 1365, 1300, 1158, 1017. ^{1}H-NMR: 0.09 (*dd*, *J* = 7.8, 4.9, 1 H); 0.51 (*dd*, *J* = 4.9, 3.5, 1 H); 0.79 (*s*, 3 H); 0.92 (*s*, 3 H); 1.03 (*ddd*, *J* = 7.8, 4.2, 3.5, 1 H); 1.06 (*s*, 3 H); 1.44 (*ddd*, *J* = 11.9, 11.2, 4.2, 1 H); 1.64–1.72 (*m*, 1 H); 1.81 (*dd*, *J* = 11.9, 6.8, 1 H); 2.16 (*ddd*, *J* = 15.7, 10.3, 2.7, 1 H); 2.37 (*ddd*, *J* = 15.7, 4.0, 2.1, 1 H); 9.72 (*dd*, *J* = 2.7, 2.1, 1 H). ^{13}C-NMR: 13.88 (*t*); 17.30 (*q*); 20.03 (*q*); 22.59 (*q*); 22.60 (*d*); 30.98 (*s*); 32.26 (*t*); 38.66 (*d*); 41.41 (*s*); 44.89 (*t*); 202.92 (*d*). MS: 166 (0.5, M^+), 151 (10), 133 (8), 123 (15), 122 (77), 108 (26), 107 (100), 97 (18), 91 (31), 81 (39), 69 (40), 55 (60), 41 (60), 29 (16). Odor: green, ketonic, bitter.

(E)-2-Methyl-4-[(1S,3S,5R)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]but-2-enal (**20**). Compound **19** (30 g, 0.18 mmol) and EtCHO (35 g, 0.61 mol; dropwise in 10 min) were successively added to a stirred 0.53M methanolic soln. of MeONa (45 ml, 24 mmol) at 25°. The mixture was stirred at r.t. for further 1.5 h, neutralized with AcOH, and the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (100 ml), washed with H_2O (3 × 80 ml),

dried ($MgSO_4$) and concentrated *in vacuo*. Purification by bulb-to-bulb distillation at 94°/0.1 Torr followed by FC (hexane/MTBE 4:1) gave **20** (16.0 g, 43%). Colorless oil. R_f (hexane/Et_2O 9:1) 0.33. $[\alpha]_D^{22} = +12.9$ ($c = 1.04$, EtOH). IR (neat): 3060, 2998, 2954, 2927, 2868, 1690, 1644, 1463, 1451, 1363, 1014. ^{1}H-NMR: 0.06 (*dd*, $J = 7.8$, 4.9, 1 H); 0.44 (*dd*, $J = 4.9$, 3.5, 1 H); 0.84 (*s*, 3 H); 0.95 (*s*, 3 H); 1.01 (*ddd*, $J = 7.8$, 4.1, 3.5, 1 H); 1.06 (*s*, 3 H); 1.32 (*dddd*, $J = 11.3$, 10.4, 6.8, 4.4, 1 H); 1.46 (*ddd*, $J = 11.9$, 11.3, 4.1, 1 H); 1.73 (*dd*, $J = 11.9$, 6.8, 1 H); 1.74 (*dm*, $J = 1.3$, 0.9, 3 H); 2.10 (*dddm*, $J = 14.5$, 10.4, 7.7, 0.9, 1 H); 2.32 (*ddd*, $J = 14.5$, 7.2, 4.4, 1 H); 6.47 (*ddq*, $J = 7.7$, 7.2, 1.3, 1 H); 9.38 (*s*, 1 H). ^{13}C-NMR: 9.20 (*q*); 13.88 (*t*); 17.31 (*q*); 19.81 (*q*); 22.38 (*d*); 22.90 (*q*); 29.76 (*t*); 31.20 (*s*); 32.40 (*t*); 41.48 (*s*); 44.11 (*d*); 139.11 (*s*); 154.83 (*d*); 195.33 (*d*). MS: 206 (1, M^+), 191 (23), 173 (12), 163 (10), 148 (7), 135 (21), 123 (59), 121 (44), 107 (55), 95 (53), 81 (100), 67 (39), 55 (52), 41 (68), 29 (19). Odor: woody, fatty, sandalwood.

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