Tertiary Alcohols with Earthy Odor

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A series of highly hindered tertiary alcohols was synthesized to define the minimun structural requirements for earthy smelling molecules. Some of the compounds described are endowed with a strong pure earthy note, similar to the odor of geosmin. Medium size (10−14 major atoms) and the presence of highly branched alkyl radicals bound to the carbinol center seem to represent the molecular parameters best related to the earthy odor. A cyclic system is not an essential requirement for this type of odor. Several among the best earthy smelling compounds described in this work are not asymmetric molecules; this result confirms previous reports indicating that the earthy odor is not related to the chirality of the molecules.

Keywords: *Olfaction; earthy odor; geosmin; tertiary alcohols*

INTRODUCTION

An earthy note is traditionally associated with the odor of damp soil, which is produced by several microorganisms. The natural molecule responsible for such odor is geosmin (**1**; Figure 1), *trans*-1,10-dimethyl-9-*cis*-decalol; Gerber and Lechevalier, 1965). Other naturally occurring compounds, such as 2-methylisoborneol and 2,4,6-trichloroanisole, also exhibit the earthy character together with other notes. The presence of geosmin and 2-methylisoborneol in foodstuff and particularly in drinking water gives an objectionable flavor and has been the cause of much concern (Maga, 1987), because of their extremely low olfactory threshold (Persson, 1992). However, the same earthy note is highly appreciated in perfumery, because it gives a distinct character to formulations that include geosmin as one of the minor components. This fact has stimulated chemical research toward both easy and economical syntheses of geosmin and design of earthy odorants of simpler structure.

The occurrence of three chiral centers in the molecule of geosmin has caused difficulties in designing a synthetic method that could be applied industrially. In addition, the presence of other isomers of 1,10-dimethyl-9-decalol, particularly those with *cis*-fused rings, adds strong undesired notes, such as camphor and moldy (Ohloff, 1971; Polak et al., 1978). In fact, it has been reported that only one of its four enantiomeric pairs is endowed with a pure earthy odor. The two enantiomers of geosmin, however, differ only in their odor intensity, not in their quality (Polak and Provasi, 1992). The preparation of geosmin was described for the first time soon after its discovery in nature (Marshall and Hochstetler, 1968). More recently, simpler and elegant synthetic routes have been reported that make use of stereospecific reactions (Gosselin et al., 1989) and make the two enantiomers readily available (Revial, 1989). With an alternative approach, new molecules have been designed and synthesized that can both reproduce the odor of geosmin and be prepared easily and economically. The first successful example of such a strategy is the synthesis of 2-ethylfenchol (Polak et al., 1978), which proved to be a good substitute for geosmin even without separating the α and β isomers that are produced in the alkylation of fenchone. Pure stereo-

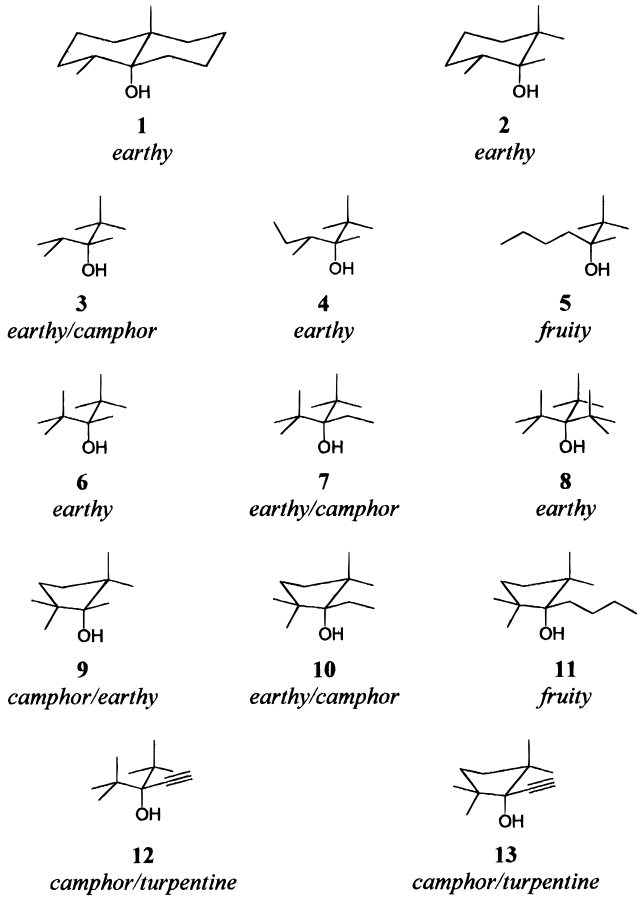

Figure 1. Structures and odors of the compounds described in this work. Geosmin (**1**) is the reference natural odorant for the "earthy" character. The tetramethylcyclohexanol (**2**) is a representative example of our first series of synthetic earthy odorants (Finato et al., 1992). Compounds **12** and **13** were synthetic intermediates for the synthesis of odorants **7** and **10**, respectively, and do not exhibit the earthy character. The odor was evaluated with 10 ppm aqueous solutions. At much higher concentrations and in the undiluted compounds, a camphor note becomes noticeable in all the derivatives.

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isomers of fenchone have since been synthesized by stereoselective syntheses, but their olfactory properties have not been described (Gosselin et al., 1990). The earthy odor has also been reported in some trimethylcyclohexenols (Gebauer et al., 1986; Weyerstahl et al., 1989) and tetramethylcycloheptanols (Matsumoto et al., 1986) in association with other notes.

In our previous paper (Finato et al., 1992) we described the synthesis of substituted cyclohexanols with strong earthy character; the derivatives that best reproduced the typical odor of geosmin were 1-alkyl-2,2,6-trimethylcyclohexanols, with the alkyl radical being methyl (**2**, Figure 1), ethyl, or propyl. The structures of these compounds are theoretically derivable from that of geosmin by opening one of the rings of the decalin system. In this paper we report the preparation of open-chain earthy odorants, theoretically derivable from geosmin by opening both cyclohexane rings. Some of the derivatives, which are highly hindered tertiary alcohols, present a pure and intense earthy note and could be used as cheaper substitutes of geosmin.

MATERIALS AND METHODS

Synthesis of Compounds. Most of the tertiary alcohols described in this work, whose structures (**3**−**13**) are reported in Figure 1, were prepared in a single step by reaction of the appropriate ketone with commercially available methyllithium (**3**, **4**, **6**, and **9**), *n*-butyllithium (**5** and **11**), *sec*-butyllithium (**4**), or *tert*-butyllithium (Lomas and Thome, 1982, and references cited therein). In the cases of the ethyl derivatives **7** and **10**, much better yields were obtained by a two-step route involving the addition of lithium acetylide to the appropriate ketone, followed by catalytic hydrogenation of the intermediate alkynols **12** and **13** so obtained. All the ketones were also commercially available with the exception of the precursor 2,2,5,5-tetramethylcyclopentanone, which was synthesized by condensation of cyclopentanone with methyl iodide in the presence of solid potassium hydroxide in dimethyl sulfoxide (Langhals and Langhals, 1990). All the compounds were purified either by double distillation under reduced pressure or by chromatography followed by distillation. Their purity, as checked by gas−liquid chromatography (GLC) on a 25-m OV-1 capillary column, was always >99.5%. In the case of derivative **4** only, two close gas chromatographic peaks of about the same intensity revealed the presence of the two expected diastereoisomers. These diastereoisomers were not separated in the samples used for NMR spectra and for odor evaluation, but individual mass spectra were obtained from the GLC peaks, confirming their close structural relationship. Mass spectra were recorded on a Fisons Instruments model Trio 2000 (with an ionization potential 70 eV) after gas chromatographic separation on a 25-m OV-1 capillary column. The ^{1}H (200 Mhz) and ^{13}C (50 Mhz) NMR spectra were recorded on a Brucher AC 200 in $CDCl_3$.

Odor Evaluation. Odor quality in aqueous solutions (10 ppm) was informally evaluated by a panel of 10 subjects, including the authors and part of the laboratory personnel. A pure sample of racemic geosmin was used as a reference for the earthy note.

RESULTS AND DISCUSSION

Synthesis of Compounds. The odorants prepared and their spectroscopic characterization are listed in Table 1. Most of the odorants are known compounds, but neither their spectra nor their olfactory properties have been reported. The mass spectra were in agreement with the expected structures, although the intensity of the molecular ion was always below the detection limit, which is not surprising in these highly branched compounds where loss of a small radical group can easily occur. In fact, intense peaks are present at *m*/*e* values corresponding to loss of groups such as methyl, *tert*-butyl, or water. In the spectrum of the cyclopentanol **13**, the intense peak at *m*/*e* 142 reveals the loss of ethylene with rearrangement from the molecular ion.

Odor Properties. The odor qualities determined for the compounds synthesized are reported in Figure 1, together with their chemical structures. The structure of geosmin (**1**) and that of a representative example of our previously synthesized earthy smelling cyclohexanols (**2**) have been included for easy reference and comparison. The first series of compounds (**3**−**8**) includes tertiary alcohols, which are generally highly branched and, in most cases, contain a *tert*-butyl radical. The earthy note is present in several of these derivatives and seems to be related to the degree of branching at carbons next to the hydroxy group. In fact, the earthy note is not present in **5** and in other derivatives bearing linear alkyl groups (prepared as part of this study, but not included in the present report). The typical earthy odor, instead, represents the main character in the three di-*tert*-butylcarbinols (**6**−**8**) as well as in derivatives **3** and **4**, which contain a *tert*-butyl group, together with another α-branched short chain (isopropyl or *sec*-butyl) next to the hydroxy group. Its seems therefore that the presence of bulky hydrophobic moieties in the proximity of the hydroxy group is at least one of the structural elements correlated with the earthy odor. This conclusion is verified with geosmin, 2-ethylfenchol, and with the polyalkylated cyclohexanols previously described (Finato et al., 1992). The reduced accessibility of the hydroxy group can result in more selective binding to only specific receptor proteins, preventing interactions with receptors for odorants of similar size and shape, such as camphor, minty, or fruity. This idea has been extensively investigated with several polycyclic compounds, where a good correlation has been verified between the ambergris odor and the accessibility of the oxygen atom, as measured by the degree of hydration (Winter, 1989).

The design of additional earthy odorants was suggested by the results of our previous study (Finato et al., 1992) that showed that replacement of one of the two cyclohexane rings in the molecule of geosmin with two short aliphatic chains preserved the typical earthy odor. The compounds described in this study can be similarly related to the earthy smelling cyclohexanols by replacement of the cyclohexane ring with two short-branched aliphatic chains.

The finding then that the di-*tert*-butylcarbinol derivatives **6**−**8** exhibited good earthy notes, close to that of geosmin, suggested the synthesis of a second series of tertiary alcohols, namely derivatives of cyclopentanol. These derivatives can be thought of as structurally related to the aforementioned carbinols by joining carbons 1 and 5 with a single bond. The odors of these compounds, therefore, were not expected to be much different from those of their corresponding open-chain analogs. The results confirmed the presence of the earthy character in the cyclic analogs (**9**, **10**) of **6** and **7**, but their odor is accompained by camphor notes that are more pronounced than those in their open-chain analogs. This result may indicate an easier fitting to a receptor site for camphor odors, not necessarily a weaker interaction with the "earthy" receptor protein. Again, the accessibility of the hydroxy group can explain these observations; in fact, the alcohol group is more exposed in the cyclic derivatives than in their corre-

Table 1. Synthesis and Spectroscopic Characterization of Tertiary Alcohols (Serial Numbers in the First Column Refer to Figure 1)

compound, MW, (#)	mass spectrum, *m*/*e* (rel intensity)	^{1}H NMR (200 MHz, $CDCl_3$), δ	^{13}C NMR
2,2,3,4-tetramethyl-3-pentanol, 144 (**3**)	55 (20), 57 (20), 59 (24), 69 (39), 71 (13), 83 (34), 87 (100), 101 (71), 129 (2)	0.87−0.97 (m, 15H); 1.00 (s, 3H); 2.02 (heptuplet, J = 7 Hz, 1H)	17.71, 19.95, 21.38, 27.08, 34.69, 39.55, 78.58
2,2,3,4-tetramethyl-3-hexanol, 158 (**4**)	(**I**): 55 (40), 57 (64), 59 (53), 69 (19), 83 (77), 85 (18), 101 (100), 102 (19), 143 (4) (**II**): 55 (30), 57 (56), 59 (33), 69 (12), 83 (52), 85 (12), 101 (100), 102 (10), 143 (3)	−[a]	−[a]
2,2,3-trimethyl-3-heptanol, 158 (**5**)	55 (33), 57 (25), 59 (28), 69 (11), 71 (11), 83 (49), 85 (12), 101 (100), 102 (11), 143 (6)	0.85−0.95 (m, 12H); 1.03 (s, 3H); 1.20−1.50 (m, 6H)	14.95, 21.45, 24.3, 26.02, 26.87, 27.43, 29.35, 36.49, 38.74, 77.00
2,2,3,4,4-pentamethyl-3-pentanol, 158 (**6**)	55 (23), 57 (43), 59 (14), 83 (54), 87 (18), 101 (100), 102 (7)	1.07 (s, 3H, 1 CH_3); 1.16 (s, 18H, 2 $C(CH_3)_3$)	22.19 (1 CH_3); 29.37 (6 CH_3, 2 $C(CH_3)_3$); 41.65 (2 $C(CH_3)_3$); 80.07 (C−OH)
2,2,4,4-tetramethyl-3-ethyl-3-pentanol, 172 (**7**)	53 (37), 55 (31), 56 (45), 57 (88), 58 (64), 59 (87), 60 (49), 67 (26), 69 (80), 70 (10), 71 (94), 72 (24), 73 (39), 79 (11), 81 (10), 83 (52), 85 (57), 87 (19), 88 (26), 97 (93), 98 (20), 99 (34), 101 (88), 115 (100), 116 (50), 143 (31)	0.93 (t, J = 7.6 Hz, 3H, CH_2-CH_3); 1.05 (s, 18H, 2 $C(CH_3)_3$); 1.71 (q, J = 7.6 Hz, 2H, CH_2-CH_3)	11.86 (1 CH_3, CH_2-C_3); 25.94 (1 CH_2, CH_2-CH_3); 29.28 (6 CH_3, 2 $C(CH_3)_3$); 43.19 ($C(CH_3)$)
2,2,4,4-tetramethyl-3-*tert*-butyl-3-pentanol, 200 (**8**)	57 (100), 59 (7), 69 (7), 87 (65), 143 (4)	1.26 (s, 27H, 3 $C(CH_3)_3$)	33.08 (9 CH_3, 3 $C(CH_3)_3$); 45.58 (3 $C(CH_3)_3$)
1,2,2,5,5-pentamethyl-cyclopentanol, 156 (**9**)	55 (10), 57 (17), 69 (19), 70 (15), 71 (45), 82 (10), 83 (11), 85 (53), 86 (100), 87 (19), 123 (30), 138 (16)	0.84 (s, 6H, 2 CH_3); 0.85 (s, 6H, 2 CH_3); 0.87 (s, 3H, CH_3); 1.52−1.26 (m, 4H, 2 CH_2)	19.79 (1C, CH_3); 25.93 (2C, 2 CH_3); 28.48 (2C, 2 CH_3); 38.66 (2C, CH_2); 46.16 (2C, C2 + C5); 84.63 (1C, C1)
1-ethyl-2,2,5,5-tetramethyl-cyclopentanol, 170 (**10**)	53 (34), 55 (73), 56 (62), 57 (76), 58 (14), 59 (29), 67 (41), 68 (49), 69 (74), 70 (87), 71 (78), 72 (89), 73 (74), 81 (21), 82 (16), 85 (30), 86 (32), 95 (29), 109 (100), 110 (24), 111 (70), 124 (94), 142 (62), 143 (6)	0.97 (t, 3H, 1 CH_3, J = 7.66 Hz); 1.01 (s, 6H, 2 CH_3); 1.04 (s, 6H, 2 CH_3); 1.40−1.69 (m, 6 H)	8.85 (CH_3, Et); 25.96 (CH_2, Et); 26.96 (2 CH_3); 27.95 (2 CH_3); 39.64 (2 CH_2) 46.98 (C2 + C_5); 85.04 (C1)
1-butyl-2,2,5,5-tetramethyl-cyclopentanol, 198 (**11**)	55 (12), 57 (31), 67 (10), 68 (49), 69 (27), 71 (37), 85 (56), 86 (47), 127 (18), 128 (100), 129 (11), 141 (5)	0.93 (t, 3H, 1 CH_3); 1.01 (s, 6H, 2 CH_3); 1.04 (s, 6H, 2 CH_3); 1.69−1.21 (m, 10 H)	14.85 (CH_3); 24.53 (CH_2,C_3'); 26.48 (CH_2, C_2'); 26.63 (2 CH_3); 28.01 (2 CH_2); 29.98 (CH_2, C_1'); 33.60 (2 CH_2); 39.59 (2 CH_2); 47.06 (C_2+C_5); 85.18 (C_1)
3-*tert*-butyl-4,4-dimethyl-1-pentyn-3-ol, 168 (**12**)	55 (13), 57 (100), 69 (15), 97 (48), 111 (33), 153 (2)	1.18 (s, 18H, 2 $C(CH_3)_3$); 2.44 (s 1H, C≡CH)	29.20 (6 CH_3, 2 $C(CH_3)_3$); 41.78 (2 $C(CH_3)_3$); 73.97 (C_2); 81.55 (C_3)
1-ethynyl-2,2,5,5-tetramethyl-cyclopentanol, 166 (**13**)	53 (18), 55 (18), 67 (16), 69 (23), 77 (14), 81 (74), 82 (14), 91 (13), 95 (45), 96 (100), 109 (19), 110 (14), 123 (25), 133 (11), 151 (69), 165 (6), 166 (3)	1.10 (s, 6H, 2 CH_3); 1.11 (s, 6H, 2 CH_3); 1.67−1.42 (m, 4H, 2 CH_2); 1.80−1.78 (m, 1H, OH); 2.47 (s, 1H)	25.63 (2C, 2 CH_3); 29.37 (2 C, 2 CH_3); 38.4 (2C, C3 + C4); 47.59 (2C, C2 + C5); 75.63 (1C, C1′); 84.63 (1C, C1); 85.23 (1C, C2′)

[a] Mixture of diastereoisomers: spectra not very informative.

sponding open-chain structures and therefore presents an improved accessibility to other receptors, such as that for camphor odors. Although the differences in molecular shape between **6** and **9** or between **7** and **10** are not great, they are sufficient to produce detectable differences in the corresponding odors.

Among the compounds described, the alcohols **3**, **4, 6**, **7**, and **8** more closely reproduce the typical odor of geosmin. We can therefore conclude that the earthy odor is not necessarily related to the presence of a bicyclic system, not even to cyclic compounds. Instead, the steric hindrance in the proximity of the alcoholic group seems a more reliable parameter, together with size requirements of 9−12 major atoms, for predicting whether the odor of an alcohol is expected to be earthy.

The two acetylenic intermediates **12** and **13** are also shown in Figure 1. Neither of these compounds exhibits the earthy note, despite their structural relationship with strong earthy odorants, but a camphor character together with an intense "turpentine" note. It seems, therefore, that the presence of a triple bond introduces electronic effects with major consequences on the odor quality.

An important fact to notice is how simple molecules, like the open-chain achiral tertiary alcohol **6** described in this work, can reproduce the odor of complex natural substances, such as geosmin. A similar observation was reported in the case of patchouli odorants (Weyerstahl et al., 1989). Another important finding is that the strong earthy charcter of **6** might further support the idea that the chiral recognition of earthy odors by the specific olfactory receptor is quite low. As already mentioned, the two enantiomeric forms of geosmin do not differ in odor quality but only in intensity (Polak and Provasi, 1992). The two enantiomers of α-ambrinol, instead, are reported to exhibit different odors; the quality of the (+) form is indicated as earthy, whereas the (−) form exhibits a different odor that is described as animal like (Naegeli and Wirz-Habersack, 1991). This observation seems to disagree with our observations

about the odor of the two enantiomeric geosmins, suggesting that the earthy odor might be related to the chirality of the molecules. However, the difference in odor quality between the two enantiomeric ambrinols does not necessarily prove that the receptor for earthy odor can discriminate well between enantiomers. In fact, the "animal-like" note, which predominates in the stronger (−) isomer, could mask an earthy note, if present. In the weaker (+) isomer, without the "animal" character, the earthy odor would become more evident. Thus it could be enough to assume that only one of the receptors involved in the perception of these complex odors is strongly asymmetric. Another report (Näf et al., 1981) also indicated an effect of optical isomerism in earthy smelling compounds. Nature-identical (−)-patchoulol exhibits a typical patchouli odor, including earthy and camphor notes, whereas its enantiomer is weaker and not reminiscent of patchouli. These observations are focused on the complex patchouli scent, rather than the earthy note, so more specific information is needed before drawing conclusions on the contribution of asymmetry to the earthy odor. Although olfactory receptors, being proteins, are asymmetric and therefore should be able in principle to discriminate between optical antipodes, the contribution of asymmetry to odor quality in olfaction seems limited to few exceptions rather than being the general rule. The data available in the literature on the earthy odor of enantiomeric pairs do not indicate any strong effect associated with this type of isomerism.

A practical aspect of the results presented here is the possibility of using these simple alcohols as substitutes for geosmin in all the formulations in which an earthy note is desired. Unlike geosmin, synthesis of these simple alcohols does not present problems of stereochemistry and can be easily and economically accomplished in a single step from relatively inexpensive commercial reagents.

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