Pergamon

Tetrahedron 56 (2000) 4253–4260

TETRAHEDRON

Odor–Structure Relationships Using Fluorine as a Probe

Dominique Michel and Manfred Schlosser*

Section de Chimie (BCh), Université, CH-1015 Lausanne, Switzerland

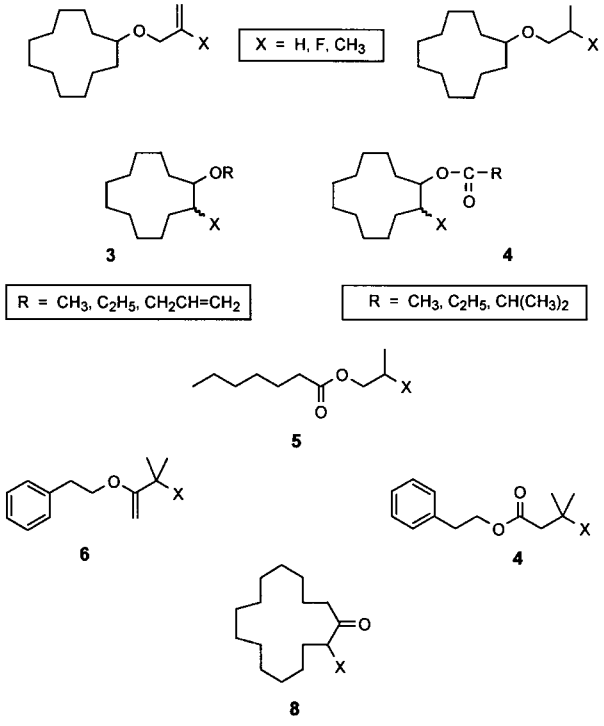
Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

Received 17 April 2000; accepted 28 April 2000

Abstract—Eight ethers, nine esters and one ketone were submitted to a systematic structural variation by replacing a hydrogen atom in the vicinity of the oxofunction by fluorine and methyl. As long as steric factors dominate, a fluorine substituent alters the olfactory properties of the parent compound much less than a methyl substituent does. However, if it occupies a position adjacent to a carbonyl group, the halogen may more profoundly affect the odor perception, presumably as a consequence of conformational changes.

The chemical and physiological size of fluorine remains an intriguing though controversial subject.[1] Seeking a new approach to the problem, we have suggested to compare the organoleptic properties of organofluorine compounds with that of analogs in which the halogen has been replaced once by hydrogen and, on the other hand, by a methyl group.[2] Whenever the interaction between the receptor and the chemical excitant is primarily determined by steric matching, the relatively small fluorine substituent should cause little difference.

The first examples examined seemed to fit such a lock-and-key situation. Fluorinated congeners of 4-(4-hydroxyphenyl)-2-butanone exhibit a similar flavor and fragrance profile as the natural product, the so-called raspberry ketone, whereas chain-lengthened or branched homologs containing one additional methylene entity differ considerably.[2] One may, however, argue that these findings are coincidental and by no means representative. Before any generalization can be attempted, the study has indeed to be extended to various classes of compounds. As a next step, we have turned to cyclododecanol derived ethers (**1**–**3**) and esters (**4**). For systematic reasons, also acyclic esters (**5**–**7**) and a cyclic ketone (**8**) were included in the comparison which encompasses a total of 54 compounds, almost all of them previously unknown. Since, unlike diastereoisomerism, enantioisomerism causes in general only moderate, if any, differences in odor perception,[3–7] we decided to restrict ourselves to racemic compounds (Scheme 1).



Scheme 1.

The cyclododecyl ethers **3** and esters **4** can exist in the *cis* or *trans* configuration. If fluorine were indeed to mimic hydrogen in all respects, the pairs of isomers and the corresponding parent compounds should display exactly the same olfactory pattern. This was, of course, not a realistic expectation.

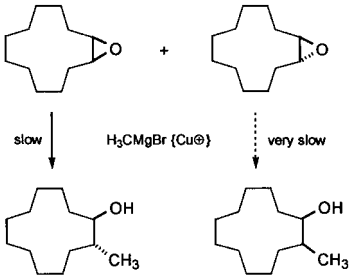
Standard methods were applied to the preparation of the halogen-free reference substances whenever possible.

Keywords: organofluorine compounds; epoxides; conformation; dipole–dipole interactions; olfactory evaluation.

* Corresponding author. Fax: +41-21-6923965.

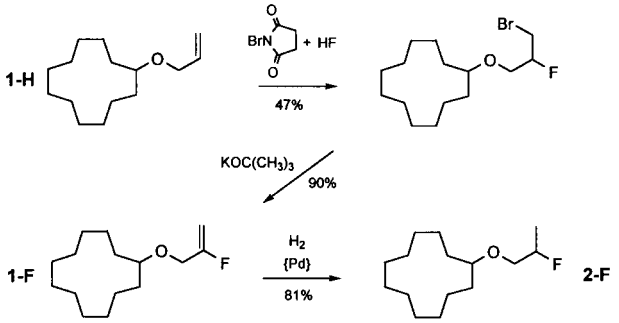
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00351-3

However, an improved and very simple access to pure *trans*-1,2-epoxycyclododecane, a key starting material, was elaborated based on a kinetic separation from its *cis* isomer. The latter could be selectively removed from the commercial stereomixture due to its higher reactivity towards methylmagnesium bromide (Scheme 2).



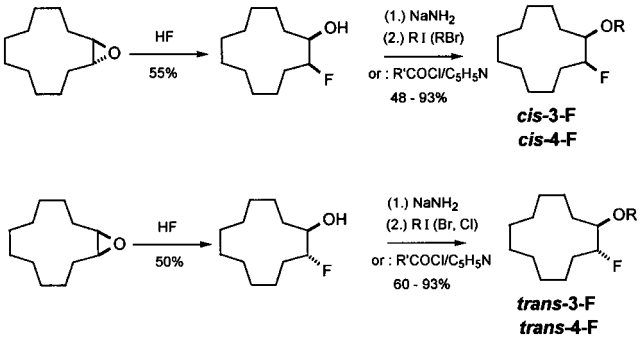
Scheme 2.

In the following text, letter labels are used to differentiate between the constituents of an 'olfactory triad' composed of the unsubstituted parent compound (**H**), the fluorinated analog (**F**) and the methyl-branched homolog (**C**). The cyclododecyl 2-fluoropropyl ether (**2-F**) was obtained by bromofluorination[8,9] of (allyloxy)cyclododecane (**1-H**) with *N*-bromosuccinimide in the presence of triethylamine tris(hydrofluoride)[10] followed by dehydrobromination with potassium *tert*-butoxide,[11] to give the cyclododecyl 2-fluoroallyl ether (**1-F**), and palladium-catalyzed hydrogenation. Alternatively, the heavier halogen can be removed from the (3-bromo-2-fluoropropyloxy)cyclododecane intermediate by reduction with tributyltin hydride[12] in a radical-chain process (Scheme 3).



Scheme 3.

Stereoselective ring opening of *trans*- and *cis*-1,2-epoxycyclododecane with ethyldiisopropylamine tris(hydrofluoride)[13] afforded *cis*- and *trans*-2-fluoro-1-cyclododecanol, respectively. The corresponding sodium alkoxides were converted into the ethers **3a-F** [R=CH_3], **3b-F** [R=C_2H_5] and **3c-F** [R=$CH_2CH{=}CH_2$] by alkylation with methyl iodide, ethyl iodide and allyl bromide and into the esters **4a-F** [R=CH_3], **4b-F** [R=C_2H_5] and **4c-F** [R=$CH(CH_3)_2$] by acylation with acetyl, propionyl and isobutyryl chloride (Scheme 4).



Scheme 4.

2-Fluoroallyl heptanoate (**5-F**) was made by acylation of 2-fluoro-2-propen-1-ol.[14] Treatment of the corresponding 2-hydroxy and 3-hydroxy esters with diethylaminosulfur trifluoride ('DAST') afforded phenylethyl 2-fluoroisobutyrate (**6-F**) and phenylethyl 3-fluoroisovalerate (**7-F**). As already described,[15] 2-fluorocyclopentadecanone was produced by the fluoride-catalyzed isomerization of 1,2-epoxy-1-fluorocyclopentadecane which, for its part, had been made by the oxidation of 1-fluorocyclopentadecene (as a 2:3 *Z*/*E* mixture) with *m*-chloroperbenzoic acid.

Details of the olfactory assessment are to be found in the Experimental. In most cases, the odor of the fluorinated derivative clearly resembles more the parent compound than the methyl analog. The space requirements of hydrogen and fluorine can hence not be too contrasting. However, the odor characteristics of the fluoro ester **6-F** and the fluoro ketone **8-F** differ significantly from those of their halogen-free counterparts. A plausible explanation can be based on dipole interactions that must exist between the carbon-halogen bond and the adjacent carbonyl group and which should cause a major conformational perturbation. Only why did 3-fluoro-4-(4-hydroxyphenyl)-2-butanone[2] not likewise exhibit a strong substituent effect? When the raspberry ketone docks onto the receptor, probably the hydroxy and the carbonyl functional group bind simultaneously. In other words, there is only a single effective conformer. The introduction of a fluorine atom may increase or diminish the extent to which it is populated at conformational equilibrium. This may modify the intensity of the odor sensation, but not its tonality.

Experimental

Generalities

Nuclear magnetic resonance spectra were recorded of samples dissolved in deuterochloroform at 250 MHz (^{1}H NMR), 400 MHz (^{1}H NMR*), 188 MHz (^{19}F NMR) and 376 MHz (^{19}F NMR*). For standard working practice and abbreviation, see recent publications[16–18] from this laboratory.

Starting materials

***trans*-1,2-Epoxycyclododecane.** Methylmagnesium bromide (0.15 mol) in diethyl ether (60 mL) and dilithium tetrachlorocuprate[19] (1.0 mmol) in tetrahydrofuran (25 mL) were mixed at −15°C. The solution was kept for 1 h at −15°C before commercial 1,2-epoxycyclododecane (*cis*/*trans* ~3:7; 20 g, 0.11 mol) in tetrahydrofuran (75 mL) was added in the course of 20 min. After being allowed to stand 150 h (6 days) at 25°C, the mixture was poured into a saturated aqueous solution (0.20 L) of ammonium chloride and extracted with diethyl ether (3×0.10 L). The residue obtained upon evaporation of the solvent was purified by column chromatography. Elution from silica gel (0.25 L) with a 1:10 (v/v) mixture of diethyl ether and hexane afforded 1,2-epoxycyclododecane having a *cis*/*trans* ratio of ≤5:95 as evidenced by gas chromatography (30 m, DB-1, 180°C; 30 m, DB-WAX, 180°C); bp 130–131°C/16 mmHg (lit.[20] bp 130°C/14 mmHg); n_D^{20} 1.4790; 55%. ^{1}H NMR: δ 2.71 (2H, dt, *J*=11.6, 2.2 Hz), 2.19 (2H, symm. m), 1.4 (16H, m), 1.03 (2H, symm. m).

***cis*-2-Fluoro-1-cyclododecanol.** Under nitrogen atmosphere, *trans*-1,2-epoxycyclododecane (*cis*/*trans* ≤5:95; see above; 5.0 g, 27 mmol) and solvent-free ethyldiisopropylamine tris(hydrofluoride)[13] (26 g, 0.14 mol) were heated 48 h to reflux (approx. 130°C). After addition of water (0.10 L), the mixture was extracted with diethyl ether (3×50 mL) and submitted to column chromatography on silica gel. When a 1:10 mixture of diethyl ether and pentane was used as the eluent, unconsumed epoxide (30%; *cis*/*trans* ratio <0.5:99.5!), *trans*-2-fluoro-1-cyclododecanol (3.5%) and the *cis*-isomer (55%) were successively collected (gas chromatography: 30 m, DB-1, 180°C; 30 m DB-WAX, 180°C). The isolated *cis*-2-fluoro-1-cyclododecanol was analytically pure; mp 84–86°C; 55%. ^{1}H NMR: δ 4.69 (1H, dtd, *J*=47.8, 6.0, 1.7 Hz), 3.9 (1H, m), 2.14 (1H, d, *J*=5.0 Hz), 1.4 (20H, m). ^{19}F NMR: δ −127.8 (m). Analysis: calcd for $C_{12}H_{23}FO$ (202.31) C 71.24, H 11.46; found C 71.41, C 11.76%.

***trans*-2-Fluoro-1-cyclododecanol.** In the same way as described in the preceding paragraph, the *trans* isomer was obtained starting with *cis*-1,2-epoxycyclododecane;[21] *cis*/*trans* ratio <1:99; mp 64–65°C; 50%. ^{1}H NMR: δ 4.56 (1H, ddt, *J*=49.6, 8.4, 4.3 Hz), 3.90 (1H, symm. m), 2.26 (1H, t, *J*=3.5 Hz), 1.4 (20H, m). ^{19}F NMR: δ −130.9 (symm. m). Analysis: calcd for $C_{12}H_{23}FO$ (202.31) C 71.24, H 11.46; found C 71.06, H 11.51%.

***cis*-2-Methyl-1-cyclododecanol.** A solution of *trans*-1,2-epoxycyclododecane (9.0 g, 0.10 mol), methylmagnesium bromide (0.15 mol) and dilithium tetrachlorocuprate (1.0 mmol) in diethyl ether (60 mL) and tetrahydrofuran (90 mL) was prepared as described above and kept 600 h (25 days) at 25°C. Neutralization with a saturated aqueous solution of ammonium chloride (0.10 L), extraction with diethyl ether (3×0.10 L), evaporation and chromatography on silica gel (0.20 L; elution with a 1:10 mixture of diethyl ether and hexane) gave a spontaneously crystallizing colorless product; *cis*/*trans* ratio >99:1 (by gas chromatography: 30 m, DB-1, 180°C; 30 m, DB-WAX; 180°C); mp 68–70°C (lit.[10] mp 71–72°C); 39%. ^{1}H NMR: δ 3.7 (1H, m), 1.7 (2H, m), 1.4 (18H, m), 1.1 (1H, m), 0.95 (3H, d, *J*=6.8 Hz).

***trans*-2-Methyl-1-cyclododecanol.** In the same way as the *trans* isomer was obtained starting with *cis*-1,2-epoxycyclododecane;[21] reaction time 100 h (4 days) at 25°C; *cis*/*trans* ratio of 2-methyl-1-cyclododecanol <1:99; mp 58–60°C (lit.[10] mp 61–62°C); 49%. ^{1}H NMR: δ 3.7 (1H, m), 1.7 (2H, m), 1.4 (18H, m), 1.2 (1H, m), 0.93 (3H, d, *J*=6.6 Hz).

Ethers

Methoxycyclododecane (**3a-H**) is a commercial product. Most of the other ethers have been obtained by the alkylation of cyclododecanols (see General working procedure). The exceptions are (2-fluoro-2-propenyloxy)cyclododecane (**1-F**) and (2-fluoropropyloxy)cyclododecane (**2-F**), which were prepared from allyloxycyclododecane.

General working procedure

Sodium amide (1.0 g, 25 mmol) was added to a solution of cyclododecanol, *cis*- or *trans*-2-fluorocyclododecan-1-ol or *cis*- or *trans*-2-methylcyclododecan-1-ol (25 mmol) in tetrahydrofuran (0.10 L). The suspension was vigorously stirred for 2 h before the alkyl halide (50 mmol) was introduced. In intervals a few drops of the reaction mixture were withdrawn and treated with water until the aqueous phase proved to be neutral. When this was the case (with methyl iodide it took only 15 min to reach this point, with primary halides 6–48 h), the mixture was absorbed on silica gel (10 mL) and the powder, when dry, placed on top of a column filled with more silica gel (0.20 L). Elution with a 1:40 (v/v) mixture of diethyl ether and hexane followed by distillation afforded the product as a colorless oil.

(Allyloxy)cyclododecane (1-H). With allyl bromide as the halide; mp −78 to −74°C; bp 88–91°C /0.6 mmHg; (lit.[22] bp 129–131°C/3 mmHg); n_D^{20} 1.4790 (lit.[22] n_D^{20} 1.4839); 89%. ^{1}H NMR: δ 5.93 (1H, ddt, *J*=17.2, 10.2, 5.7 Hz), 5.28 (1H, dq, *J*=17.2, 1.6 Hz), 5.15 (1H, ddt, *J*=10.2, 1.6, 1.0 Hz), 3.98 (2H, dt, *J*=5.7, 1.6 Hz), 3.47 (1H, symm. m), 1.4 (22H, m). Analysis: calcd for $C_{15}H_{28}O$ (224.39) C 80.29, H 12.58; found C 80.22, H 12.78%.

(2-Fluoro-2-propenyloxy)cyclododecane (1-F). A solution of allyloxycyclododecane (11.2 g, 50 mmol), *N*-bromosuccinimide (17.8 g, 100 mmol) and triethylamine tris(hydrofluoride) (11.5 mL, 11.3 g, 70 mmol) in dichloromethane (0.10 L) was kept 10 h in an ice bath. The mixture was absorbed on silica gel (25 mL) and the powder, when dry, placed on top of a column filled with more silica (0.20 L). Elution with a 1:40 (v/v) mixture of diethyl ether and hexane followed by evaporation afforded **(3-bromo-2-fluoropropyloxy)cyclododecane** as a colorless oil; mp −60 to −55°C; bp 148–152°C/1 mmHg; n_D^{20} 1.4924; 47%. ^{1}H NMR: δ 4.75 (1H, dq, *J*=47.0, 5.1 Hz), 3.6 (5H, m), 1.4 (22H, m). ^{19}F NMR: δ −121.6 (dtt, *J*=47, 20, 19 Hz). Analysis: calcd for $C_{15}H_{28}BrFO$ (323.29) C 55.73, H 8.73; found C 55.38, H 8.85%. The latter product (4.8 g, 20 mmol) and potassium *tert*-butoxide (4.5 g, 40 mmol) were simultaneously dissolved in tetrahydrofuran (50 mL). After 6 h at 25°C, the unsaturated product **1-F** was

isolated by gas chromatography using a 1:40 (v/v) mixture of diethyl ether and hexane as the eluent; mp −38 to −34°C; bp 71–73°C/1 mmHg; n_D^{20} 1.4700; 90%. ^{1}H NMR: δ 4.71 (1H, dd, *J*=16.8, 2.7 Hz), 4.55 (1H, dd, *J*=48.7, 2.7 Hz), 4.00 (2H, d, *J*=12.5 Hz), 3.54 (1H, symm. m), 1.4 (22H, m). ^{19}F NMR: δ −42.7 (ddt, *J*=49, 17, 13 Hz). Analysis: calcd for $C_{15}H_{27}FO$ (242.38) C 74.33, H 11.22; found C 74.42, H 11.19%.

(Methallyloxy)cyclododecane (1-C). A suspension containing sodium amide and cyclododecanol in xylene was stirred 2 h at 25°C. After addition of methallyl (2-methylprop-2-enyl) chloride, the mixture was heated to reflux for 72 h before being worked up as usual (see above). Upon distillation a colorless oil was collected; mp −77 to −73°C; bp 100–104°C/1 mmHg (lit.[22] bp 130–135°C/3 mmHg); n_D^{20} 1.4795 (lit.[22] n_D^{20} 1.4814); 59%. ^{1}H NMR: δ 4.97 (1H, symm. m), 4.87 (1H, symm. m), 3.86 (2H, symm. m), 3.45 (1H symm. m), 1.75 (3H, symm. m), 1.4 (22H, m). Analysis: calcd for $C_{16}H_{30}O$ (238.42) C 80.61, H 12.68; found C 80.72, H 12.74%.

(Propyloxy)cyclododecane (2-H). With propyl iodide as the halide; mp −64 to −61°C; bp 82–83°C/0.1 mmHg (lit.[22] bp 124–127°C/3 mmHg); n_D^{20} 1.4690 (lit.[12] n_D^{20} 1.4694); 53%. ^{1}H NMR: δ 3.38 (1H, symm. m), 3.38 (2H, t, *J*=6.7 Hz), 1.4 (24H, m), 0.92 (3H, t, *J*=7.4 Hz). Analysis: calcd for $C_{15}H_{30}O$ (226.40) C 79.58, H 13.36; found 79.57, H 13.16%.

(2-Fluoropropyloxy)cyclododecane (2-F). (2-Fluoro-2-propenyloxy)cyclododecane (2.4 g, 10 mmol), palladium (approx. 1 mmol) on charcoal and ethanol (0.10 L) were filled into a small autoclave which was pressurized with hydrogen gas to 50 atm. After 10 h of shaking, the mixture was filtered and concentrated. Distillation afforded a colorless oil; mp −72 to −69°C; bp 95–97°C/2 mmHg; n_D^{20} 1.4634; 81%. ^{1}H NMR: δ 4.78 (1H, dqdd, *J*=49.0, 6.7, 6.5, 5.1 Hz), 3.5 (3H, m), 1.4 (22H, m), 1.33 (3H, dd, *J*=24.1, 6.7 Hz). ^{19}F NMR*: δ −116.9 (dqdd, *J*=49, 24, 22, 20 Hz). Analysis: calcd for $C_{15}H_{29}FO$ (244.40) C 73.72, H 11.96; found C 74.04, H 12.01%.

(Isobutyloxy)cyclododecane (2-C). With isobutyl (2-methylpropyl) iodide as the halide; mp −61 to −58°C; bp 112–114°C/1 mmHg (lit.[22] bp 133–138°C/4 mmHg); n_D^{20} 1.4680 (lit.[22] n_D^{20} 1.4728); 49%. ^{1}H NMR: δ 3.36 (1H, symm. m), 3.17 (2H, d, *J*=6.8 Hz), 1.80 (1H, nont, *J*=6.8 Hz), 1.4 (22H, m), 0.90 (6H, d, *J*=6.8 Hz). Analysis: calcd for $C_{16}H_{32}O$ (240.43) C 79.93, H 13.42; found C 80.25, H 13.28%.

Methoxycyclododecane (3a-H). With methyl iodide as the halide; bp 87–90°C/1 mmHg (lit.[22] bp 95–98°C/2 mmHg; n_D^{20} 1.4736 (lit.[22] n_D^{20} 1.4742); 94%. ^{1}H NMR: δ 3.33 (3H, s), 3.30 (1H, symm. m), 1.4 (22H, m).

***cis*-1-Fluoro-2-methoxycyclododecane (*cis*-3a-F).** With methyl iodide as the halide; mp 32–34°C; 93%. ^{1}H NMR: δ 4.77 (1H, dddd, *J*=48.0, 7.3, 5.5, 1.4 Hz), 3.5 (1H, m), 3.44 (3H, s), 1.5 (20H, m). ^{19}F NMR*: −188.1 (m). Analysis: calcd for $C_{13}H_{25}FO$ (216.34) C 72.18, H 11.65; found C 72.52, H 11.46%.

***trans*-1-Fluoro-2-methoxycyclododecane (*trans*-3a-F).** With methyl iodide as the halide; mp −8 to −5°C; bp 105–107°C/6 mmHg; n_D^{20} 1.4662; 93%. ^{1}H NMR: δ 4.60 (1H, dm, *J*=49.5 Hz), 3.47 (3H, s), 3.4 (1H, m), 1.4 (20H, m). ^{19}F NMR: δ −128.5 (dm, *J*=49 Hz). Analysis: calcd for $C_{13}H_{25}FO$ (216.34) C 72.18, H 11.65; found C 72.16, H 11.92%.

***cis*-1-Methoxy-2-methylcyclododecane (*cis*-3a-C).** With methyl iodide as the halide; mp −63 to −60°C; bp 85–88°C/1 mmHg; n_D^{20} 1.4712; 88%. ^{1}H NMR: δ 3.34 (3H, s), 3.2 (1H, m), 1.8 (1H, m), 1.4 (19H, m), 1.1 (1H, m), 0.89 (3H, d, *J*=6.8 Hz). Analysis: calcd for $C_{14}H_{28}O$ (212.38) C 79.18, H 13.29; found C 78.84, H 12.99%.

***trans*-1-Methoxy-2-methylcyclododecane (*trans*-3a-C).** With methyl iodide as the halide; mp −66 to −63°C; bp 84–87°C/1 mmHg; n_D^{20} 1.4732; 82%. ^{1}H NMR: δ 3.35 (3H, s), 3.08 (1H, td, *J*=6.7, 3.3 Hz), 1.4 (20H, m), 1.0 (1H, m), 0.93 (3H, d, *J*=6.7 Hz). Analysis: calcd for $C_{14}H_{28}O$ (212.38) C 79.18, H 13.29; found C 79.36, H 13.14%.

Ethoxycyclododecane (3b-H). With ethyl iodide as the halide; mp −38 to −36°C; bp 116–119°C/3 mmHg (lit.[22] bp 117–119°C/3 mmHg); n_D^{20} 1.4693 (lit.[22] n_D^{20} 1.4740); 54%. ^{1}H NMR: δ 3.49 (2H, q, *J*=7.1 Hz), 3.40 (1H, symm. m), 1.4 (22H, m), 1.19 (3H, t, *J*=7.1 Hz). Analysis: calcd for $C_{14}H_{28}O$ (212.38) C 79.18, C 13.29; found C 78.91, H 13.32%.

***cis*-1-Ethoxy-2-fluorocyclododecane (*cis*-3b-F).** With ethyl iodide as the halide; mp −47 to −46°C; bp 128–130°C/8 mmHg; n_D^{20} 1.4670; 48%. ^{1}H NMR: δ 4.75 (1H, symm. dm, *J*=48.0 Hz), 3.6 (3H, m), 1.4 (20H, m), 1.21 (3H, t, *J*=7.0 Hz). ^{19}F NMR*: δ −124.3 (m). Analysis: calcd for $C_{14}H_{27}FO$ (230.36) C 72.99, H 11.81; found C 72.82, H 12.11%.

***trans*-1-Ethoxy-2-fluorocyclododecane (*trans*-3b-F).** With ethyl iodide as the halide; mp −55 to −51°C; bp 105–107°C/3 mmHg; n_D^{20} 1.4653; 60%. ^{1}H NMR: δ 4.61 (1H, symm. dm, *J*=49.5 Hz), 3.65 (2H, symm. m), 3.6 (1H, m), 1.4 (20H, m), 1.22 (3H, t, *J*=7.0 Hz). ^{19}F NMR: δ −129.0 (dm, *J*=49 Hz). Analysis: calcd for $C_{14}H_{27}FO$ (230.36) C 72.99, H 11.81; found C 72.86, H 11.95%.

***cis*-1-Ethoxy-2-methylcyclododecane (*cis*-3b-C).** With ethyl iodide as the halide; mp −70 to −67°C; bp 115–119°C/2 mmHg; n_D^{20} 1.4731; 65%. ^{1}H NMR: δ 3.51 (1H, dq, *J*=7.0, 2.8 Hz), 3.46 (1H, dq, *J*=7.0, 2.8 Hz), 3.3 (1H, m), 1.8 (1H, m), 1.4 (19H, m), 1.19 (3H, t, *J*=7.0 Hz), 1.1 (1H, m), 0.89 (3H, d, *J*=6.8 Hz). Analysis: calcd for $C_{15}H_{30}O$ (226.40) C 79.58, H 13.36; found C 79.66, H 13.21%.

***trans*-1-Ethoxy-2-methylcyclododecane (*trans*-3b-C).** With ethyl iodide as the halide; mp −76 to −72°C; bp 100–101°C/3 mmHg; n_D^{20} 1.4710; 69%. ^{1}H NMR: δ 3.62 (1H, dq, *J*=9.4, 7.0 Hz), 3.37 (1H, dq, *J*=9.4, 7.0 Hz), 3.16 (1H, symm. m), 1.7 (2H, m), 1.4 (18H, m), 1.18 (3H, t, *J*=7.0 Hz), 1.0 (1H, m), 0.94 (3H, d, *J*=6.6 Hz). Analysis: calcd for $C_{15}H_{30}O$ (226.40) C 79.58, H 13.36; found C 79.78, H 13.34%.

Allyloxycyclododecane (3c-H≡1-H). See above (immediately after the General working procedure).

***cis*-1-Allyloxy-2-fluorocyclododecane (*cis*-3-F).** With allyl bromide as the halide; mp −58 to −57°C; bp 118–120°C/3 mmHg; n_D^{20} 1.4739; 88%. ^{1}H NMR: δ 5.92 (1H, symm. m), 5.3 (1H, dm, *J*=17.2 Hz), 5.2 (1H, dm, *J*=10.2 Hz), 4.75 (1H, symm. dm, *J*=48.0 Hz), 4.17 (1H, symm. dm, *J*=13.0 Hz), 4.04 (1H, symm. dm, *J*=13.0 Hz), 3.64 (1H, symm. dm, *J*=22.0 Hz), 1.4 (20H, m). ^{19}F NMR*: δ −124.5 (m). Analysis: calcd for $C_{15}H_{27}FO$ (242.38) C 74.33, H 11.23; found C 74.19, H 11.21%.

***trans*-1-Allyloxy-2-fluorocyclododecane (*trans*-3-F).** With allyl bromide as the halide; mp −70 to −67°C; bp 120–121°C/1 mmHg; n_D^{20} 1.4730; 80%. ^{1}H NMR: δ 6.0 (1H, m), 5.3 (1H, dm, *J*=17.0 Hz), 5.2 (1H, dm, *J*=10.2 Hz), 4.66 (1H, symm. dm, *J*=49.5 Hz), 4.2 (1H, dm, *J*=12.0 Hz), 4.1 (1H, dm, *J*=12.0 Hz), 3.6 (1H, m), 1.4 (20H, m). ^{19}F NMR: δ −128.3 (m). Analysis: calcd for $C_{15}H_{27}FO$ (242.38) C 74.33, H 11.23; found C 74.31, H 11.15%.

***cis*-1-Allyloxy-2-methylcyclododecane (*cis*-3-C).** With allyl bromide as the halide; mp −70 to −66°C; bp 110–113°C/1 mmHg; n_D^{20} 1.4788; 64%. ^{1}H NMR: δ 5.92 (1H, ddt, *J*=17.1, 10.5, 6.0 Hz), 5.26 (1H, ddt, *J*=17.1, 1.9, 1.5 Hz), 5.15 (1H, ddt, *J*=10.5, 1.9, 1.5 Hz), 4.16 (2H, symm. m), 3.6 (1H, m), 1.4 (20H, m), 0.91 (3H, d, *J*=7.0 Hz). Analysis: calcd for $C_{16}H_{30}O$ (238.42) C 80.61, H 12.68; found C 80.81, H 12.87%.

***trans*-1-Allyloxy-2-methylcyclododecane (*trans*-3-C).** With allyl bromide as the halide; mp −72 to −71°C; bp 103–106°C/0.9 mmHg; n_D^{20} 1.4796; 40%. ^{1}H NMR: δ 5.92 (1H, ddt, *J*=17.1, 10.0, 5.9 Hz), 5.27 (1H, ddt, *J*=17.1, 1.9, 1.5 Hz), 5.14 (1H, ddt, *J*=10.0, 1.9, 1.5 Hz), 4.10 (1H, ddt, *J*=12.9, 6.1, 1.5 Hz), 3.88 (1H, ddt, *J*=12.9, 6.1, 1.5 Hz), 3.25 (1H, td, *J*=7.1, 3.0 Hz), 1.4 (20H, m), 1.0 (1H, m), 0.95 (3H, d, *J*=7.0 Hz). Analysis: calcd for $C_{16}H_{30}O$ (238.42) C 80.61, H 12.68; found C 80.74, H 12.52%.

Ester

General working procedure. The acyl chloride (25 mmol), pyridine (2.0 mL, 2.0 g, 25 mmol) and the alcohol (25 mmol) were consecutively dissolved in dichloromethane (50 mL). After 5 h at 25°C, the mixture was absorbed on silica gel (10 m) if the product was a cyclododecanol derivative. It was eluted with a 1/10 (v/v) mixture of diethyl ether and pentane from a column filled with silica gel (0.10 mL). If the ester was a derivative of 2-propen-1-ol, 2-fluoro-2-propen-1-ol, 2-methyl-2-propen-1-ol or 2-phenylethanol, the mixture was washed with water (2×10 mL) and brine (10 mL) before being dried and evaporated. The product was isolated by distillation under reduced pressure.

Cyclododecyl acetate[23] (4a-H). Bp 141–142°C/11 mmHg; n_D^{20} 1.4719; 85%.

***cis*-2-Fluorocyclododecyl acetate (*cis*-4a-F).** Mp −37 to −36°C; n_D^{20} 1.4719; 83%. ^{1}H NMR: δ 5.15 (1H, dddd, *J*=26.5, 7.5, 5.0, 1.4 Hz), 4.7 (1H, dm, *J*=48.1 Hz), 2.09 (3H, s), 1.4 (20H, m). ^{19}F NMR: δ −128.1 (m). Analysis: calcd for $C_{14}H_{25}FO_2$ (244.36) C 68.82, H 10.31; found C 69.03, H 10.08%.

***trans*-2-Fluorocyclododecyl acetate (*trans*-4a-F).** Mp −39 to −37°C; n_D^{20} 1.4662; 41%. ^{1}H NMR: δ 5.26 (1H, ddt, *J*=12.6, 8.0, 4.5 Hz), 4.68 (1H, ddt, *J*=49.0, 8.3, 4.5 Hz), 2.11 (3H, s), 1.4 (20H, m). ^{19}F NMR: δ −130.4 (dm, *J*=49 Hz). Analysis: calcd for $C_{14}H_{25}FO_2$ (244.36) C 68.82, H 10.31; found C 69.13, H 10.20%.

***cis*-2-Methylcyclododecyl acetate (*cis*-4a-C).** Mp −39 to −37°C; n_D^{20} 1.4712; 83%. ^{1}H NMR: δ 5.1 (1H, m), 2.04 (3H, s), 1.7 (2H, m), 1.4 (18H, m), 1.1 (1H, m), 0.89 (3H, d, *J*=6.8 Hz). Analysis: calcd for $C_{15}H_{28}O_2$ (240.39) C 74.95, H 11.74; found C 75.26, H 11.75%.

***trans*-2-Methylcyclododecyl acetate (*trans*-4a-C).** Mp −42 to −40°C; n_D^{20} 1.4713; 83%. ^{1}H NMR: δ 4.95 (1H, symm. m), 2.03 (3H, s), 1.8 (2H, m), 1.4 (18H, m), 1.1 (1H, m), 0.87 (3H, d, *J*=6.7 Hz). Analysis: calcd for $C_{15}H_{28}O_2$ (240.39) C 74.95, H 11.74; found C 74.73, H 11.78%.

Cyclododecyl propionate[24] (4b-H). Bp 97–99°C/0.8 mmHg; n_D^{20} 1.4700; 69%.

***cis*-2-Fluorocyclododecyl propionate (*cis*-4b-F).** Mp −47 to −45°C; n_D^{20} 1.4644; 85%. ^{1}H NMR: δ 5.18 (1H, dddd, *J*=26.5, 7.5, 5.0, 1.4 Hz), 4.66 (1H, dddd, *J*=48.3, 8.0, 6.1, 1.4 Hz), 2.37 (2H, q, *J*=7.5 Hz), 1.7 (4H, m), 1.4 (16H, m), 1.15 (3H, t, *J*=7.5 Hz). ^{19}F NMR: δ −128.1 (m). Analysis: calcd for $C_{15}H_{27}FO_2$ (258.38) C 69.73, H 10.53; found C 70.13, H 10.76%.

***trans*-2-Fluorocyclododecyl propionate (*trans*-4b-F).** Mp −50 to −49°C; n_D^{20} 1.4656; 48%. ^{1}H NMR: δ 5.25 (1H, ddt, *J*=12.8, 8.1, 5.0 Hz), 4.67 (1H, ddt, *J*=49.0, 8.1, 4.5 Hz), 2.35 (1H, q, *J*=7.7 Hz), 2.35 (1H, q, *J*=7.3 Hz), 1.4 (20H, m), 1.16 (3H, t, *J*=7.5 Hz). ^{19}F NMR: δ −130.5 (dm, *J*=49 Hz). Analysis: calcd for $C_{15}H_{27}FO_2$ (258.38) C 69.73, H 10.53; found C 69.68, H 10.35%.

***cis*-2-Methylcyclododecyl propionate (*cis*-4b-C).** Mp −50 to −48°C; 1.4700; 95%. ^{1}H NMR: δ 5.0 (1H, m), 2.32 (2H, q, *J*=7.5 Hz), 1.7 (2H, m), 1.4 (18H, m), 1.15 (3H, t, *J*=7.5 Hz), 1.1 (1H, m), 0.89 (3H, d, *J*=6.8 Hz). Analysis: calcd for $C_{16}H_{30}O_2$ (254.42) C 75.54, H 11.89; found C 75.76, H 11.82%.

***trans*-2-Methylcyclododecyl propionate (*trans*-4b-C).** Mp −57 to −55°C; n_D^{20} 1.4703; 73%. ^{1}H NMR: δ 4.97 (1H, symm. m), 2.32 (2H, q, *J*=7.6 Hz), 1.8 (2H, m), 1.4 (18H, m), 1.14 (3H, t, *J*=7.6 Hz), 1.1 (1H, m), 0.87 (3H, d, *J*=6.7 Hz). Analysis: calcd for $C_{16}H_{30}O_2$ (254.42) C 75.54, H 11.89; found C 75.88, H 11.88%.

Cyclododecyl isobutyrate (4c-H). Bp −63 to −61°C; bp 60–63°C/0.3 mmHg; n_D^{20} 1.4668; 80%. ^{1}H NMR*: δ 5.00 (1H, tt, *J*=7.2, 4.7 Hz), 2.51 (1H, sept, *J*=7.0 Hz), 1.7 (2H, m), 1.4 (20H, m), 1.17 (6H, d, *J*=7.0 Hz). Analysis: calcd for $C_{16}H_{30}O_2$ (254.42) C 75.54, H 11.89; found C 75.94, H 12.02%.

***cis*-2-Fluorocyclododecyl isobutyrate (*cis*-4c-C).** Mp −53 to −52°C; n_D^{20} 1.4610; 82%. ^{1}H NMR: δ 5.16 (1H, symm. dm, *J*=26.5 Hz), 4.64 (1H, symm. dm, *J*=48.2 Hz), 2.59 (1H, sept, *J*=7.0 Hz), 1.7 (4H, m), 1.4 (16H, m), 1.18 (6H, d, *J*=7.0 Hz). ^{19}F NMR: δ −128.1 (m). Analysis: calcd for $C_{16}H_{29}FO_2$ (272.41) C 70.55, H 10.73; found C 70.35, H 10.90%.

***trans*-2-Fluorocyclododecyl isobutyrate (*trans*-4c-C).** Mp −54 to −53°C; n_D^{20} 1.4617; 88%. ^{1}H NMR: δ 5.22 (1H, ddt, *J*=12.7, 8.0, 5.0 Hz), 4.65 (1H, ddt, *J*=49.0, 8.0, 4.5 Hz), 2.56 (1H, sept, *J*=7.0 Hz), 1.4 (20H, m), 1.17 (6H, d, *J*=7.0 Hz). ^{19}F NMR: δ −130.7 (dm, *J*=49 Hz). Analysis: calcd for $C_{16}H_{29}FO_2$ (272.41) C 70.55, H 10.73; found C 70.43, H 10.83%.

***cis*-2-Methylcyclododecyl isobutyrate (*cis*-4c-F).** Mp −55 to −53°C; n_D^{20} 1.4672; 92%. ^{1}H NMR: δ 5.0 (1H, m), 2.53 (1H, sept, *J*=7.0 Hz), 1.7 (2H, m), 1.4 (18H, m), 1.17 (3H, d, *J*=7.0 Hz), 1.15 (3H, d, *J*=7.0 Hz), 1.1 (1H, m), 0.89 (3H, d, *J*=6.7 Hz). Analysis: calcd for $C_{17}H_{32}O_2$ (268.44) C 76.06, H 12.02; found C 76.01, H 12.12%.

***trans*-2-Methylcyclododecyl isobutyrate (*trans*-4c-C).** Mp −61 to −59°C; n_D^{20} 1.4682; 59%. ^{1}H NMR: δ 4.95 (1H, symm. m), 2.53 (1H, sept, *J*=7.0 Hz), 1.8 (2H, m), 1.4 (18H, m), 1.16 (6H, d, *J*=7.0 Hz), 1.1 (1H, m), 0.90 (3H, d, *J*=6.9 Hz). Analysis: calcd for $C_{17}H_{32}O_2$ (268.44) C 76.06, H 12.02; found C 76.00, H 12.09%.

Allyl heptanoate (5-H). Employing 2-propen-1-ol (2.0 mL, 1.7 g, 30 mmol); mp −69 to −66°C; bp 88–89°C/12 mmHg, n_D^{20} 1.4308; 68%. ^{1}H NMR: δ 5.92 (1H, ddt, *J*=17.2, 10.4, 5.8 Hz), 5.31 (1H, dq, *J*=17.2, 1.5 Hz), 5.23 (1H, dq, *J*=10.4, 1.5 Hz), 4.58 (2H, dt, *J*=5.8, 1.5 Hz), 2.33 (2H, t, *J*=7.6 Hz), 1.63 (2H, symm. m), 1.3 (6H, m), 0.9 (3H, m). Analysis: calcd for $C_{10}H_{18}O_2$ (170.25) C 70.55, H 10.66; found C 70.40, H 10.47%.

2-Fluoroallyl heptanoate (5-F). Employing 2-fluoro-2-propen-1-ol[14] (2.5 mL, 2.3 g, 30 mmol); mp −59 to −58°C; bp 75–76°C/5 mmHg; n_D^{20} 1.4198; 69%. ^{1}H NMR: δ 4.81 (1H, dd, *J*=15.9, 3.1 Hz), 4.63 (1H, dd, *J*=47.5, 3.1 Hz), 4.60 (2H, d, *J*=14.5 Hz), 2.37 (2H, t, *J*=7.5 Hz), 1.6 (2H, m), 1.3 (6H, m), 0.9 (3H, m). ^{19}F NMR*: δ −42.7 (ddt, *J*=47, 16, 14 Hz). Analysis: calcd for $C_{10}H_{17}FO_2$ (188.24) C 63.81, H 9.10; found C 64.05, H 9.10%.

Methallyl heptanoate (5-C). Employing 2-methyl-2-propen-1-ol (2.5 mL, 2.2 g, 30 mmol); mp −55 to −53°C; bp 79–82°C/5 mmHg; n_D^{20} 1.4321; 59%. ^{1}H NMR: δ 5.0 (2H, m), 4.5 (2H, s, broad), 2.36 (2H, t, *J*=7.5 Hz), 1.8 (3H, m), 1.6 (2H, m), 1.3 (6H, m), 0.9 (3H, m). Analysis: calcd for $C_{11}H_{20}O_2$ (184.28) C 71.70, H 10.94; found C 71.87, H 10.97%.

2-Phenylethyl isobutyrate[25] (6-H). Bp 121–123°C/15 mmHg; n_D^{20} 1.4899.

2-Phenylethyl 2-fluoro-2-methylpropionate (6-F). At 0°C, diethylaminosulfur trifluoride ('DAST'; 0.59 mL, 0.77 g, 4.8 mmol) was added dropwise to a solution of 2-phenylethyl 2-hydroxy-2-methylpropionate[26] (1.2 mL, 1.0 g, 4.8 mmol) in dichloromethane (30 mL). After 1 h at 0°C, the mixture was absorbed on silica gel and a colorless liquid isolated by elution with a 1:10 (v/v) mixture of diethyl ether and hexane; n_D^{20} 1.4773; 78%. ^{1}H NMR: δ 7.3 (5H, m), 4.39 (2H, t, *J*=7.0 Hz), 2.99 (2H, t, *J*=7.0 Hz), 1.52 (6H, d, *J*=21.3 Hz). ^{19}F NMR: δ −82.5 (sept, *J*=21 Hz). Analysis: calcd for $C_{12}H_{15}FO_2$ (210.25) C 68.55, H 7.19; found C 68.86, H 7.41%.

2-Phenylethyl pivalate[27] (6-C). Bp 132–133°C/13 mmHg; n_D^{20} 1.4887.

2-Phenylethyl isovalerate[28] (7-H). Bp 141–143°C/7 mmHg; n_D^{20} 1.4855.

2-Phenylethyl 3-fluoro-3-methylbutyrate (7-F). Zinc was added to a solution of 2-phenylethyl bromo-acetate[29] (11 mL, 15 g, 60 mmol) and acetone (7.3 mL, 5.8 g, 0.10 mol) in benzene (0.10 L). The mixture was heated to reflux for 6 h before being poured into a saturated aqueous solution (0.10 L) of ammonium chloride. The organic layer was decanted, concentrated and absorbed on silica gel. Elution with a 1:5 (v/v) mixture of diethyl ether and pentane followed by distillation gave **2-phenylethyl 3-hydroxy-3-methylbutyrate**; bp 131–132°C/6 mmHg; n_D^{20} 1.4978; 74%. ^{1}H NMR*: δ 7.31 (2H, tt, *J*=7.0, 1.4 Hz), 7.2 (3H, m), 4.35 (2H, t, *J*=7.0 Hz), 3.43 (1H, s), 2.96 (2H, t, *J*=7.0 Hz), 2.47 (2H, s), 1.24 (6H, s). Analysis: calcd for $C_{13}H_{18}O_3$ (222.28) C 70.25, H 8.16; found C 70.36, H 7.99%. This product (3.5 mL, 3.3 g, 15 mmol) was dissolved in dichloromethane (100 mL) and diethylaminosulfur trifluoride ('DAST'; 1.8 mL, 2.4 g, 15 mmol) was added at 0°C. After 15 min, the organic phase was washed with water (3×50 mL) and absorbed on silica gel. Elution with a 1:10 (v/v) mixture of diethyl ether and pentane gave **7-F** as a colorless oil; bp 130–133°C/7 mmHg; n_D^{20} 14787; 65%. ^{1}H NMR: δ 7.3 (2H, m), 7.2 (3H, m), 4.33 (2H, t, *J*=7.0 Hz), 2.95 (2H, t, *J*=7.0 Hz), 2.65 (2H, d, *J*=15.9 Hz), 1.44 (6H, d, *J*=21.8 Hz). ^{19}F NMR*: δ −95 (1F, septt, *J*=22, 16 Hz). Analysis: calcd for $C_{13}H_{17}FO_2$ (224.27) C 69.62, H 7.64; found C 69.45, H 7.70%.

2-Phenylethyl 3,3-dimethylbutyrate (7-C). A mixture of 2-phenylethanol (6.0 mL, 6.1 g, 50 mmol), 3,3-dimethylbutyric acid (6.4 mL, 5.9 g, 50 mmol), toluene-4-sulfonic acid (1.0 g, 5.3 mmol) and toluene (60 mL) was heated to reflux and the water formed removed by means of a Dean–Stark trap. Upon distillation, a colorless liquid was collected; bp 163–165°C/35 mmHg; n_D^{20} 1.4820; 83%. ^{1}H NMR*: δ 7.3 (5H, m), 4.28 (2H, t, 7.0), 2.94 (2H, t, *J*=7.0 Hz), 2.18 (2H, s), 1.00 (9H, s). Analysis: calcd for $C_{14}H_{20}O_2$ (220.31) C 76.33, H 9.15; found C 76.35, H 9.22%.

Ketones

Cyclopentadecanone (8-H).[30] Mp 63°C,[30] 61–62°C,[31] 57–58°C,[32] 65–67°C;[33] bp 120°C/0.3 mmHg,[30] 101–103°C/0.2 mmHg,[31] 110–120°C/0.01 mmHg;[32] nn_D^{20} 1.4637.[20]

2-Fluorocyclopentadecanone (8-F).[15] Mp 54–55°C.

2-Methylcyclopentadecanone (8-C).[34] Mp −56 to −53°C; bp 171–173°C/12 mmHg; n_D^{20} 1.4785.

Sensory evaluation

The symbols *hn* and *fs* mean 'headnote' and 'fonds', respectively. The olfactory properties of the H/F/C-'triads' **1**–**6** and **8** were assessed by experts panels at Givaudan–Roure. The series **7** was withdrawn from the tests since 2-phenylethyl 3-fluoro-3-methylbutyrate (**7-F**) proved to be unstable, eliminating hydrogen fluoride.

1-H *hn*: green, metallic, fatty; *fs*: woody, slightly fruity, carveyl acetate.
1-F *hn* and *fn*: similar to **1-H**.
1-C *hn*: green, fatty, earthy: *fs*: like **1-H**, but very weak.
2-H *hn*: slightly waxy and hot-iron, very weak; *fs*: woody, resinous, incense, campheraceous, slightly musky.
2-F *hn*: strongly waxy and hot-iron; *fs*: woody, rum, fruity, fermented, fusel oil.
2-C *hn*: waxy, hot-iron; *fs*: valeriate, camomile, tagetol.
3aH *hn:* woody, tabacco, plum, fatty, burning candle; *fs*: woody, weak.
cis-**3a-F** *hn:* woody, green beans, bitter, chemical (thiophene); *fs*: woody, green, bitter.
trans-**3a-F** *hn*: putrid, sulfurous (dimethyl sulfide); *fs*: woody, dry, amber.
cis-**3a-C** *hn:* green, aldehydic, resinous; *fs*: woody, tabacco, resinous, burning candle.
trans-**3a-C** *hn*: sewage, sulfurous, fermented, naphthalene, putrefaction; *fs*: metallic, fatty, burned, dry, woody.
3b-H *hn:* fatty, woody, green, beans, chemical, slightly burned; *fs*: tabacco, woody.
cis-**3b-F** *hn*: ethereal, chemical, metallic; *fs*: campheraceous, woody, fatty, slightly burned.
trans-**3b-F** *hn*: woody, chemical, burning candle; *fs*: woody, tabacco, slightly fatty, slightly amber.
cis-**3b-C** *hn:* chemical, green, fatty; *fs*: woody, campheraceous, all in all very weak.
trans-**3b-C** *hn*: slightly woody, campheraceous; *fs*: like *cis*-**3b-C**, in addition metallic.
3c-H *hn*: woody, cedar, ambra, slightly campheraceous.
cis-**3c-F** *hn:* similar to **3c-H**, but greener; *fs*: vetiver.
trans-**3c-F** *hn*: similar to **3c-H**, fruity, fatty; *fs*: like **3c-H**, but less campheraceous.
cis-**3c-C** *hn:* anise, bitter, burning candle; *fs*: musty, mushroom, slightly woody.
trans-**3c-C** *hn*: mushroom, burned, machine oil; *fs*: woody, dusty, slightly musty.
4a-H *hn*: green, fruity, resinous; *fs*: woody, slightly campheraceous, slightly amber, medicinal, dusty.
cis-**4a-F** *hn*: weak; *fs*: slightly woody, slightly campheraceous, vegetable.
trans-**4a-F** woody, slightly campheraceous, slightly amber, earthy, potato cellar.
cis-**4a-C** woody, earthy, spicy, slightly fruity, fatty, oily.
trans-**4a-C** woody, earthy, spicy, fatty, dry.
4b-H woody, earthy.
cis-**4b-F** slightly woody, earthy, rooty, vetiver (*fs*).
trans-**4b-F** *hn*: ethereal, gasoline, woody; *fs*: slightly musky.
cis-**4b-C** woody, campheraceous, earthy, resinous.
trans-**4b-C** like *cis*-**4b-C**, though stronger and bitter.
4c-H *hn*: flowery, medicinal, methyl benzoate; *fs*: woody, mossy, earthy, dusty.
cis-**4c-F** green, rooty, earthy bitter; valeric acid (*hn*).
trans-**4c-F** earthy, dry, buttery; valeric acid (*hn*); all relatively weak.
cis-**4c-C** woody, slightly fruity.
trans-**4c-C** woody, slightly fruity, confiture.
5-H *hn*: fruity, pineapple; *fs*: weak.
5-F *hn*: fruity, pineapple; slightly fatty; *fs*: weak.
5-C *hn*: waxy, fruity, burnt, slightly caramel; *fs*: weak.
6-H *hn*: fruity, rosy, strongly cinnamic; *fs*: weak.
6-F *hn*: fresh rubber, marine; *fs*: burnt rubber.
6-C *hn*: herbaceous, fresh, agrestic.
8-H *hn*: musky, powdery; *fs*: musky, ambrette.
8-F *hn*: musky, campheraceous, woody, relatively weak; *fs*: weak, slightly waxy and musky.
8-C *hn*: resinous; *fs*: musky, ambrette, similar to **8-H** though stronger.

Acknowledgements

This work was financially supported by the *Schweizerische Forschungsgemeinschaft zur Förderung der wissenschaftlichen Forschung* (grant 20-41'887-94), Bern. The authors also wish to express their gratitude to the staff of *Givaudan–Roure*, Dübendorf, for valuable hints and for offering access to sensory evaluations.

References

1. Schlosser, M. In *Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999, pp 613–659.
2. Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99–108.
3. Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials*, 2nd ed.; VCH: Weinheim, 1990.
4. Ohloff, G. *Riechstoffe und Geruchssinn: Die molekulare Welt der Düfte*, Springer: Berlin, 1990.
5. *Perfumes: Art, Science and Technology*, Müller, P. M., Lamparski, D., Eds.; Elsevier: London, 1991.
6. Weyerstahl, P. *J. Prakt. Chem., Chem.-Ztg.* **1994**, *336*, 95–109.
7. Rossiter, K. J. *Chem. Rev.* **1996**, *96*, 3201–3240.
8. Haufe, G.; Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* **1986**, *27*, 4449–4452; Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562–564; Alvernhe, G.; Anker, D.; Laurent, A.; Haufe, G.; Béguin, C. *Tetrahedron* **1988**, *44*, 3551–3563.
9. Haufe, G.; Alvernhe, G.; Laurent, A.; Ernet, T.; Goj, O.; Kröger, S.; Sattler, A. *Org. Synth.* **1999**, *76*, 159–168.
10. Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423–434.
11. Suga, H.; Hamatani, T.; Guggisberg, Y.; Schlosser, M. *Tetrahedron* **1990**, *46*, 4255–4260.
12. Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2855–2863.
13. Suga, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1990**, *46*, 4247–4254.
14. Nagakura, I.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta.* **1980**, *63*, 1257–1263.
15. Michel, D.; Schlosser, M. *Tetrahedron* **1996**, *52*, 2429–2434.
16. Schlosser, M.; Michel, D.; Guo, Z.-W.; Sih, C. J. *Tetrahedron* **1996**, *52*, 8257.

17. Desponds, O.; Franzini, L.; Schlosser, M. *Synthesis* **1997**, 150–152.
18. Michel, D.; Witschard, M.; Schlosser, M. *Liebigs Ann.* **1997**, 517–519.
19. Fouquet, G.; Schlosser, M. *Angew. Chem.* **1974**, *86*, 50–51; *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82–82; s.a.: Schlosser, M.; Bossert, H. *Tetrahedron* **1991**, *47*, 7323–7328.
20. Sicher, J.; Svoboda, M.; Pánková, M.; Závada, J. *Collect. Czech. Chem. Commun.* **1971**, *36*, 3633–3649.
21. Nozaki, H.; Noyori, R. *J. Org. Chem.* **1962**, *30*, 1652–1654.
22. Dutch Patent 6,411,715 (Cl. C07c, filed on 8 October 1993, issued on 9 April 1965; to Haarmann and Reimer); *Chem. Abstr.* **1965**, *63*, 8228b.
23. Kobelt, M.; Barman, P.; Prelog, V.; Ruzicka, L. *Helv. Chim. Acta.* **1949**, *32*, 256–265.
24. Vandenheuvel, W. J. A.; Gardiner, W. L.; Horning, E. C. *J. Chromatogr.* **1965**, *19*, 263–276.
25. Morel, C. *Soap, Perfumery & Cosmetics* **1950**, *23*, 732–734; *Chem. Abstr.* **1950**, *44*, 11037a.
26. Svirbely, W. J.; Eareckson, W. M.; Matsuda, K.; Pickard, H. B.; Solet, I. S.; Tuemmler, W. B. *J. Am. Chem. Soc.* **1949**, *71*, 507–509.
27. Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401–2404.
28. Cheng, Y. S.; von Rudloff, E. *Phytochemistry* **1970**, *9*, 2517–2527.
29. Gertler, S. I.; Feldmesse, J.; Rebois, R. V. *J. Agric. Food Chem.* **1958**, *6*, 843–844; *Chem. Abstr.* **1959**, *53*, 15461d; s.a.: Fuji, K.; Node, M.; Kawabata, T.; Fujimoto, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1043–1048.
30. Ruzicka, L.; Stoll, M.; Schinz, H. *Helv. Chim. Acta.* **1926**, *9*, 249–264.
31. Nozaki, H.; Yamamoto, H.; Mori, T. *Can J. Chem.* **1969**, *47*, 1107–1112.
32. Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta.* **1975**, *58*, 2409–2422.
33. Büchi, G.; Wüest, H. *Helv. Chim. Acta.* **1979**, *62*, 2661–2672.
34. Ruzicka, L.; Schinz, H.; Pfeifer, M. *Helv. Chim. Acta.* **1928**, *11*, 686–700.