Odor Properties of Some Tetrahydropyranyl Ethers

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Several tetrahydropyranyl derivatives of phenols and alcohols have been prepared with the aim of reproducing the floral note of hydroxycitronellal in compounds of easier and cheaper synthesis. Some of the derivatives, particularly those prepared from *cis*-4-methylcyclohexanol and *p*-alkylphenols, present a pleasant floral character as the main note and could be used as detergent additives and in other products of pH above neutrality. This research also represents a contribution toward the understanding of the relationships between molecular structure and the odor of muguet.

INTRODUCTION

The characteristic odor of the lily of the valley (muguet) has been for a long time the subject of great interest and research work (Jellinek, 1960; Cook, 1970). The essential oil contains a great number of compounds, but no one of them reproduces the typical note of muguet (Boelens et al., 1980). Hydroxycitronellal (3,7-dimethyl-7-hydroxyoctanal), which presents an odor close to that of the fresh flowers, has not been found so far in the oil.

Despite the great interest in perfumery for this odor, natural lily of the valley flower oil is not commercially available; therefore, synthetic substitutes have been sought and employed with some success. Hydroxycitronellal has an odor very similar to, although rather weak, that of muguet but presents some disadvantages, due to its poor stability at both low and high pH and to the fact that it has been proved to be an irritant for the skin (Ford et al., 1988). Therefore, other synthetic compounds have been synthesized with the aim of replacing hydroxycitronellal. These include cyclamen aldehyde [2-methyl-3-(*p*-isopropylphenyl)propanal], lilial [2-methyl-3-(*p*-*tert*-butylphenyl)propanal], lyral [4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde], and bourgeonal [3-(*p*-*tert*-butylphenyl)propanal]. All of these compounds contain an aldehyde group, susceptible to oxidation, with consequent odor instability.

Despite the many compounds synthesized, however, the molecular parameters related to the odor of white flowers have not yet been clearly defined. Some results seem to indicate strict requirements in the stereochemistry of the odorants, within certain classes of compounds, such as hydroxyketones and hydroxyaldehydes, derivatives of the *p*-menthane and iridane, where cis/trans isomers or diastereoisomers differ dramatically in their odor potency (Olhoff and Giersch, 1980). However, the presence of two functional groups does not seem requisite for the odor of muguet, as it is well reproduced in the compounds above cited that contain an aldehydic carbonyl as the sole functional group.

To provide more information on the relationships between chemical structure and the odor of white flower, epitomized by the note of muguet, we have synthesized a series of tetrahydropyranyl ethers, bearing some similarity in molecular shape to the structures already known.

The choice of this class of compounds was mainly motivated by their easy synthesis and purification, which could allow a large screening of odorants.

Compounds similar to those synthesized in this work have been described: a Japanese patent (Hasegawa, 1984) reports the odor of tetrahydropyranyl ethers of some alkenols as being sweet, green, or fruity. Another patent (Lamberti and Winnegrad, 1969) indicates tetrahydropyranyl (THP) ethers particularly suitable as additives to

Table I. Odor Description of the Tetrahydropyranyl Ethers Synthesized from the Listed Alcohols

alcohol	no. of C	main odor	secondary note
phenols			
p-methylphenol	7	floral	green
p-ethylphenol	8	floral	green
p-isopropylphenol	9	floral	musk
p-*tert*-butylphenol	10	white flower	musk
cycloalkanols			
cyclohexanol	6	leather	green
cis-4-methylcyclohexanol	7	floral	sweet
trans-4-methylcyclohexanol	7	fruity	green
3,5-dimethylcyclohexanol	8	musk	urinous
cycloheptanol	7	ethereal	green
alkanols			
1-pentanol	5	green	fruity
3-methyl-1-butanol	5	rose	fruity
1-hexanol	6	green	floral
4-methyl-1-pentanol	6	apple	pineapple
2-hexanol (I)	6	bitter almond	walnut
2-hexanol (II)	6	green	walnut
3-hexanol	6	minty	herbaceous
1-heptanol	7	green	fruity
1-octanol	8	aldehydic	citrus
2-octanol (I)	8	ethereal	green
2-octanol (II)	8	green	labdanum
3-octanol	8	fruity	green
1-nonanol	9	aldehydic	waxy
2-nonanol (I)	9	fruity	green
2-nonanol (II)	9	green	herbaceous
3-nonanol (I)	9	fruity	green
3-nonanol (II)	9	floral	anise
2-decanol (I)	10	green	mushroom
2-decanol (II)	10	floral	green
alkenols			
2-buten-1-ol	4	green	camomile
2-hexen-1-ol	6	green	fruity
3-hexen-1-ol	6	green	fruity
4-hexen-1-ol	6	green	metallic
5-hexen-1-ol	6	green	floral
1-hepten-3-ol (I)	7	green	parsley
1-hepten-3-ol (II)	7	green	celery
1-octen-3-ol	8	mushroom	green
10-undecen-1-ol	11	waxy	aldehydic
alkynol			
2-methyl-3-butyn-2-ol	5	fecal	camphor

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Table II. Spectral Data of the Tetrahydropyranyl Ethers Synthesized from the Listed Alcohols

alcohol	^{1}H NMR (100 MHz, $CDCl_3$), δ	MS (15 eV), *m/e* (% relative intensity)
p-ethylphenol	1.20 (t, 3 H), 1.51–2.10 (m, 6 H), 2.59 (q, 2 H), 3.59 (m, 1 H), 3.93 (m, 1 H), 5.38 (t, 1 H), 6.97 (d, 2 H), 7.10 (d, 2 H)	*206* (*19*), 122 (100), 85 (19)
p-isopropylphenol	1.22 (d, 6 H), 1.51–2.11 (m, 6 H), 2.85 (m, 1 H), 3.60 (m, 1 H), 3.93 (m, 1 H), 5.38 (t, 1 H), 6.98 (d, 2 H), 7.13 (d, 2 H)	*220* (*32*), 136 (100), 121 (38), 85 (42)
cis-4-methylcyclohexanol	0.85 (d, 3 H), 1.1–1.95 (m, 15 H), 3.43 (m, 1 H), 3.71–3.95 (m, 2 H), 4.60 (dd, 1 H)	*198* (*34*), 155 (38), 103 (88), 97 (98), 85 (100), 56 (47)
trans-4-methylcyclohexanol	0.83 (d, 3 H), 0.88–2.05 (m, 15 H), 3.35–3.60 (m, 2 H), 3.87 (m, 1 H), 4.67 (m, 1 H)	*198* (*18*), 155 (15), 103 (36), 97 (98), 85 (100), 56 (11)
cycloheptanol	1.25–2 (m, 18 H), 3.45 (m, 1 H), 3.77 (m, 1 H), 3.88 (m, 1 H), 4.63 (dd, 1 H)	*198* (*18*), 180 (4), 155 (4), 101 (57), 97 (70), 85 (100), 56 (31)
1-heptanol	0.75 (t, 3 H), 1.07–1.28 (br p, 8 H), 1.3–1.75 (m, 8 H), 3.20 (m, 1 H), 3.32 (m, 1 H), 3.58 (m, 1 H), 3.70 (m, 1 H), 4.43 (dd, 1 H)	199 (8), 127 (4), 115 (6), 101 (8), 85 (100), 57 (9)
3-nonanol (I)	0.8–0.95 (m, 6 H), 1.2–1.4 (bs, 8 H), 1.4–1.9 (m, 10 H), 3.48 (m, 1 H), 3.57 (m, 1 H), 3.93 (m, 1 H), 4.66 (dd, 1 H)	229 (7), 199 (20), 170 (4), 143 (32), 126 (14), 101 (67), 85 (100), 71 (10), 56 (26)
3-nonanol (II)	0.8–1.1 (m, 6 H), 1.17–1.4 (m, 8 H), 1.4–1.9 (m, 10 H), 3.48 (m, 1 H), 3.55 (m, 1 H), 3.92 (m, 1 H), 4.66 (dd, 1 H)	229 (5), 199 (25), 170 (8), 143 (3), 126 (5), 101 (13), 85 (100), 56 (7)
2-decanol (I)	0.87 (t, 3 H), 1.10 (d, 3 H), 1.2–1.9 (m, 20 H), 3.49 (m, 1 H), 3.77 (m, 1 H), 3.89 (m, 1 H), 4.71 (dd, 1 H)	243 (3), 198 (3), 140 (7), 129 (33), 101 (39), 85 (100), 71 (6), 56 (14)
2-decanol (II)	0.87 (t, 3 H), 1.23 (d, 3 H), 1.2–1.35 (b, 12 H), 1.43–1.90 (m, 8 H), 3.48 (m, 1 H), 3.71 (m, 1 H), 3.92 (m, 1 H), 4.62 (dd, 1 H)	243 (4), 198 (5), 140 (12), 129 (60), 101 (57), 85 (100), 71 (7), 56 (14)
2-hexen-1-ol	0.87 (t, 3 H), 1.37 (m, 2 H), 1.4–1.9 (m, 6 H), 1.98 (dd, 2 H), 3.47 (m, 1 H), 3.85 (m, 1 H), 3.90 (dd, 1 H), 4.15 (dd, 1 H), 4.61 (dd, 1 H), 5.45–5.77 (m, 2 H)	185 (2), 141 (5), 123 (6), 109 (10), 101 (17), 98 (9), 85 (100), 83 (54), 56 (5)
1-hepten-3-ol (I)	0.75–0.95 (m, 3 H), 1.2–1.9 (m, 12 H), 3.45 (m, 1 H), 3.86 (m, 1 H), 4.05 (m, 1 H), 4.63 (dd, 1 H), 5.07–5.2 (m, 2 H), 5.5–5.7 (m, 1 H)	199 (3), 152 (4), 141 (18), 123 (7), 110 (8), 101 (14), 97 (55), 85 (100), 55 (13)
1-hepten-3-ol (II)	0.75–0.95 (m, 3 H), 1.15–1.9 (m, 12 H), 3.45 (m, 1 H), 3.90 (m, 1 H), 4.10 (m, 1 H), 4.7 (dd, 1 H), 5.03–5.27 (m, 2 H), 5.77–5.96 (m, 1 H)	199 (2), 152 (4), 141 (18), 123 (4), 110 (7), 97 (35), 85 (100), 55 (6)

improve the odor of detergents, because of their stability in alkaline medium.

We hope that the information obtained in this study could help in the design of molecules belonging to different chemical classes but having similar odor.

MATERIALS AND METHODS

Synthesis of Compounds. All of the compounds have been prepared by direct derivatization of the alcohols with dihydropyran in the presence of a catalytic amount of acid (hydrochloric or *p*-toluenesulfonic), according to the routine method of alcohol protection. In some cases a modified procedure has been employed, as described by Bongini et al. (1979): accordingly, a mixture of the alcohol and dihydropyran was chromatographed through a column of silica gel and Amberlyst H-15, eluting with petroleum ether; the derivatization and the purification are thus accomplished in one step. When a phenol was used as starting compound, purification of the derivative was easily performed by simple washing with alkaline water solution.

Particular care was taken in establishing the purity of the final compounds, as in several cases the starting alcohol or phenol exhibits a strong and disagreeable odor. Therefore, after the purity was assured by GLC on a 25-m OV-1 capillary column, a smell test was performed to identify traces of the starting alcohol in case they were still present.

Separation of diastereoisomeric mixtures was done by column chromatography on silica gel, using petroleum ether with 1% diethyl ether as the eluent.

Odor Evaluation. Odor description for all of the synthesized compounds was performed using undiluted samples of the odorants. Odor profiles for selected compounds were determined on 10% solutions in diethyl phthalate. In both cases a panel of 10 expert perfumers was employed; the method used for odor profiles involved a preliminary specification of the appropriate descriptors, followed by quantitative estimate for each of them.

RESULTS AND DISCUSSION

Table I lists the compounds synthesized with their odor description. The number of carbon atoms for the corresponding alcohol ranges from 4 to 11, most between 6 and 9. Only 7 of the 38 compounds exhibit a floral odor as the main character; two more are green with a floral secondary note. Among the other compounds, green and fruity are the most represented odors; only one had a definite unpleasant odor, probably due to the presence of a triple bond.

The floral note is present in all of the aromatic compounds synthesized, the corresponding phenols having 7–10 carbon atoms. The derivative prepared from *cis*-4-methylcyclohexanol also exhibited a floral note, being similar in molecular shape to the *p*-methylphenol THP. Among the open-chain saturated alcohols, only two derivatives were found to have a floral character, namely one of the two diastereoisomers obtained from 3-nonanol and one from 2-decanol, although associated with secondary notes, that modify their overall impact.

None of the unsaturated compounds had a floral odor, most of them being "green"; this result, however, cannot be correlated with the presence of a double bond until the series is completed with derivatives of 9- and 10-carbon alcohols: in the saturated series, in fact, the floral odor was only present in molecules of this size.

Table II reports the spectral data relative to those compounds that, to the best of our knowledge, have not been previously found in the literature. Mass spectra run at the standard value of 70 eV, and not reported, showed extensive fragmentation, which prevented detection of the molecular ions. Therefore, the mass spectra of Table II were run at the ionization potential of 15 eV. In such conditions, the molecular ions are present in most of the spectra, although their abundance is not high. With some compounds, the molecular ions have been found at one mass unit above or below the expected molecular weight, indicating a likely capture or loss of an hydrogen atom. The base peak occurs in all but one of the spectra at mass 85, corresponding to the tetrahydropyranyl radical.

In Figure 1 the odor profiles for the best floral odorants are compared with that of hydroxycitronellal; lilial has been included as a reference.

The THP of *cis*-4-methylcyclohexanol proved to be the closest in odor quality to hydroxycitronellal but much more intense. It was also the best candidate for reproducing the odor of muguet in perfume formulations. Next was rated the *p*-*tert*-butylphenol THP and then the three other aromatic compounds; these four odorants, although pre-

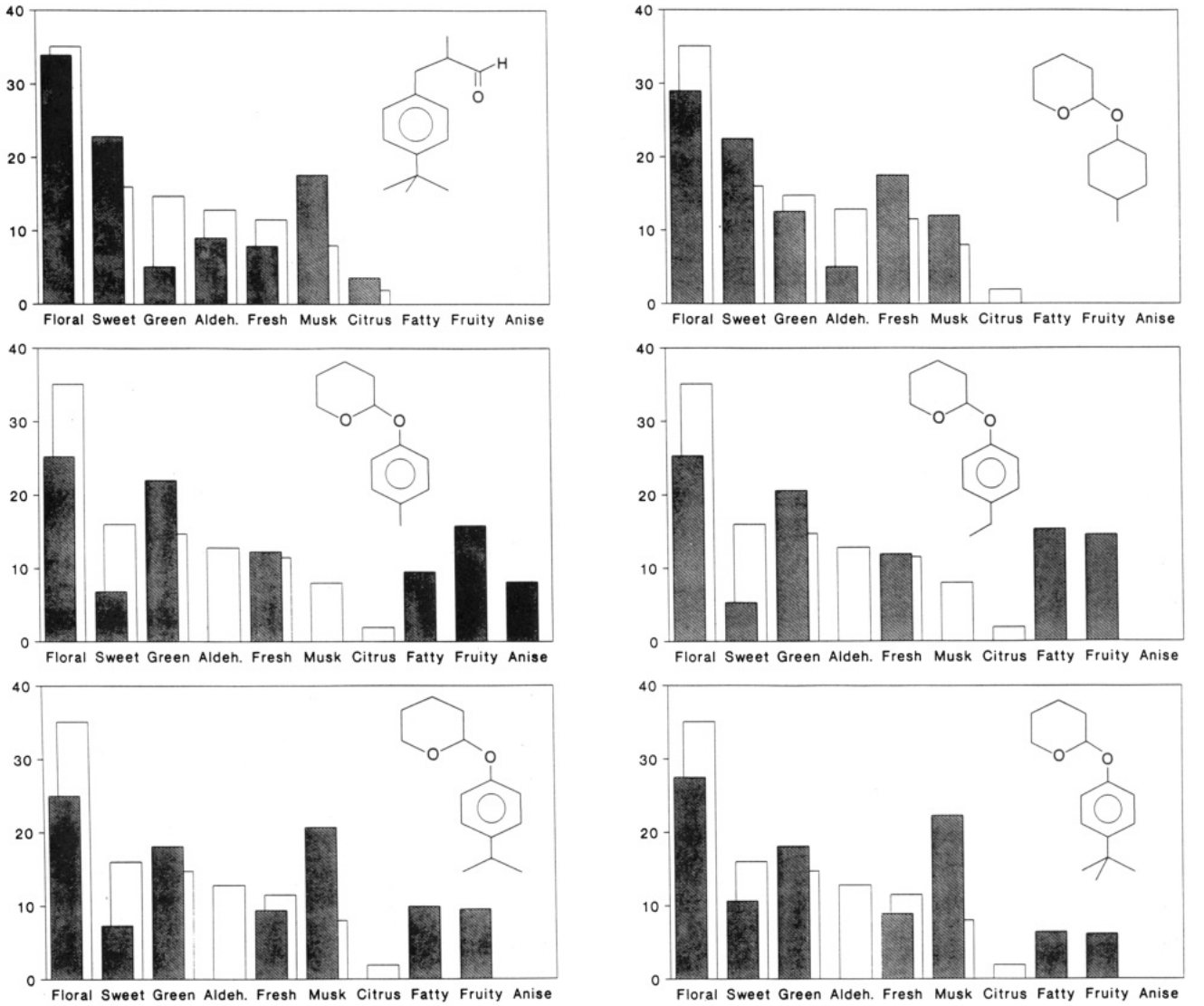

Figure 1. Odor profiles of selected odorants (structures shown) compared with that of hydroxycitronellal (blank bars in the background). The intensities of the different notes are indicated as percent of total odor.

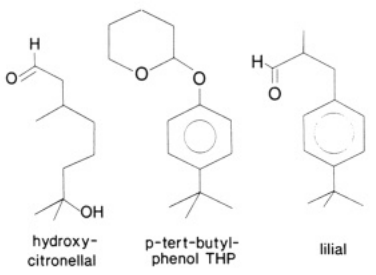

Figure 2. Comparison between the structures of hydroxycitronellal, tetrahydropyranyl ether of *p-tert*-butylphenol, and lilial.

senting an intense floral note associated in some of them with a pleasant musky character, also exhibit less desirable components, such as fruity and fatty. A comparison of the molecular profiles of the *p*-isopropylphenol THP and the *p-tert*-butylphenol THP with cyclamen aldehyde and lilial, respectively, indicates some similarity in shape, particularly in the hydrocarbon part of the molecules, that well supports the observed odor similarity.

From these results, we could speculate that the molecule of hydroxycitronellal, which belongs to the same odor class, might adopt, when interacting with olfactory receptors, a conformation, as in Figure 2, similar to the structures of lilial and the *p-tert*-butylphenol derivative. It also appears that the hydroxyl group in the hydroxycitronellal molecule is not strictly essential as a functional group, only providing the necessary bulkiness at that end of the molecule; it could also prevent the molecule from folding back on itself in aqueous medium, because of its hydrophilicity. Such a problem does not exist with the other aromatic molecules because of their relatively rigid structures.

It is not difficult to explain the floral odor of 4-methylcyclohexanol THP on the basis of its similarity with the *p*-methylphenol derivative, although the different odors showed by the two geometrical isomers are not easily accounted for. The two other compounds showing a floral note, namely 3-nonanol THP and 2-decanol THP, could easily adopt a conformation with the hydrocarbon chain folded in such a way as to mimic the shape of the aromatic floral odorants. However, then we would expect to find the same odor also in other compounds, such as the derivatives of 2-octanol and 2-nonanol, whose profiles are similar to those of the 3-nonanol and 2-decanol derivatives, respectively.

These observations could indicate that the olfactory receptor for floral odor has very strict requirements, so that one carbon atom less or in a different position could prevent a good fitting. Alternatively, we could assume that there is no specific receptor for floral odors, which would result from the combination of several elementary

sensations; this hypothesis is in agreement with the low potency of all floral odorants so far described.

In any case, the small number of floral odorants reported in the literature, particularly among flexible molecules, could be explained by the fact that these structures can also fit other receptors, generating notes, like green or fruity, that could mask a weak floral odor, if present.

We can thus summarize the results of the present work: (a) New compounds, with a white flower odor, have been prepared, comparable in quality to odorants like hydroxycitronellal and lilial but more potent in strength; they are very easy to prepare and can be used in perfume formulations, provided the pH of the medium is kept above neutrality to prevent their hydrolysis. (b) The information derived from this structure/odor study can be used for designing new compounds with similar odor and different chemical behavior. For instance, the oxygen external to the ring seems not essential for the odor, as can be argued from a comparison between the tetrahydropyranyl ethers and structures like cyclamen aldehyde and lilial; therefore, we expect that by substituting that oxygen with a carbon atom we could increase the stability of the molecules without greatly modifying their odors.

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Registry No. *p*-Methylphenol, 106-44-5; *p*-ethylphenol, 123-07-9; *p*-isopropylphenol, 99-89-8; *p-tert*-butylphenol, 98-54-4; cyclohexanol, 108-93-0; *cis*-4-methylcyclohexanol, 7731-28-4; *trans*-4-methylcyclohexanol, 7731-29-5; 3,5-dimethylcyclohexanol, 5441-52-1; cycloheptanol, 502-41-0; 1-pentanol, 71-41-0; 3-methyl-1-butanol, 123-51-3; 1-hexanol, 111-27-3; 4-methyl-1-pentanol, 626-89-1; 2-hexanol, 626-93-7; 3-hexanol, 623-37-0; 1-heptanol, 111-70-6; 1-octanol, 111-87-5; 2-octanol, 123-96-6; 3-octanol, 589-98-0; 1-nonanol, 143-08-8; 2-nonanol, 628-99-9; 3-nonanol, 624-51-1; 2-decanol, 1120-06-5; 2-buten-1-ol, 6117-91-5; 2-hexen-1-ol, 2305-21-7; 3-hexen-1-ol, 544-12-7; 4-hexen-1-ol, 6126-50-7; 5-hexen-1-ol, 821-41-0; 1-hepten-3-ol, 4938-52-7; 1-octen-3-ol, 3391-86-4; 10-undecen-1-ol, 112-43-6; 2-methyl-3-butyn-2-ol, 115-19-5; *p*-methylphenol THP, 13481-09-9; *p*-ethylphenol THP, 140226-52-4; *p*-isopropylphenol THP, 140226-53-5; *p-tert*-butylphenol THP, 17356-00-2; cyclohexanol THP, 709-83-1; *cis*-4-methylcyclohexanol THP, 140226-54-6; *trans*-4-methylcyclohexanol THP, 140226-55-7; 3,5-dimethylcyclohexanol THP, 140226-56-8; cycloheptanol THP, 140226-57-9; 1-pentanol THP, 32767-70-7; 3-methyl-1-butanol THP, 60564-80-9; 1-hexanol THP, 1927-63-5; 4-methyl-1-pentanol THP, 140226-58-0; 2-hexanol THP (isomer 1), 140226-59-1; 2-hexanol THP (isomer 2), 140226-60-4; 3-hexanol THP, 28659-10-1; 1-heptanol THP, 132336-04-0; 1-octanol THP, 70690-19-6; 2-octanol THP (isomer 1), 140387-66-2; 2-octanol THP (isomer 2), 140387-67-3; 3-octanol THP, 140387-68-4; 1-nonanol THP, 88773-83-5; 2-nonanol THP (isomer 1), 140226-61-5; 2-nonanol THP (isomer 2), 140226-62-6; 3-nonanol THP (isomer 1), 140226-63-7; 3-nonanol THP (isomer 2), 140226-64-8; 2-decanol THP (isomer 1), 140226-65-9; 2-decanol THP (isomer 2), 140226-66-0; 2-buten-1-ol THP, 4203-40-1; 2-hexen-1-ol THP, 140226-67-1; 3-hexen-1-ol THP, 72727-72-1; 4-hexen-1-ol THP, 140226-68-2; 5-hexen-1-ol THP, 77022-44-7; 1-hepten-3-ol THP (isomer 1), 140226-69-3; 1-hepten-3-ol THP (isomer 2), 140226-70-6; 1-octen-3-ol THP, 50999-80-9; 10-undecen-1-ol THP, 76063-02-0; 2-methyl-3-butyn-2-ol THP, 27943-46-0; hydroxycitronellal, 107-75-5.