14. Preparation and Absolute Configuration of Some *Iris* Essential Oil Constituents of the 5-Methylsafranic-Acid Series[1])

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The β-dienoate (+)-(5*S*)-**13a** (86% ee; meaning of α and β as in α- and β-irone, resp.) was obtained from (−)-(5*S*)-**9a** *via* acid-catalyzed dehydration of the diastereoisomer mixture of allylic tertiary alcohols (+)-(1*S*,5*S*)-**15**/(+)-(1*R*,5*S*)-**15** (*Scheme 3*). Prolonged treatment gave clean isomerization *via* a [1,5]-H shift to the α-isomer (−)-(*R*)-**16a** with only slight racemization (76% ee; *Scheme 4*). In contrast, the $SnCl_4$-catalyzed stereospecific cyclization of (+)-(*Z*)-**6** to (+)-*trans*-**8a** (*Scheme 2*), followed by a diastereoselective epoxidation to (+)-**11** gave, *via* acid-catalyzed dehydration of the intermediate allylic secondary alcohol (−)-**12**, the same ester (+)-**13a** (*Scheme 3*), but with poor optical purity (13% ee), due to an initial rapid [1,2]-H shift. The absolute configuration of (−)-**16a–c** was confirmed by chemical correlation with (−)-*trans*-**19** (*Scheme 4*). ^{13}C-NMR Assignments and absolute configurations of the intermediate esters, acids, aldehydes, and alcohols are presented.

Introduction. – Mainly motivated by the precious orris, violet-like olfactive properties of irones, associated with its very high cost[2]), analysis of the highly prized *Iris* essential oil, coupled with important synthetic efforts, has attracted considerable attention during the past 50 years (see ref. cit. in [1]).

In 1981, a new carboxylic acid of molecular formula $C_{11}H_{16}O_2$ was isolated in trace amounts by *Garnero* and *Joulain* [2]. Among eleven possible 2,5,6,6-tetrasubstituted cyclohexadienecarboxylic-acid isomers, the hypothetical structure **13b** was assigned on the basis of a single MS analysis[3]) of its methyl ester **13a**, with respect to its similarity with methyl β-safranate. In a more recent analysis, *Maurer* and coworkers isolated the parent aldehyde **13c**, assigned on the basis of its MS and ^{1}H-NMR analysis; its attempted synthesis from **16c** unfortunately failed[4]) [5].

Goaded by our interest in this field [6], we resolved to prepare optically active **13a–c** starting from readily available chirons.

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[1]) Presented in part at the XVth Conference on Isoprenoids, 20–25 September 1993, Zakopane, Poland.

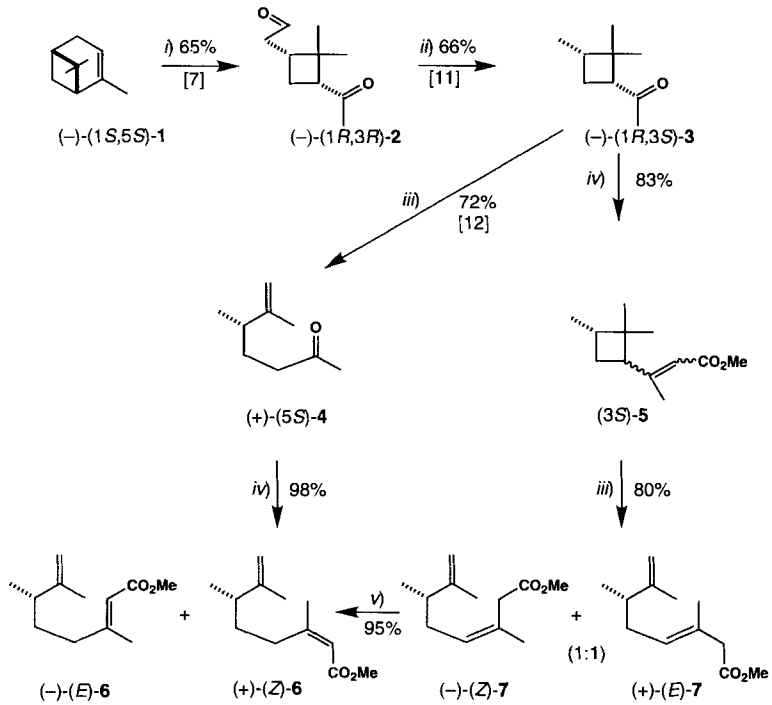
[2]) *Ca.* 18000 US$/kg of absolute oil.

[3]) We are indebted to Prof. *J. Garnero* and *D. Joulain* for a copy of this analysis.

[4]) This is an energetically unfavorable (uphill) transformation. Indeed, **13c** is totally converted into **16c** under basic conditions (MeONa, MeOH, 0.1 mol-equiv., 25°; 90%). For a comparison of the thermodynamic stability of **13c** and **16c**, calculated by semi-empirical method PM3 (negative values in kcal/mol ±2.0, MOPAC 6.0 QCPE), see [3], and for stereoisomer comparison, based on MM2 calculations (positive values in KJ/mol, MACROMODEL 4.0), see [4]. Thus, *trans*-**8a**: 103.4, −103.5; *cis*-**8a**: 107.6, −102.9; **9a**: −107.2; *trans*-**8b**: 44.0, −111.6; *cis*-**8b**: 48.0, −111.0; **9b**: −115.1; *trans*-**10a**: 98.8, −73.9; *cis*-**10a**: 103.8, −69.8; *trans*-**10b**: 38.9, −82.0; *cis*-**10b**: 44.9, −80.7; **13a**: −80.3; **13b**: −88.2; **13c**: −31.5; **16a**: −82.2; **16b**: −90.8; **16c**: −36.0.

Results and Discussion. – The preliminary research, initiated immediately after the publication of the two French authors, was based on the reported decarbonylation of pinonal ((−)-**2** [7][5])), using *Wilkinson* catalyst [11]. The resulting ketone (−)-**3** was thermolyzed (320°, sealed tube; 72% [12]) according to *Conia* to afford the known key intermediate (+)-**4**[6]) of the same optical purity (76% ee[7]) as the starting (−)-α-pinene ((−)-**1**; *Scheme 1*).

Scheme 1



i) 1) O_3, CH_2Cl_2, AcOH; 2) Me_2S, N_2. *ii*) [$Rh(PPh_3)_3Cl$], toluene, 110°. *iii*) Sealed tube, 320°. *iv*) $(MeO)_2P(O)CH_2CO_2Me$, MeONa, MeOH, cyclohexane; (*E*)/(*Z*) 7:3. *v*) *t*-BuOK, *t*-BuOH; (*E*)/(*Z*) 4:1.

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[5]) For an alternative access *via* ozonolysis of (+)-2- or (+)-3-carene [8], followed by decarbonylation ([$Rh(PPh_3)_3Cl$], toluene, 110°; 92%), see [9]. For a hydrogenolytic decarbonylation of (−)-**2** (*Raney*-Ni *W4*, H_2, 180 atm, 240°, 5 h; 70%) followed by reoxidation to (−)-**3**, see [10].

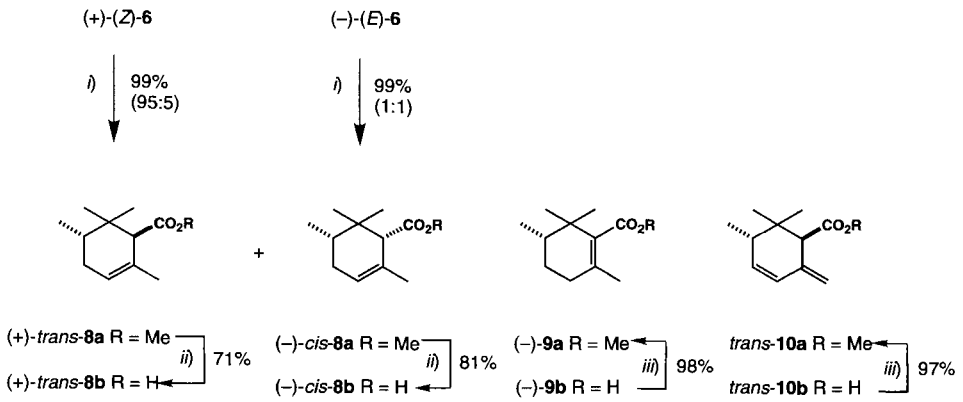
[6]) $[\alpha]_D^{20} = +3.73$, $[\alpha]_{365}^{20} = -5.86$ (*c* = 1.5 cyclohexane); [12]: $[\alpha]_D^{20} = +2.37$, $[\alpha]_{365}^{20} = -5.55$ (cyclohexane). We are indebted to Prof. *J. Goré* for confirming both a printing error in [12] and the (5*S*) absolute configuration of (+)-**4** which follows logically from the starting material used [7b–f]. Alternatively, (+)-**4** was obtained by ozonolysis of (+)-limonene [13] followed by decarbonylation ([$Rh(PPh_3)_3Cl$], toluene, 110°; 20% yield). The use of 5% Pd/C (180° neat, 6% by weight; 78%) gave essentially 5,6-dimethylhept-5-en-2-one, while 5% Rh/Al_2O_3 (180° neat, 6% by weight; 30%) afforded mainly (+)-(*S*)-1-(4-isopropenylcyclopent-1-enyl)ethan-1-one [14]. For a stereoselective synthesis of eremophilane and valencane starting from **4**, see [15].

[7]) Retention times t_R in min on a permethylated β-cyclodextrin capillary column (9 m, 0.25 mm, 80–110°, 3.8 psi) [16]: (−)-α-pinene ((−)-**1**), 6.8; (+)-α-pinene ((+)-**1**), 7.7; (+)-**4**, 19.7; (−)-**4**, 21.1; (−)-**18**, 28.1; (+)-**18**, 28.5; (+)-*trans*-**19**, 29.0; (−)-*trans*-**19**, 29.4; (−)-*cis*-**19**, 33.1; (+)-*cis*-**19**, 34.1; (−)-(1*S*,3*R*,6*R*)-**20**, 30.4; (+)-(1*R*,3*S*,6*S*)-**20**, 30.8; (+)-(1*S*,3*S*,6*S*)-**20**, 31.8; (−)-(1*R*,3*R*,6*R*)-**20**, 33.7; (−)-(1*S*,3*S*,6*R*)-**20**, 32.7; (+)-(1*R*,3*R*,6*S*)-**20**, 33.0; (−)-(1*R*,3*S*,6*R*)-**20**, 38.2; (+)-(1*S*,3*R*,6*S*)-**20**, 40.0.

Subsequent *Horner-Wittig* condensation ($(MeO)_2P(O)CH_2CO_2Me$, MeONa, MeOH, cyclohexane; 98%) gave methyl esters (−)-(*E*)-**6**/(+)-(*Z*)-**6** in a 7:3 ratio which were separated by prep. GC (for racemate, see [17]). Alternatively, the condensation was conducted directly on (−)-**3** to give (3*S*)-**5** (83%) as an inseparable (*E*)/(*Z*)- and/or *cis*/*trans*-mixture (2:5:3). Thermolysis of the latter afforded a 1:1 mixture (−)-(*Z*)-**7**/(+)-(*E*)-**7** in 80% yield which was either separated by prep. GC for analysis or transformed (*t*-BuOK, *t*-BuOH; 95%) to a 4:1 mixture (−)-(*E*)-**6**/(+)-(*Z*)-**6**.

When (+)-(*Z*)-**6** was cyclized with a *Lewis* acid [18] ($SnCl_4$, 0.4 mol-equiv., toluene, 12 h, 0–25°), the thermodynamically more stable[4]) methyl ester (+)-*trans*-**8a** was obtained quantitatively and practically as a single diastereoisomer ($\geq$ 95%), but unfortunately with a high degree of racemization[8]). In contrast, under the same conditions, (−)-(*E*)-**6** gave quantitatively a GC-separable 1:1 mixture (+)-*trans*-**8a**/(−)-*cis*-**8a**, due to thermodynamic equilibration of the preformed less stable *cis*-diastereoisomer[4])[8])[9]) (*Scheme 2*).

Scheme 2



i) $SnCl_4$, toluene, 0°. *ii*) PhSH, KOH, DMF, 100°. *iii*) CH_2N_2, Et_2O.

This racemization may be explained by a rapid [1,2]-H shift between the C(6) and C(7) carbocationic centers, a reaction which has often been applied for the synthesis of irones [20][11]). The corresponding α-acids (meaning of α and β as in α- and β-irone, resp.), (+)-*trans*-**8b** and (−)-*cis*-**8b**, were selectively obtained by C(alkyl)–O bond cleavage (PhSH, KOH, DMF, 100°; 71 and 81% yield, resp. [22]) of their methyl esters (for racemic **8** and **9**, see [17a] [23]). To introduce the β-isomeric cyclic system, methyl ester (−)-*cis*-**8a** was epoxidized stereoselectively on its less hindered face to give

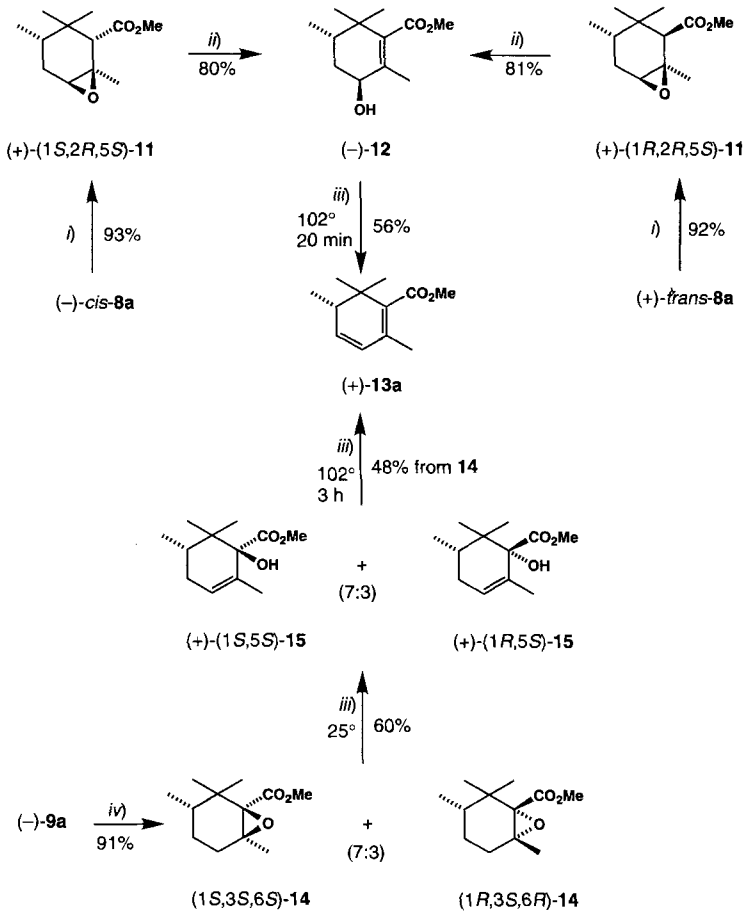
[8]) After reduction to the corresponding alcohols (+)-*trans*-**19** and (+)-*cis*-**19** [1], 13% ee[7]).

[9]) Under the cyclization conditions, a 7:3 mixture was obtained after 70 h, and a 3:1 mixture reached after 170 h. A slower cyclization rate than (*E*/*Z*)-isomerization or a worse stereoselectivity due to the sterically less congested (*E*) transition state are not excluded. Cyclization of (−)-(*E*)-**6**/(+)-(*Z*)-**6** 4:1 gave (+)-*trans*-**8a**/(−)-*cis*-**8a** 3:2, while *Brønsted* acidic conditions [19] (*Filtrol*® *G24*[10]), 50% by weight, toluene, 110°, 4 h; 68%) gave (+)-*trans*-**8a**/(−)-*cis*-**8a**/(−)-**9a** 55:30:15 in $\leq$ 10% ee[7]).

[10]) *Filtrol*® is a registered trade name for a H_2SO_4 acid supported on seasand rich in diatomea.

[11]) For 6-membered-ring acidic cyclizations and mechanistic discussions, see [21] and refs. cit. therein.

Scheme 3



i) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°. *ii*) MeONa, MeOH, 65°. *iii*) *Filtrol*®, dioxan. *iv*) Maleic anhydride, 70% aq. H_2O_2, CH_2Cl_2.

(+)-(1*S*,2*R*,5*S*)-**11** (3-$ClC_6H_4CO_3H$, CH_2Cl_2, 0°; 93%) which was opened (MeONa, MeOH, 65°; 80% [24]) to allylic alcohol (−)-**12** (*Scheme 3*). Alternatively, (−)-**12** was also obtained by diastereoselective epoxidation (92% yield[12]) of (+)-*trans*-**8a**, followed by basic treatment (81%). Finally, acidic dehydration (*Filtrol*®[10]), dioxan, 102°, 20 min; 56%) gave the desired β-ester (+)-**13a** without apparent loss of optical purity (by ^{1}H-NMR analysis[13])).

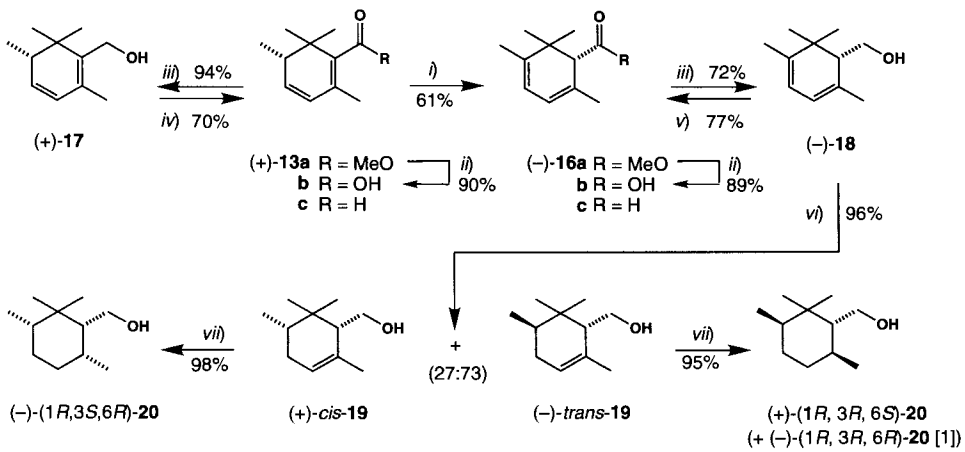
The poor chiral efficiency of this approach prompted us to change our strategy. The recently reported β-acid (−)-**9b** (86% ee [1]) was thus quantitatively esterified (CH_2N_2, Et_2O) to (−)-**9a**. Epoxidation (maleic anhydride, 70% aq. H_2O_2, CH_2Cl_2, 25°; 91%) gave

[12]) By capillary GC and ^{1}H-NMR analysis, de > 95%. For similar stereoselectivity, see [18a] [25]. For a recent rationalization, see [26].

[13]) In the presence of tris{3-[(heptafluoropropyl)hydroxymethylidene]-(+)-camphorato}europium(III).

an inseparable 7:3 mixture of diastereoisomers (1*S*,3*S*,6*S*)- and (1*R*,3*S*,6*R*)-**14**[14]) (*Scheme 3*). Treatment with *Filtrol*® (25°, 60%) afforded the corresponding tertiary allylic alcohol mixture (+)-(1*S*,5*S*)-**15**/(+)-(1*R*,5*S*)-**15**, from which the major diastereoisomer was isolated by chromatography. Treatment of **14** or **15** using more drastic conditions (*Filtrol*®, dioxan, 102°; 3 h; 48% [27]) gave the desired ester (+)-**13a** (86% ee; by ^{1}H-NMR[13])), readily separated by chromatography from the unreacted (+)-(1*R*,5*S*)-**15**, which is less prone to elimination due to its pseudoequatorial OH group[15]). The ester (+)-**13a** was smoothly saponified (PhSH, KOH, DMF, 100°; 90%) to the target carboxylic acid (+)-**13b**, without isomerization[16]), and also reduced ($LiAlH_4$, Et_2O, 0°; 94%) to allylic alcohol (+)-**17** (*cf. Scheme 4*) before reoxidation (MnO_2, CH_2Cl_2; 70%) to the naturally occurring aldehyde (+)-**13c**.

Scheme 4



i) *Filtrol*®, dioxan, 102°, 144 h. *ii*) PhSH, KOH, DMF, 100°. *iii*) $LiAlH_4$, Et_2O. *iv*) MnO_2, CH_2Cl_2. *v*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. *vi*) *Raney*-Ni, H_2, EtOH. *vii*) PtO_2, H_2, AcOH.

Prolonged treatment of the β-esters (+)-**13a**, (3*S*)-**14**, or (+)-**15** (*Filtrol*®, dioxan, 102°, 144 h; 61%) resulted in elimination of residual alcohol (+)-(1*R*,5*S*)-**15** and displaced the dienic system to the α-position. We were gratified to find that a minimum of racemization had occurred during this isomerization to (−)-**16a** (76% ee[13])).

The same sequence was also applied to (−)-**16a** (PhSH, KOH, DMF, 100°; 89%) to obtain the isomerically pure α-acid (−)-**16b** and alcohol (−)-**18** ($LiAlH_4$, Et_2O, 0°; 72%) which was subsequently reoxidized to aldehyde (−)-**16c** ($(COCl)_2$, DMSO, Et_3N, CH_2Cl_2;

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[14]) A 3:1 mixture was obtained using 3-$ClC_6H_4CO_3H$ in CH_2Cl_2.

[15]) The allylic rearrangement product **12**, as putative intermediate, was also detected (1%) by GC analysis.

[16]) We thank Dr. *C. Fehr* and *J. Galindo* for communicating us their conditions prior to publication [22]. More drastic conditions (KOH, H_2O, DMSO, 100°; 73%) gave a 65:13:4:18 mixture **16b**(α)/**13b**(β)/*cis*-**10b**(γ)/*trans*-**10b**(γ) which was purified by prep. GC. The *trans*-**10b** or -**10a** (CH_2N_2, Et_2O; 97%; *Scheme 2*) was still contaminated by 8% of its *cis*-isomer, which precludes a strict assignment of the chiroptical properties; furthermore, **16b** was substantially racemized (17% ee[7])).

77%; for racemate, see [5]). To determine the absolute configuration of (−)-**16a–c** and (−)-**18**, the latter was hydrogenated (H_2, EtOH; 96%) in the presence of deactivated *Raney*-Ni to give a 27:73 mixture of the known alcohols (+)-*cis*- and (−)-*trans*-**19** [1] (76% ee[7])), separable by chromatography. The hydrogenation is presumably directed by the complexation of the OH group with the catalyst [28]. The (1*R*)-configuration of (−)-**16a–c** and (−)-**18** which follows from this chemical correlation implies either a stereospecific [1,5]-H shift [29] or a stereoselective protonation on the less hindered face by the *Filtrol*®-supported acid during the isomerization of (+)-**13a** (β) to (−)-**16a** (α). Finally, pure (+)-*cis*-**19** was stereoselectively perhydrogenated (PtO_2, AcOH, H_2; 98%) to the all-*cis*-alcohol (−)-(1*R*,3*S*,6*R*)-**20**, while pure (−)-*trans*-**19** gave, under the same conditions, a 2:1 mixture (95%) of (−)-(1*R*,3*R*,6*R*)-**20** [1] and (+)-(1*R*,3*R*,6*S*)-**20** which were chromatographically separable.

In conclusion, the MS analysis of (+)-**13a** was fully superimposable with that of *Garnero* and *Joulain* [2], in contrast to those of *cis*-**10a**[17]), *trans*-**10a**, and (−)-**16a**, thus confirming the initial hypothesis of these authors. The homochiral 5-methyl-damascenone[18]) and didehydroirone analogues derived from **13** and **16** will be reported in due course.

We are indebted to Dr. *J. Y. de Saint Laumer* for MM2 and PM3 calculations, Drs. *P.-A. Blanc* and *D. Kastner* for olfactive evaluations, Mr. *W. Thommen* and *R. Brauchli* for NMR analysis, as well as Mrs. *B. Baer*, Mrs. *C. Noizat-Cantatore*, Mr. *M. Barthe*, Mr. *B. L. Muller*, and Mr. *H. Pamingle* for their experimental skill.

Experimental Part

General. See [30]. Prep. GC: *Aerograph* autoprep. model *A-700*, *Carbowax 20M* 15% (3 m, 5 mm), 120° isotherm; t_R in min. CC = column chromatography.

(3'S)-Methyl 3-(2',2',3'-Trimethylcyclobutyl)but-2-enoate (3*S*-**5**). Ketone (−)-**3** (39 g, 278 mmol), methyl (dimethoxyphosphoryl)acetate (56 g, 309 mmol), and MeONa (50 g, 926 mmol) in petroleum ether (110 ml) were refluxed (80°) for 1 h. H_2O (15 ml) was cautiously added, the mixture extracted with Et_2O (3 × 100 ml), and the extract washed to neutral with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated: 44.7 g of an oil. Distillation (15-cm *Vigreux* column) gave (−)-**3** (29%) and (3*S*)-**5** (59%) as a 2:5:3 mixture (GC). B.p. 45°/0.06 Torr. α_D^{20} (neat) = +4.8° (2:5:3 mixture). IR: 2980, 1720, 1640, 1220, 1150. ^{1}H-NMR: 0.78–1.35 (3*s*, 9 H); 2.15 (br. *s*, 3 H); 3.70 (*s*, 3 H); 5.5 (br. *s*, 1 H). MS: 196 (1, M^+), 179 (1), 164 (2), 139 (10), 127 (58), 111 (5), 95 (32), 79 (5), 70 (100), 55 (40), 41 (22).

(−)-Methyl (6S,2E)-3,6,7-Trimethylocta-2,7-dienoate ((−)-(*E*)-**6**). MeONa (54 g, 30% in MeOH, 300 mmol) was added slowly under N_2 and vigorous stirring to a soln. of (+)-**4** (42 g, 300 mmol) and methyl (dimethoxyphosphoryl)acetate (60 g, 330 mmol) during 1.5 h. After 1.5 h at reflux, the reaction was quenched with H_2O (40 ml), the mixture extracted with Et_2O, and the extract washed to neutral, dried ($MgSO_4$), and evaporated. Distillation through a *Vigreux* column gave (−)-(*E*)-**6**/(+)-(*Z*)-**6** 7:3 (71%). A quant. yield was obtained with 2 mol-equiv. of base and methyl (dimethylphosphoryl)acetate. Prep. GC (*DB Wax*, 100–140°) gave (−)-(*E*)-**6**: t_R 7.48. B.p. 42°/0.05 Torr. $[\alpha]_D^{20} = -4.4$ (*c* = 1.6, CCl_4). IR: 3080, 1720, 1650, 1640, 895. ^{1}H-NMR: 1.02 (*d*, *J* = 7, 3 H); 1.45 (*m*, 1 H); 1.52 (*m*, 1 H); 1.64 (*s*, 3 H); 2.06 (*t*, *J* = 7, 2 H); 2.14 (*m*, 1 H); 2.16 (*d*, *J* = 2, 3 H); 3.68 (*s*, 3 H); 4.69 (*s*, 1 H); 4.73 (*m*, 1 H); 5.67 (*s*, 1 H). ^{13}C-NMR: 18.9 (*Me*–C(3)); 18.9 (*Me*–C(7)); 19.7 (*Me*–C(6)); 32.7 (C(4)); 38.9 (C(5)); 40.8 (C(6)); 50.8 (MeO); 110.1 (C(8)); 115.1 (C(2)); 149.2 (C(7)); 160.6 (C(3)); 167.3 (C(1)). MS: 196 (4, M^+), 181 (7), 164 (3), 149 (10), 139 (33), 122 (80), 95 (80), 83 (80), 70 (100), 55 (95), 41 (98). Petitgrain.

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[17]) MS: 194 (17, M^+), 179 (15), 163 (11), 135 (100), 119 (59), 105 (40), 91 (28), 77 (20), 73 (15), 59 (31).

[18]) The β-damascenone analogue derived from **13** has a typical cork, β-damascone scent [27]. The following olfactive properties were also found for the damascone analogues derived from *trans*-**8a**: floral, α-damascone-like, weakly cork; *cis*-**8a**: α-damascone-like with cork character; **9a**: β-damascone-like character [17a].

(+)-Methyl (6S,2Z)-3,6,7-Trimethylocta-2,7-dienoate ((+)-(*Z*)-**6**). At 25° (−)-(*Z*)-**7**/(+)-(*E*)-**7** 1:1 (1.5 g, 7.65 mmol) in *t*-BuOH (15 ml) was treated with *t*-BuOK (900 mg, 8 mmol) for 1 h. H_2O was added, the mixture extracted with Et_2O, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue bulb-to-bulb distilled: (−)-(*E*)-**6**/(+)-(*Z*)-**6** 4:1 (95%). Prep. GC separation (*DB Wax*, 100–140°) gave (+)-(*Z*)-**6**: t_R 6.45. B.p. 41°/0.05 Torr. $[\alpha]_D^{20} = +1.65$ (*c* = 1.8, CCl_4). IR: 3080, 1715, 1660, 1645, 895. ^{1}H-NMR: 1.05 (*d*, *J* = 7, 3 H); 1.42 (*m*, 1 H); 1.52 (*m*, 1 H); 1.69 (*s*, 3 H); 1.88 (*d*, *J* = 2, 3 H); 2.18 (*sext.*, *J* = 7, 1 H); 2.48 (*m*, 1 H); 2.55 (*m*, 1 H); 3.68 (*s*, 3 H); 4.70 (*d*, *J* = 2, 2 H); 5.62 (*s*, 1 H). ^{13}C-NMR: 18.9 (*Me*−C(7)); 19.6 (*Me*−C(6)); 25.2 (*Me*−C(3)); 31.8 (C(4)); 33.3 (C(5)); 41.6 (C(6)); 50.8 (MeO); 109.7 (C(8)); 115.5 (C(2)); 149.7 (C(7)); 161.1 (C(3)); 166.7 (C(1)). MS: 196 (1, M^+), 181 (2), 164 (2), 149 (3), 139 (22), 122 (70), 114 (85), 95 (80), 83 (100), 70 (60), 55 (70), 41 (85). Petitgrain, lemon, citral.

(+)-Methyl (6S,3E)-3,6,7-Trimethylocta-3,7-dienoate ((+)-(*E*)-**7**). Prep. GC (*DB Wax*, 100–140°) of (−)-(*Z*)-**7**/(+)-(*E*)-**7** (see below) gave (+)-(*E*)-**7**: t_R 6.52. $\alpha_D^{20} = +1.64$. IR: 3080, 1735, 1640, 895. ^{1}H-NMR: 1.0 (*d*, *J* = 6, 3 H); 1.68 (*s*, 6 H); 2.00–2.22 (*m*, 2 H); 3.00 (*s*, 2 H); 3.65 (*s*, 3 H); 4.70 (*m*, 2 H); 5.24 (*t*, *J* = 6, 1 H). ^{13}C-NMR: 16.4 (*Me*−C(3)); 19.1 (*Me*−C(6)); 19.7 (*Me*−C(7)); 33.6 (C(5)); 41.1 (C(6)); 44.9 (C(2)); 51.7 (MeO); 109.3 (C(8)); 128.1 (C(4)); 128.8 (C(3)); 149.9 (C(7)); 172.6 (C(1)). MS: 196 (1, M^+), 181 (1), 164 (3), 137 (7), 122 (75), 107 (15), 95 (95), 85 (100), 69 (60), 59 (30), 41 (95). Earthy, pungent.

(−)-Methyl (6S,3Z)-3,6,7-Trimethylocta-3,7-dienoate ((−)-(*Z*)-**7**). Under N_2, (3*S*)-**5** (2 g, 10.2 mmol) was heated at 300° for 1 h in a sealed glass tube under N_2. Bulb-to-bulb distillation gave (−)-(*Z*)-**7**/(+)-(*E*)-**7** 1:1 (80%). Prep. GC (*DB Wax*, 100–140°) yielded (−)-(*Z*)-**7**: t_R 5.88. B.p. 40°/0.05 Torr. $[\alpha]_D^{20} = -0.5$ (*c* = 0.6, CCl_4). IR: 3080, 1740, 1640, 890. ^{1}H-NMR: 1.0 (*d*, *J* = 6, 3 H); 1.68 (*s*, 3 H); 1.78 (*d*, *J* = 2, 3 H); 1.95–2.2 (*m*, 3 H); 3.05 (*s*, 2 H); 3.65 (*s*, 3 H); 4.68 (*m*, 2 H); 5.28 (*t*, *J* = 6, 1 H). ^{13}C-NMR: 19.2 (*Me*−C(6)); 19.7 (*Me*−C(7)); 24.0 (*Me*−C(3)); 33.6 (C(5)); 37.5 (C(2)); 41.1 (C(6)); 51.8 (MeO); 109.4 (C(8)); 127.7 (C(4)); 128.5 (C(3)); 149.8 (C(7)); 172.0 (C(1)). MS: 196 (2, M^+), 181 (2), 165 (3), 135 (8), 122 (70), 107 (19), 95 (90), 85 (100), 69 (58), 59 (32), 41 (80). Earthy, pungent.

(+)-Methyl (1S,5S)-2,5,6,6-Tetramethylcyclohex-2-ene-1-carboxylate ((+)-*trans*-**8a**). As described for (−)-*cis*-**8a**, (+)-(*Z*)-**6** (31 mg, 0.158 mmol) was cyclized in toluene: (−)-*cis*-**8a**/(+)-*trans*-**8a** 5:95 (quant.). Prep. GC (*DB Wax*, 100–140°) gave (+)-*trans*-**8a**: t_R 4.78. B.p. 87°/5.6 Torr. $[\alpha]_D^{20} = +20.6$ (*c* = 1.95, $CHCl_3$). IR: 2960, 1730, 1460, 1425, 1320, 1240, 1200, 1140, 1015, 800. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.83 (*d*, *J* = 7, 3 H); 0.93 (*s*, 3 H); 1.62 (*s*, 3 H); 1.65 (*m*, 1 H); 2.08 (*m*, 2 H); 2.59 (*s*, 1 H); 3.67 (*s*, 3 H); 5.55 (br. *s*, 1 H). ^{13}C-NMR: 15.0 (*Me*−C(5)); 20.9 (*Me*−C(6), *cis* to Me); 22.8 (*Me*−C(2)); 25.5 (*Me*−C(6), *trans* to Me); 31.2 (C(5)); 32.0 (C(4)); 34.7 (C(6)); 51.4 (MeO); 59.1 (C(1)); 124.4 (C(3)); 129.7 (C(2)); 174.5 (C=O). MS: 196 (39, M^+), 164 (33), 137 (63), 127 (73), 121 (92), 95 (70), 83 (40), 70 (100), 55 (49), 41 (43). Chemical.

(−)-Methyl (1R,5S)-2,5,6,6-Tetramethylcyclohex-2-ene-1-carboxylate ((−)-*cis*-**8a**). At 0° (−)-(*E*)-**6** (31 mg, 0.158 mmol) in toluene (0.31 ml) was slowly added under N_2 to a soln. of $SnCl_4$ (7.5 µl, 0.063 mmol) in toluene (0.31 ml). After 30 min, the mixture was equilibrated at 25° for 12 h and then quenched with sat. aq. $NaHCO_3$ soln. The mixture was extracted with Et_2O and the extract washed with H_2O to neutral, dried ($MgSO_4$), and evaporated: (−)-*cis*-**8a**/(+)-*trans*-**8a** 1:1 (quant.). Prep. GC (*DB Wax*, 100–140°) gave (−)-*cis*-**8a**: t_R 5.89. B.p. 89°/6 Torr. $\alpha_D^{20} = -1.5$. IR: 2970, 1730, 1440, 1330, 1260, 1200, 1160, 1020, 915, 800. ^{1}H-NMR: 0.79 (*s*, 3 H); 0.87 (*d*, *J* = 7, 3 H); 1.01 (*s*, 3 H); 1.47 (*m*, 1 H); 1.62 (*m*, 3 H); 1.78 (*m*, 1 H); 1.91 (*m*, 1 H); 2.93 (*m*, 1 H); 3.68 (*s*, 3 H); 5.50 (*m*, 1 H). ^{13}C-NMR: 15.2 (*Me*−C(5)); 15.5 (*Me*−C(6), *cis* to *Me*); 21.6 (*Me*−C(2)); 26.8 (*Me*−C(6), *trans* to Me); 31.8 (C(4)); 35.2 (C(6)); 38.2 (C(5)); 51.1 (MeO); 59.0 (C(1)); 124.0 (C(3)); 130.1 (C(2)); 173.8 (C=O). MS: 196 (17, M^+), 136 (30), 127 (70), 121 (35), 95 (40), 70 (100), 67 (28), 55 (40), 41 (38). Cork, camphor.

Reduction of (−)-*cis*-**8a**/(+)-*trans*-**8a** 1:1 with $LiAlH_4$ gave (+)-*cis*-**19**/(+)-*trans*-**19** 1:1 (quant.; 13% ee[7]).

(−)-(1R,5S)-2,5,6,6-Tetramethylcyclohex-2-ene-1-carboxylic Acid ((−)-*cis*-**8b**). As described for (+)-*trans*-**8b**, (−)-*cis*-**8a** (13 mg, 0.066 mmol) was saponified and (−)-*cis*-**8b** (81%) purified. $[\alpha]_D^{20} = -1.15$ (*c* = 1.75, $CHCl_3$). IR: 3200, 2980, 1700, 1450, 1410, 1370, 1300, 1215. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.89 (*d*, *J* = 7, 3 H); 1.08 (*s*, 3 H); 1.49 (*m*, 1 H); 1.69 (*d*, *J* = 2, 3 H); 1.70–1.96 (*m*, 2 H); 2.94 (br. *s*, 1 H); 5.54 (*m*, 1 H); 11.5 (br. *s*, 1 H). ^{13}C-NMR: 15.1 (*Me*−C(5)); 15.4 (*Me*−C(6), *cis* to Me); 21.6 (*Me*−C(2)); 27.0 (*Me*−C(6), *trans* to Me); 31.7 (C(4)); 35.1 (C(6)); 38.1 (C(5)); 58.7 (C(1)); 124.4 (C(3)); 129.4 (C(2)); 179.8 (CO_2H). MS: 182 (22, M^+), 137 (6), 121 (11), 113 (30), 70 (100), 55 (18).

(+)-(1S,5S)-2,5,6,6-Tetramethylcyclohex-2-ene-1-carboxylic Acid ((+)-*trans*-**8b**). KOH (3.3 mg, 0.06 mmol) was added to a soln. of PhSH (6.5 µl, 0.063 mmol) and (+)-*trans*-**8a** (13 mg, 0.066 mmol) in DMF (0.15 ml) and heated at 100° for 18 h. The mixture was diluted with Et_2O, then extracted with 15% aq. NaOH soln. Et_2O was added to the aq. phase, and conc. HCl was added at 0°. After several extraction with Et_2O, the org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (SiO_2, toluene/AcOEt 95:5→5:95): pure (+)-*trans*-**8b** (71%). M.p. 73–74°. $[\alpha]_D^{20} = +14.2$ (*c* = 1.5, $CHCl_3$). IR: 3200, 2960, 1705, 1460, 1415, 1300, 1220. ^{1}H-NMR: 0.83

(*s*, 3 H); 0.85 (*d*, *J* = 7, 3 H); 1.02 (*s*, 3 H); 1.68 (*m*, 1 H); 1.70 (*s*, 3 H); 2.08 (*m*, 2 H); 2.59 (*s*, 1 H); 5.58 (br. *s*, 1 H); 12.5 (br. *s*, 1 H). ^{13}C-NMR: 15.0 (*Me*–C(5)); 20.9 (*Me*–C(6), *cis* to Me); 22.8 (*Me*–C(2)); 25.5 (*Me*–C(6), *trans* to Me); 31.1 (C(5)); 32.0 (C(4)); 34.6 (C(6)); 58.9 (C(1)); 124.8 (C(3)); 129.4 (C(2)); 180.3 (CO_2H). MS: 182 (6, M^+), 137 (5), 121 (10), 113 (15), 95 (12), 82 (18), 70 (100), 67 (11), 55 (21). Slightly woody, weak.

(–)-Methyl (5S)-2,5,6,6-Tetramethylcyclohex-1-ene-1-carboxylate ((–)-**9a**). For 10 min, (–)-**9b** (820 mg, 4.5 mmol) was esterified with an excess of CH_2N_2 in Et_2O. AcOH was finally added, and the soln. was washed with 15% aq. NaOH soln. and H_2O, dried (Na_2SO_4), evaporated, and bulb-to-bulb distilled: (–)-**9a** (98%). Heating (–)-**9b** (5.05 g, 28 mmol) and $CH(OMe)_3$ (12.6 ml, 115 mmol) in an autoclave at 190°/10 bar for 4 h also gave (–)-**9a** (80%). B.p. 100°/0.24 Torr. $[\alpha]_D^{20} = -59.0$ (*c* = 1.4, $CHCl_3$). IR: 2970, 1725, 1430, 1365, 1280, 1225, 1095, 1030. ^{1}H-NMR: 0.90 (*d*, *J* = 7, 3 H); 1.00 (*s*, 3 H); 1.04 (*s*, 3 H); 1.46 (*m*, 2 H); 1.60 (*m*, 1 H); 1.64 (*s*, 3 H); 2.00 (*m*, 2 H); 3.75 (*s*, 3 H). ^{13}C-NMR: 15.8 (*Me*–C(5)); 21.3 (*Me*–C(2)); 21.8 (*Me*–C(6), *cis* to Me); 26.7 (C(4)); 27.1 (*Me*–C(6), *trans* to Me); 30.4 (C(3)); 36.0 (C(6)); 38.3 (C(5)); 50.9 (MeO); 133.3 (C(1)); 135.9 (C(2)); 171.4 (C=O). MS: 196 (18, M^+), 181 (34), 165 (21), 149 (100), 137 (42), 121 (55), 107 (37), 95 (48), 79 (38), 67 (20), 55 (22), 41 (37). Woody, vaguely floral.

trans-*Methyl 5,6,6-Trimethyl-2-methylidenecyclohex-3-ene-1-carboxylate* (*trans*-**10a**). As described for (–)-**9a**, from *trans*-**10b** by esterification with CH_2N_2 (97% yield). GC (*DB1*, 130–180°): t_R 1.68 (*cis*-**10a**), 1.75 (*trans*-**10a**). IR: 3040, 2975, 2890, 1735, 1435, 1375, 1280, 1215, 1040. ^{1}H-NMR: 0.76 (*s*, 3 H); 0.96 (*d*, *J* = 7, 3 H); 1.01 (*s*, 3 H); 2.59 (*m*, 1 H); 3.02 (*s*, 1 H); 3.65 (*s*, 3 H); 4.94 (*s*, 1 H); 4.99 (*s*, 1 H); 5.57 (*d*, *J* = 11, 1 H); 6.10 (*dd*, *J* = 3, 11, 1 H). ^{13}C-NMR: 14.8 (*Me*–C(5)); 22.2 (*Me*–C(6), *cis* to Me); 25.5 (*Me*–C(6), *trans* to Me); 35.0 (C(6)); 51.4 (MeO); 58.0 (C(1)); 114.5 (CH_2=); 126.0 (C(3)); 135.6 (C(4)); 140.3 (C(2)); 173.0 (C=O). MS: 194 (13, M^+), 179 (11), 135 (100), 119 (43), 105 (18), 91 (22), 79 (19), 59 (12).

trans-*5,6,6-Trimethyl-2-methylidenecyclohex-3-ene-1-carboxylic Acid* (*trans*-**10b**). For 4 h, (+)-**13a** (210.2 mg, 1.08 mmol) and KOH (106.2 mg, 1.89 mmol) in DMSO (1.3 ml) and H_2O (0.2 ml) were heated at 100°. The cold mixture was diluted with 15% aq. NaOH soln. (2 ml) and extracted with Et_2O. The basic phase in presence of Et_2O was acidified with 15% HCl soln. at 0° extracted, dried (Na_2SO_4) and evaporated to give **16b**(α)/**13b**(β)/*cis*-**10b**(γ)/*trans*-**10b**(γ) 65:13:4:18 (73% yield) which was purified by prep. GC (*DB Wax*, 130–180°): t_R 6.8 (*cis*-**10b**), 7.15 (*trans*-**10b**). *trans*-**10b**: IR: 3200, 2970, 1710, 1650, 1420, 1280, 1230, 1200, 950, 900, 820. ^{1}H-NMR: (90 MHz): 0.8 (*s*, 3 H); 0.98 (*d*, *J* = 7, 3 H); 1.08 (*s*, 3 H); 2.60 (*m*, 1 H); 2.98 (br. *s*, 1 H); 5.00 (br. *s*, 2 H); 5.53 (br. *d*, *J* = 10, 1 H); 6.09 (*dd*, *J* = 3, 10, 1 H); 12.5 (br. *s*, OH). MS: 180 (33, M^+), 165 (12), 147 (5), 135 (100), 121 (82), 105 (41), 91 (38), 79 (46), 65 (13), 53 (12), 41 (30).

(+)-Methyl (1S,2R,5S)-2,3-Epoxy-2,5,6,6-tetramethylcyclohexane-1-carboxylate ((+)-(1*S*,2*R*,5*S*)-**11**). At 0°, (–)-*cis*-**8a** (1.96 g, 10 mmol) in CH_2Cl_2 (10 ml) was added to a soln. of 3-$ClC_6H_4CO_3H$ (3.34 g, 60%, 11.6 mmol) in CH_2Cl_2 (10 ml). After 3 h, the mixture was diluted with CH_2Cl_2 (30 ml), the org. phase washed with 10% aq. $NaHSO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue purified by CC (SiO_2 (150 g), cyclohexane/AcOEt 97:3→9:1): (+)-(1*S*,2*R*,5*S*)-**11** (93%). $[\alpha]_D^{20} = +3.0$ (*c* = 0.5, CCl_4). IR: 2980, 1730, 1450, 1435, 1380, 1360, 1340, 1300, 1250, 1200, 1175. ^{1}H-NMR: 0.80 (*d*, *J* = 7, 3 H); 0.82 (*s*, 3 H); 0.91 (*s*, 3 H); 1.30 (*s*, 3 H); 1.36 (*m*, 1 H); 1.59 (*m*, 1 H); 1.98 (*dd*, *J* = 5, 12, 1 H); 2.62 (*s*, 1 H); 2.97 (br. *s*, 1 H), 3.70 (*s*, 3 H). ^{13}C-NMR: 14.7 (*Me*–C(5)); 14.7 (*Me*–C(6), *cis* to Me); 22.6 (*Me*–C(2)); 25.9 (*Me*–C(6), *trans* to Me); 30.9 (C(4)); 33.8 (C(5)); 34.6 (C(6)); 51.1 (MeO); 57.2 (C(2)); 58.9 (C(1)); 59.8 (C(3)); 172.90 (C=O). MS: 212 (0, M^+), 181 (12), 143 (99), 114 (47), 83 (56), 70 (57), 59 (100), 55 (48), 43 (48). Damascone, fruity, slightly camphoraceous and wine cellar.

(+)-Methyl (1R,2R,5S)-2,3-Epoxy-2,5,6,6-tetramethylcyclohexane-1-carboxylate ((+)-(1*R*,2*R*,5*S*)-**11**). As described for (+)-(1*S*,2*R*,5*S*)-**11**, from (+)-*trans*-**8a** (92% yield). M.p. 49–50°. $[\alpha]_D^{20} = +4.7$ (*c* = 1.5, CCl_4). IR: 2980, 1730, 1450, 1435, 1380, 1360, 1340, 1300, 1250, 1200, 1175. ^{1}H-NMR: 0.79 (*d*, *J* = 7, 3 H); 0.80 (*s*, 3 H); 0.93 (*s*, 3 H); 1.42 (*s*, 3 H); 1.50 (*m*, 1 H); 2.00 (*dd*, *J* = 5, 12, 1 H); 2.21 (*m*, 1 H); 2.49 (*s*, 1 H); 3.01 (br. *s*, 1 H); 3.71 (*s*, 3 H). ^{13}C-NMR: 14.8 (*Me*–C(5)); 21.2 (*Me*–C(6), *cis* to Me); 24.9 (*Me*–C(2)); 24.9 (*Me*–C(6), *trans* to Me); 26.8 (C(5)); 30.9 (C(4)); 33.2 (C(6)); 51.2 (MeO); 55.7 (C(1)); 57.2 (C(2)); 60.1 (C(3)); 171.0 (C=O). MS: 212 (0, M^+), 143 (68), 135 (48), 129 (58), 111 (40), 97 (100), 83 (64), 70 (43), 59 (81), 55 (48), 43 (46). Damascone, fruity, camphoraceous, wine cellar.

(–)-Methyl (3S,5S)-3-Hydroxy-2,5,6,6-tetramethylcyclohex-1-ene-1-carboxylate ((–)-**12**). A soln. of (+)-(1*S*,2*R*,5*S*)- or (+)-(1*R*,2*R*,5*S*)-**11** (3.27 g, 15.4 mmol) in MeOH (50 ml) and freshly prepared MeONa (830 mg, 15.4 mmol) were refluxed for 5 h. The soln. was neutralized at 0° with 10% aq. HCl soln., concentrated, and extracted with Et_2O, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue crystallized in petroleum ether (30–50°): (–)-**12** (81%). M.p. 78–80°. $[\alpha]_D^{20} = -5.3$ (*c* = 3.1, CCl_4). IR: 3500, 2970, 1720, 1450, 1380, 1230, 1100, 1040, 940. ^{1}H-NMR: 0.93 (*d*, *J* = 7, 3 H); 0.97 (*s*, 3 H); 1.03 (*s*, 3 H); 1.70 (*m*, 3 H); 1.77 (*s*, 3 H); 1.81 (br. *s*, OH); 3.56 (*s*, 3 H); 3.92 (br. *s*, 1 H). ^{13}C-NMR: 15.7 (*Me*–C(5)); 18.7 (*Me*–C(2)); 19.9 (*Me*–C(6), *cis* to Me); 26.3 (*Me*–C(6), *trans* to Me); 33.3 (C(5)); 36.2 (C(4)); 36.7 (C(6)); 51.2 (MeO); 68.3 (C(3)); 132.6 (C(1));

139.8 (C(2)); 170.8 (C=O). MS: 212 (4, M^{+}), 197 (17), 181 (14), 165 (22), 153 (52), 142 (100), 137 (44), 110 (99), 95 (38), 83 (38), 69 (35), 55 (33), 43 (73).

(+)-Methyl (5S)-2,5,6,6-Tetramethylcyclohexa-1,3-diene-1-carboxylate ((+)-**13a**). For 3 h, (−)-**14** (2.85 g, 13 mmol) in dioxane (28 ml) was refluxed in presence of *Filtrol®* (950 mg). Then the mixture was filtered over *Celite*, the filtrate evaporated, and the residue purified from residual (+)-(1*R*,5*S*)-**15** by CC (SiO_2 (200 g), toluene): pure (+)-**13a** (48%). Alternatively, *Filtrol®* (2.5 g) and (−)-**12** (5.0 g, 23.6 mmol) in toluene (50 ml) were heated at reflux for 20 min under H_2O separation. The resulting soln. was filtered over *Celite*, the filtrate evaporated, and the residue bulb-to-bulb distilled: (+)-**13a** (56%). GC (*DB1*, 130–180°): t_R 1.67. B.p. 80°/0.95 Torr. $[\alpha]_D^{20} = +171.4$ ($c = 0.3$, CCl_4; from (−)-**14**), $[\alpha]_D^{20} = +12.1$ ($c = 0.8$, CCl_4; from (−)-**12**). IR: 2970, 1720, 1280, 1230, 1050. ^{1}H-NMR: 0.96 (*d*, $J \approx 7$, 3 H); 1.00 (*s*, 3 H); 1.12 (*s*, 3 H); 1.79 (*s*, 3 H); 2.14 (*dq*, $J = 3, 7, 1$ H); 3.77 (*s*, 3 H); 5.74 (*m*, 2 H). ^{13}C-NMR: 13.8 (*Me*−C(5)); 19.4 (*Me*−C(2)); 19.7 (*Me*−C(6), *cis* to Me); 25.6 (*Me*−C(6), *trans* to Me); 36.5 (C(6)); 40.2 (C(5)); 50.9 (MeO); 126.7 (C(3)); 130.9 (C(1) or C(2)); 133.5 (C(2) or C(1)); 135.5 (C(4)); 170.6 (C=O). MS: 194 (28, M^{+}), 179 (29), 163 (18), 147 (28), 135 (96), 119 (100), 105 (55), 91 (61), 77 (32), 59 (37), 41 (20).

rac-**13a**: weakly floral, camphor, β-damascone.

(+)-(5S)-2,5,6,6-Tetramethylcyclohexa-1,3-diene-1-carboxylic Acid ((+)-**13b**). PhSH (54 mg, 0.49 mmol) was added to a soln. of (+)-**13a** (100 mg, 0.52 mmol) in DMF (1 ml), followed by KOH (25.7 mg, 0.46 mmol), and the mixture was heated at 100° for 2 h. The cold. soln. was diluted with 15% aq. NaOH soln. and extracted with Et_2O. Et_2O and 15% aq. HCl soln. were added at 0° to the aq. phase. The org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2, toluene/AcOEt 95:5→5:95): (+)-**13b** (90%). GC (*DB Wax*, 130–180°): t_R 6.17. B.p. 150°/0.01 Torr. $[\alpha]_D^{20} = +79.3$ ($c = 1.5$, $CHCl_3$). IR: 3500, 2970, 1685, 1450, 1290, 750, 690. ^{1}H-NMR: 0.97 (*d*, $J = 7$, 3 H); 1.07 (*s*, 3 H); 1.19 (*s*, 3 H); 1.92 (*s*, 3 H); 2.13 (*m*, 1 H); 5.78 (*m*, 2 H); 8.10 (br. *s*, 1 H). ^{13}C-NMR: 13.8 (*Me*−C(5)); 19.8 (*Me*−C(6), *cis* to Me); 19.9 (*Me*−C(2)); 25.5 (*Me*−C(6), *trans* to Me); 36.6 (C(6)); 40.5 (C(5)); 126.7 (C(3)); 132.1 or 133.6 (C(1) or C(2)); 136.6 (C(4)); 175.0 (CO_2H). MS: 180 (19, M^{+}), 165 (17), 135 (58), 121 (100), 105 (81), 91 (43), 79 (36), 77 (39), 65 (18).

(+)-(5S)-2,5,6,6-Tetramethylcyclohexa-1,3-diene-1-carbaldehyde ((+)-**13c**). Under N_2, a mixture of MnO_2 (593 mg, 6.8 mmol) and (+)-**17** (59.3 mg, 0.35 mmol) in CH_2Cl_2 (1.2 ml) was stirred for 24 h and then filtered over *Celite*. The filtrate was evaporated and the residue purified by CC (SiO_2 (50 g), toluene): (+)-**13c** (70%). B.p. 65°/1 Torr. $[\alpha]_D^{20} = +168$ ($c = 0.5$, $CHCl_3$). IR: 2970, 1670, 1560, 1460, 1375, 1280, 1145. ^{1}H-NMR: 0.97 (*d*, $J = 7$, 3 H); 1.13 (*s*, 3 H); 1.20 (*s*, 3 H); 2.17 (*m*, 1 H); 2.17 (*s*, 3 H); 5.85 (*dd*, $J = 2, 9$, 1 H); 6.05 (*dd*, $J = 4, 9$, 1 H); 10.13 (*s*, 1 H). ^{13}C-NMR: 13.9 (*Me*−C(5)); 17.8 (*Me*−C(2)); 20.5 (*Me*−C(6), *cis* to Me); 25.9 (*Me*−C(6), *trans* to Me); 36.0 (C(6)); 41.6 (C(5)); 128.3 (C(3)); 137.0 (C(1)); 141.4 (C(4)); 145.9 (C(2)); 192.4 (C=O). MS: 164 (23, M^{+}), 149 (36), 135 (29), 121 (100), 105 (87), 91 (89), 79 (62), 65 (20), 51 (19), 41 (28).

Methyl (1S,3S,6S)-1,6-Epoxy-2,2,3,6-tetramethylcyclohexane-1-carboxylate ((1*S*,3*S*,6*S*)-**14**). H_2O_2 (2.3 g, 70%, 46 mmol) was added to a soln. of (−)-**9a** (3.5 g, 18 mmol) and maleic anhydride (3.0 g, 30 mmol) in CH_2Cl_2 (10 ml). After 3 h, the mixture was extracted with Et_2O, the extract washed with $NaHSO_3$ and H_2O, dried (Na_2SO_4), and evaporated, and the residue bulb-to-bulb distilled: (1*S*,3*S*,6*S*)-**14**/(1*R*,3*S*,6*R*)-**14** 7:3 (91%; inseparable mixture). B.p. 90°/0.36 Torr. $[\alpha]_D^{20} = -37.95$ ($c = 1.7$, $CHCl_3$; 7:3 mixture). IR (7:3 mixture): 2970, 1735, 1460, 1380, 1280, 1095, 1025, 900, 765. ^{1}H-NMR ((1*S*,3*S*,6*S*)-**14** in mixture): 0.79 (*d*, $J = 7$, 3 H); 1.03 (*s*, 3 H); 1.06 (*s*, 3 H); 1.22 (*s*, 3 H); 1.27 (*m*, 2 H); 1.62 (*m*, 1 H); 1.79 (*m*, 1 H); 1.89 (*m*, 1 H); 3.76 (*s*, 3 H). ^{13}C-NMR ((1*S*,3*S*,6*S*)-**14** in mixture): 15.5 (*Me*−C(3)); 18.1 (*Me*−C(2), *cis* to *Me*−C(3)); 22.6 (*Me*−C(6)); 23.9 (*Me*−C(2), *trans* to *Me*−C(3)); 25.1 (C(4)); 27.6 (C(5)); 32.8 (C(3)); 35.3 (C(2)); 51.5 (MeO); 63.4 (C(6)); 72.1 (C(1)); 170.1 (C=O). MS (7:3 mixture): 212 (3, M^{+}), 170 (21), 155 (21), 138 (20), 128 (22), 109 (23), 96 (37), 83 (53), 73 (100), 69 (73), 55 (56), 43 (57).

Methyl (1R,3S,6R)-1,6-Epoxy-2,2,3,6-tetramethylcyclohexane-1-carboxylate ((1*R*,3*S*,6*R*)-**14**). Data from (1*S*,3*S*,6*S*)-**14**/(1*R*,3*S*,6*R*)-**14** 7:3: ^{1}H-NMR: 0.81 (*d*, $J = 7$, 3 H); 0.96 (*s*, 3 H); 1.05 (*s*, 3 H); 1.27 (*s*, 3 H); 1.28 (*m*, 2 H); 1.60–1.95 (*m*, 3 H); 3.74 (*s*, 3 H). ^{13}C-NMR: 16.0 (*Me*−C(3)); 17.4 (*Me*−C(2), *cis* to *Me*−C(3)); 22.2 (*Me*−C(2), *trans* to *Me*−C(3)); 25.1 (C(4)); 26.1 (*Me*−C(6)); 31.3 (C(5)); 34.5 (C(2)); 39.0 (C(3)); 51.3 (MeO); 64.3 (C(6)); 71.2 (C(1)); 169.9 (C=O).

(+)-Methyl (1S,5S)-1-Hydroxy-2,5,6,6-tetramethylcyclohex-2-ene-1-carboxylate ((+)-(1*S*,5*S*)-**15**). At 25° (−)-**14** (100 mg, 0.47 mmol) in dioxane (1 ml) was stirred for 170 h in presence of *Filtrol®* (33 mg) or *Nafion NR 50* (35 mg), and then filtered. The filtrate was evaported and the residue purified by CC (SiO_2 (20 g), cyclohexane/AcOEt 95:5): pure (+)-(1*S*,5*S*)-**15** (60%). $[\alpha]_D^{20} = +81.9$ ($c = 1.3$, CCl_4). IR: 3510, 2970, 1720, 1435, 1250, 1110, 1060, 1035, 820. ^{1}H-NMR: 0.80 (*s*, 3 H); 0.88 (*d*, $J = 7$, 3 H); 0.89 (*s*, 3 H); 1.10 (*s*, OH); 1.63 (br. *s*, 3 H); 1.78 (*m*, 1 H); 2.00 (*m*, 2 H); 3.80 (*s*, 3 H); 5.66 (*m*, 1 H). ^{13}C-NMR: 14.7 (*Me*−C(5)); 16.6 (*Me*−C(6), *cis* to Me); 19.2 (*Me*−C(2)); 21.4 (*Me*−C(6), *trans* to Me); 31.7 (C(4)); 32.0 (C(5)); 39.6 (C(6)); 52.2 (MeO); 81.4 (C(1)); 127.5

(C(3)); 131.6 (C(2)); 176.2 (C=O). MS: 212 (1, $M^{+\cdot}$), 194 (10), 153 (50), 142 (52), 135 (10), 109 (25), 82 (100), 55 (14), 43 (33).

(+)-Methyl (1R,5S)-1-Hydroxy-2,5,6,6-tetramethylcyclohex-2-ene-1-carboxylate ((+)-(1*R*,5*S*)-**15**) was obtained pure on purification of (+)-**13a** by CC (SiO_2, toluene/AcOEt 100:0→7:3). $[\alpha]_D^{20} = +29.0$ ($c = 0.8$, $CHCl_3$). IR: 3510, 2970, 1720, 1435, 1250, 1110, 1060, 1035, 820. ^{1}H-NMR: 0.80 (*s*, 3 H); 0.87 (*d*, $J = 7$, 3 H); 0.87 (*s*, 3 H); 1.10 (*s*, OH); 1.57 (br. *s*, 3 H); 1.78 (*m*, 1 H); 2.00 (*m*, 1 H); 2.30 (*m*, 1 H); 3.80 (*s*, 3 H); 5.64 (*m*, 1 H). ^{13}C-NMR: 15.4 (*Me*–C(6), *cis* to Me); 15.6 (*Me*–C(5)); 18.3 (*Me*–C(2)); 21.8 (*Me*–C(6), *trans* to Me); 31.6 (C(4)); 33.4 (C(5)); 40.2 (C(6)); 53.0 (MeO); 81.8 (C(1)); 126.6 (C(3)); 133.1 (C(2)); 177.0 (C=O). MS: 212 (1, $M^{+\cdot}$), 194 (4), 153 (66), 135 (14), 109 (50), 82 (100), 55 (20), 43 (92).

(−)-Methyl (R)-2,5,6,6-Tetramethylcyclohexa-2,4-diene-1-carboxylate ((−)-**16a**). For 144 h, (−)-**14** (880 mg, 4.15 mmol) or (+)-**13a** (805 mg, 4.15 mmol) in dioxane (8.8 ml) was heated at reflux in presence of *Filtrol*® (390 mg) to give (−)-**16a**/(+)-**13a** 64:36. The cold soln. was filtered over *Celite*, the filtrate evaporated, and the residue purified by CC (SiO_2 (90 g), toluene): pure (−)-**16a** (61%). GC (*DB1*, 130–180°): t_R 1.61. B.p. 80°/1 Torr. $[\alpha]_D^{20} = -361.9$ ($c = 1.1$, $CHCl_3$). IR: 3040, 2970, 1745, 1440, 1220, 1130, 1025. ^{1}H-NMR: 1.03 (*s*, 3 H); 1.07 (*s*, 3 H); 1.73 (*s*, 3 H); 1.78 (*s*, 3 H); 2.69 (*s*, 1 H); 3.65 (*s*, 3 H); 5.57 (br. *d*, $J = 5$, 1 H); 5.70 (br. *d*, $J = 5$, 1 H). ^{13}C-NMR: 18.7 (*Me*–C(5)); 22.2 (*Me*–C(2)); 22.2 (*Me*–C(6), *cis* to COOMe); 26.2 (*Me*–C(6), *trans* to COOMe); 36.9 (C(6)); 51.2 (MeO); 58.2 (C(1)); 118.7 (C(4)); 121.7 (C(3)); 128.9 (C(2)); 140.2 (C(5)); 172.8 (C=O). MS: 194 (20, $M^{+\cdot}$), 179 (12), 135 (100), 119 (52), 105 (28), 91 (22), 77 (8), 59 (15).

(−)-(R)-2,5,6,6-Tetramethylcyclohexa-2,4-diene-1-carboxylic Acid ((−)-**16b**). As described for (+)-**13b**, with PhSH (5 mg, 0.049 mmol), (−)-**16a** (10 mg, 0.052 mmol), DMF (0.1 ml), and KOH (2.6 mg, 0.046 mmol; 2.5 h). The org. phase was not washed but dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2 (1 g), toluene/AcOEt 97:3→7:3): pure (−)-**16b** (89%). GC (*DB Wax*, 130–180°): t_R 5.89. M.p. 93°. $[\alpha]_D^{20} = -122.7$ ($c = 0.2$, $CHCl_3$). IR: 3100, 2970, 1760, 1710, 1440, 1310, 1230, 825. ^{1}H-NMR: 1.08 (*s*, 3 H); 1.20 (*s*, 3 H); 1.78 (*s*, 3 H); 1.88 (*s*, 3 H); 2.70 (br. *s*, 1 H); 5.70 (*m*, 2 H); 12.5 (br. *s*, OH). ^{13}C-NMR: 18.7 (*Me*–C(5)); 22.3 (*Me*–C(6), *cis* to COOH); 22.5 (*Me*–C(2)); 25.9 (*Me*–C(6), *trans* to COOH); 36.7 (C(6)); 58.3 (C(1)); 118.7 (C(4)); 121.7 (C(3)); 129.1 (C(2)); 140.6 (C(5)); 176.4 (CO_2H). MS: 180 (50, $M^{+\cdot}$), 165 (9), 135 (100), 121 (80), 119 (51), 105 (51), 91 (24), 77 (19), 70 (12), 43 (19).

(−)-(R)-2,5,6,6-Tetramethylcyclohexa-2,4-diene-1-carbaldehyde ((−)-**16c**). To a soln. of $(COCl)_2$ (8.6 µl, 0.1 mmol) in CH_2Cl_2 (0.2 ml) was added at −78° DMSO (14.1 µl, 0.19 mmol) followed by (−)-**18** (15 mg, 0.09 mmol) and, after 15 min, Et_3N (63 µl, 0.45 mmol). The temp. was equilibrated to 25°. After 1 h, the mixture was diluted with Et_2O, the org. phase washed with H_2O to neutral, dried ($MgSO_4$), and evaporated, and the residue purified (SiO_2 (1.5 g), toluene/AcOEt 95:5): pure (−)-**16c** (77%). $[\alpha]_D^{20} = -309.0$ ($c = 0.8$, $CHCl_3$). Data: see [5].

(+)-(5S)-2,5,6,6-Trimethylcyclohexa-1,3-diene-1-methanol ((+)-**17**). A soln. of (+)-**13a** (100 mg, 0.52 mmol) in Et_2O (1 ml) was added to a suspension of $LiAlH_4$ (15 mg, 0.38 mmol) in Et_2O (1 ml). After 24 h, the mixture was poured onto ice and extracted with Et_2O, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue purified by CC (SiO_2 (10 g), toluene/AcOEt 95:5): pure (+)-**17** (94%). GC (*DB Wax*, 80–110°): t_R 5.78. B.p. 100°/0.8 Torr. $[\alpha]_D^{20} = +177.7$ ($c = 0.65$, $CHCl_3$). IR: 3360, 2970, 1650, 1460, 1380, 1170, 1140, 985. ^{1}H-NMR: 0.93 (*d*, $J = 7$, 3 H); 0.99 (*s*, 3 H); 1.13 (*s*, 3 H); 1.84 (*s*, 3 H); 2.07 (*m*, 1 H); 4.20 (*d*, $J = 13$, 1 H); 4.28 (*d*, $J = 13$, 1 H); 5.62 (*dd*, $J = 4$, 8, 1 H); 5.71 (*dd*, $J = 2$, 8, 1 H). ^{13}C-NMR: 14.0 (*Me*–C(5)); 17.9 (*Me*–C(2)); 20.6 (*Me*–C(6), *cis* to Me); 26.5 (*Me*–C(6), *trans* to Me); 36.7 (C(6)); 40.7 (C(5)); 59.0 (CH_2OH); 127.4 (C(3)); 128.8 (C(2)); 133.5 (C(4)); 137.0 (C(1)). MS: 166 (16, $M^{+\cdot}$), 148 (24), 133 (100), 121 (83), 105 (96), 91 (82), 77 (36), 65 (18), 41 (29).

(−)-(R)-2,5,6,6-Tetramethylcyclohexa-2,4-diene-1-methanol ((−)-**18**). A soln. of (−)-**16a** (225 mg, 1.16 mmol) in Et_2O (1 ml) was added to a suspension of $LiAlH_4$ (32 mg, 0.87 mmol) in Et_2O (1 ml). After 1 h, H_2O (32 µl), 15% aq. NaOH soln. (32 µl), and H_2O (96 µl) were successively added. The mixture was filtered over *Celite*, the filtrate evaporated, and the residue purified by CC (SiO_2 (20 g), toluene/AcOEt 95:5): pure (−)-**18** (72%). GC (*DB Wax*, 80–110°): t_R 4.13. B.p. 80°/0.8 Torr. $[\alpha]_D^{20} = -252.3$ ($c = 0.85$, $CHCl_3$). IR: 3370, 2965, 1655, 1435, 1360, 1025, 820. ^{1}H-NMR: 0.99 (*s*, 3 H); 1.14 (*s*, 3 H); 1.70 (*s*, 3 H); 1.70 (*m*, 1 H); 1.85 (*s*, 3 H); 3.69 (*dd*, $J = 4$, 13, 1 H); 3.77 (*dd*, $J = 4$, 13, 1 H); 5.47 (br. *d*, $J = 4$, 1 H); 5.70 (br. *d*, $J = 4$, 1 H). ^{13}C-NMR: 18.6 (*Me*–C(5)); 22.2 (*Me*–C(6), *cis* to CH_2OH); 22.9 (*Me*–C(2)); 26.3 (*Me*–C(6), *trans* to CH_2OH); 36.4 (C(6)); 53.0 (C(1)); 61.8 (CH_2OH); 118.8 (C(4)); 120.6 (C(3)); 133.2 (C(2)); 141.6 (C(5)). MS: 166 (23, $M^{+\cdot}$), 135 (100), 119 (79), 105 (48), 91 (47), 77 (19), 41 (12).

(−)-(1R,5R)-2,5,6,6-Tetramethylcyclohex-2-ene-1-methanol ((−)-*trans*-**19**). A soln. of (−)-**18** (138 mg, 0.83 mmol) in EtOH (2 ml) was hydrogenated over *Raney*-Ni and then filtered over *Celite*. Evaporation gave (+)-*cis*-**19**/(−)-*trans*-**19** 27:73 (96%) which were separated by CC (SiO_2 (15 g), toluene/AcOEt 95:5). (−)-*trans*-**19**: $[\alpha]_D^{20} = -53.5$ ($c = 0.3$, $CHCl_3$). Data: see [1].

(−)-(1R,3S,6R)-2,2,3,6-Tetramethylcyclohexane-1-methanol ((−)-(1*R*,3*S*,6*R*)-**20**). A soln. of (+)-*cis*-**19** (50 mg, 0.30 mmol) in AcOH (0.5 ml) was hydrogenated in presence of PtO_2 (5 mg), and then filtered over *Celite*. After washing with Et_2O, the org. phase was extracted with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$) and evaporated: (−)-(1*R*,3*S*,6*R*)-**20** (98%; single diastereoisomer). GC (*DB Wax*, 110–150°): t_R 5.75. M.p. 56–57°. $[\alpha]_D^{20} = -24.1$ ($c = 0.3$, $CHCl_3$). IR: 3400, 2980, 2920, 1460, 1390, 1020, 1010. ^{1}H-NMR: 0.70 (*s*, 3 H); 0.83 (*d*, $J = 7$, 3 H); 0.95 (*d*, $J = 7$, 3 H); 0.97 (*s*, 3 H); 1.20–1.45 (*m*, 5 H); 1.57 (*m*, 2 H); 2.15 (*m*, 1 H); 3.65 (*t*, $J = 10$, 1 H); 3.90 (*dd*, $J = 4$, 10, 1 H). ^{13}C-NMR: 14.7 (Me_{ax}–C(6)); 16.0 (Me_{eq}–C(3)); 17.6 (Me_{ax}–C(2)); 26.5 (C(4)); 28.3 (C(6)); 28.9 (Me_{eq}–C(2)); 32.8 (C(5)); 35.8 (C(2)); 42.7 (C(3)); 52.3 (C(1)); 61.4 (CH_2OH). MS: 170 (4, $M^{+\cdot}$), 152 (6), 137 (42), 109 (53), 95 (45), 83 (85), 69 (71), 55 (100), 41 (67).

(+)-(1R,3R,6S)-2,2,3,6-Tetramethylcyclohexane-1-methanol ((+)-(1*R*,3*R*,6*S*)-**20**). As described for (−)-(1*R*,3*S*,6*R*)-**20**, from (−)-*trans*-**19** (34.3 mg, 0.204 mmol): (−)-(1*R*,3*R*,6*R*)-**20**/(+)-(1*R*,3*R*,6*S*)-**20** 2:1 (95%). The mixture was separated by CC (SiO_2 (4 g), toluene/AcOEt 97:3) and then prep. GC (*DB Wax*, 110–150°): t_R 4.17 ((−)-(1*R*,3*R*,6*R*)-**20**), 4.25, ((+)-(1*R*,3*R*,6*S*)-**20**). (+)-(1*R*,3*R*,6*S*)-**20**: B.p. 70°/0.9 Torr. $[\alpha]_D^{20} = +1.35$ ($c = 0.7$, $CHCl_3$). IR (3350, 2980, 2940, 1460, 1370, 1090, 1030, 990. ^{1}H-NMR: 0.90 (*m*, 2 H); 0.93 (*d*, $J = 7$, 3 H); 0.97 (*s*, 3 H); 0.98 (*s*, 3 H); 1.02 (*d*, $J = 7$, 3 H); 1.09 (*dt*, $J = 4$, 12, 1 H); 1.25 (*m*, 2 H); 1.40 (*m*, 1 H); 1.60 (*m*, 1 H); 1.85 (*tt*, $J = 4$, 12, 1 H); 3.65 (*dd*, $J = 4$, 12, 1 H); 3.82 (*dd*, $J = 4$, 12, 1 H). ^{13}C-NMR: 14.9 (Me_{ax}–C(3)); 21.0 (Me_{eq}–C(6)); 24.7 (Me_{ax}–C(2)); 28.3 (Me_{eq}–C(2)); 28.8 (C(4)); 30.2 (C(5)); 30.8 (C(6)); 35.6 (C(2)); 40.9 (C(3)); 49.6 (C(1)); 62.6 (CH_2OH). MS: 170 (5, $M^{+\cdot}$), 152 (4), 137 (23), 109 (39), 97 (37), 83 (100), 69 (78), 55 (90), 41 (39).

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