173. New Aromatic Musk Odorants: Design and Synthesis

by **Charles Fehr***, **José Galindo**, **Rolf Haubrichs**, and **Roland Perret**

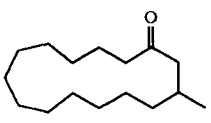
Firmenich SA, Research Laboratories, CH–1211 Geneva 8

Dedicated to Dr. *G. Ohloff* on the occasion of his 65th birthday

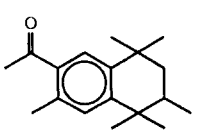
(17.VII.89)

By appropriate structural modification of known musk odorants, new strong musk odorants have been discovered. Incorporation of supplementary CH_3 or CH_2 groups into the basic musk skeleton of type **G** only slightly modifies the global shape of the molecule but leads to densely packed structures of enhanced lipophilicity. For the construction of these highly substituted 1,2,3,4-tetrahydronaphthalenes, new annulation sequences (intramolecular mono- and dialkylations; see *Schemes 3, 6,* and *8*) have been developed and, in certain cases, the design of the target molecules was dictated by both structure-activity-relationship and synthetic considerations (*e.g.* **46** and **47**, *Scheme 6*). This work also presents an original solution to an analytical problem: the distinction between a C_2- and a C_s-symmetrical aromatic hydrocarbon (*viz.* **71** and **72**) by conversion into a [$Cr(CO)_3$arene]complex.

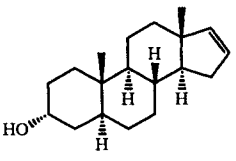
Introduction. – *The Musk Family.* The outstanding place of musk odorants in perfumery derives from their characteristic odor which is referred to as warm, sensual, animal, natural. Interestingly, this typical odor is found in a large variety of very different structural types such as the precious macrocyclic musks (*e.g.* muscone)[1]) [1] [2], the widely applied aromatic musks (*e.g. Tonalid*®)[1]) [2–5] and the small group of steroid musks (*e.g.* androstenol) [1][2]).



muscone



Tonalid®

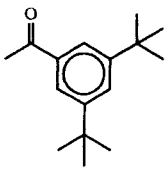


androstenol

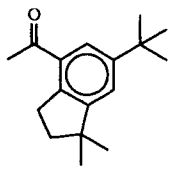
Nitro-Free Aromatic Musks and Structure-Activity Relationships (SAR). The importance of aromatic musks in perfumery is reflected by the impressive number of publications devoted to this subject since the discovery of the first synthetic musk – a nitroaromatic musk – in 1888 [6]. The discovery of the first nitro-free aromatic musk in 1948 [7] led to a real recrudescence of research activities, and today several hundred structurally related compounds of different odor strength are known [2–5]. Some typical examples of known aromatic musk odorants are compounds **1**–**14**.

[1]) Commercial products: muscone *(Firmenich); Tonalid*® *(Polak's Frutal Works).*

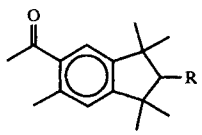
[2]) Although the musk odor is well defined, it should be made clear that there are substantial odor differences between the different musk categories and sometimes even between representatives of the same structural class.



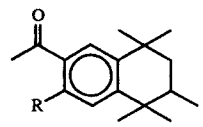
1 medium, not persistent



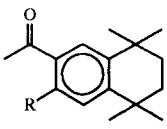
2 strong (*Celestolide*®[a]))



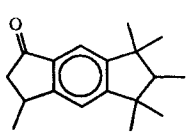
3 R = H, medium
4 R = CH_3, strong (*Phantolid*®[a]))



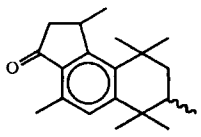
5 R = H, medium, persistent
6 R = CH_3, very strong, persiste (*Tonalid*®[a]))



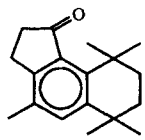
7 R = H, non musk
8 R = CH_3, medium
9 R = Et, strong
10 R = $(CH_3)_2CH$, weak



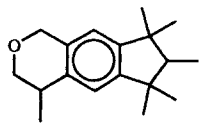
11 strong



12 strong



13 odorless



14 strong (*Galaxolide*

a) See *Footnotes 2* and *5*.

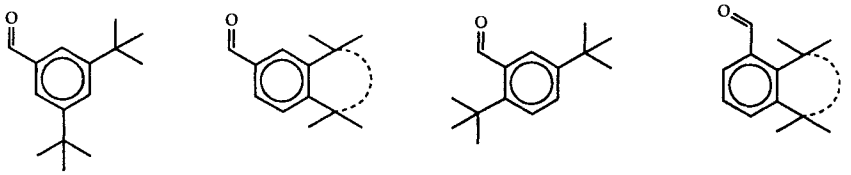
In the context of SAR studies, *Beets* [2] and *Theimer* and *Davies* [5] have established the most important structural requirements for musk odor in the class of nitro-free aromatic musks: *1)* 14 to 20 C-atoms (optimum at C_{16} to C_{18}), *2)* 2 quaternary centers (or at least 1 quaternary and 1 tertiary center) attached at *ortho* or *meta* position to the aromatic system, *3)* an acyl group at the aromatic nucleus[3]), *4)* sterically unhindered position of the functional group, *5)* orientation of the molecular dipole axis, and *6)* closely packed structure.

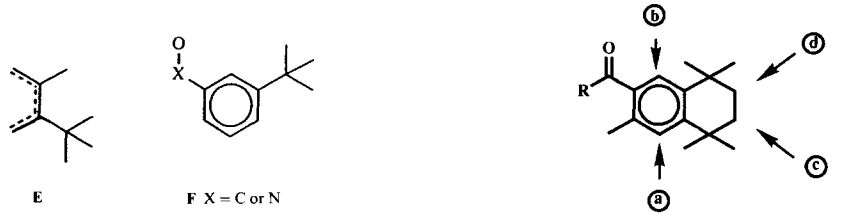
These rules which allow a qualitative prediction on whether or not a compound of a specific structure possesses a musk odor (see **A** and **B**) are of great value because they also contain discriminative, negative molecular descriptors. *E.g.*, a molecule with two quaternary centers *para*-positioned at the aromatic nucleus (contrary to rules *2* and *4*) as shown in type **C** or with an acyl group placed next to a quaternary center (type **D**, contrary to rules *4* and *5*) is expected to be either a non-musk or a weak musk odorant.

The odor *intensity* is strongly dependent on the presence of additional alkyl substituents. *E.g.*, in compounds **7**–**10**, R shields the C=O group and exerts an influence on the conformation of the C=O group. Therefore, both the polarity and the global shape of the molecule are changed. It is well established that a sterically hindered C=O group leads to extinction of the musk odor, but this is not necessarily due to an unfavorable orientation of the C=O group, as both rigid ketones **11** and **12**, with opposite orientations of the C=O group[4]), are strong musks.

With respect to computer-assisted SAR studies, statistical methods have been applied to select the most significant molecular descriptors for musk odor [10]. The goal was to elucidate general structural features encompassing all classes of musks; however, appreciable prediction rates could only be achieved within a well defined subclass, and the most relevant substructure **E** for the classification of musks and non-musks was found

[3]) In certain cases, the acyl group can be replaced by an ether [8] or a nitrile function [9].
[4]) Supposing that the indane/tetralin systems are optimally superimposed.
[5]) Commercial products: *Celestolide*®, *Galaxolide*® *(International Flavors and Fragrances)*; *Phantolid*® *(Polak's Frutal Works)*.





intuitively. In another study [11], a substructure **F**, common to the nitro- and nitro-free aromatic musks has been proposed; however, this substructure does not permit accurate predictions, due to its lack of discrimination.

Our Concept: A Combination of SAR and Synthetic Considerations. The aim of our work was not only to predict whether or not a given substance should be organoleptically active, but to find new strong aromatic musk compounds. We thus carefully examined what structural modifications provoke changes in odor *intensities*[6]), and we became aware of the fact that in addition to known structural requirements [2–5], incorporation of Me groups at positions where the mobility of the C=O group would only be slightly affected, may lead to stronger musks (*cf.* **3** *vs.* **4**, **7**–**9**, **7** *vs.* **8** and **5**, **8** and **5** *vs.* **6**).

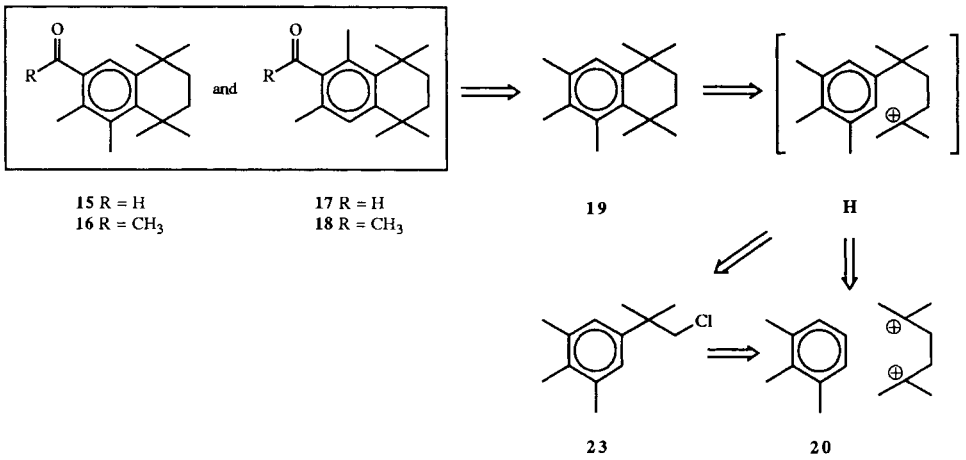
Previously, the importance of high alkyl substitution in a closely packed spherical structure had not been entirely appreciated. One plausible reason why this approach has not been extensively pursued is the synthetic problem of constructing sterically congested molecules [12]. We expected that incorporation of supplementary CH_3 or CH_2 groups into the basic musk skeleton of type **G** at the positions indicated should give access to new strong musks and allow delineation of the structural requirements for the β-carbonyl substituents. These structural modifications should only slightly modify the global shape of the molecule but lead to densely packed structures of enhanced lipophilicity.

Results. – *Polymethylated Tetralins (= 1,2,3,4-Tetrahydronaphthalenes) by a Novel Annulation Sequence.* Our first target molecules were the hitherto unknown tetralins **15**–**18** *(Scheme 1)*. Retrosynthetic analysis of **15**–**18** leads logically to the hydrocarbon **19** and ultimately to 1,2,3-trimethylbenzene **20**.

The preparation of tetralins using dichloride **21** [12] *(Scheme 2)* has been reported to give excellent yields from either toluene or *o*-xylene in the presence of $AlCl_3$, but fails with *m*-xylene where competing intermolecular alkylation predominates. Indeed, when we applied the literature conditions [12] to **20**, the undesired diaryl compound **22** was

[6]) Computer-assisted classification into only two groups (musks and non-musks) is not helpful and can even be misleading, when the file for musks also contains all the compounds which are only weakly active [10] [11].

Scheme 1



15 R = H
16 R = CH_3

17 R = H
18 R = CH_3

19

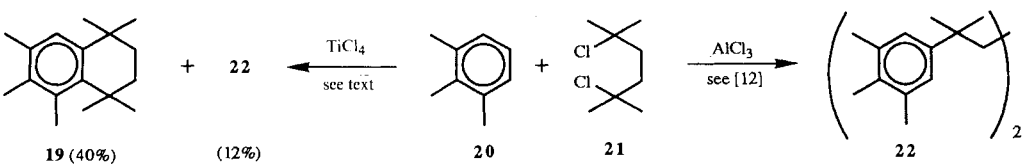
H

23

20

isolated exclusively *(Scheme 2)*. Nevertheless, this selectivity could be reversed by inverting the introduction of reactants. Slow addition of **20** to a solution of **21** and $TiCl_4$ (0.08 mol-equiv.) in 1,2-dichloroethane afforded tetralin **19** in 40% yield together with minor amounts of **22**.

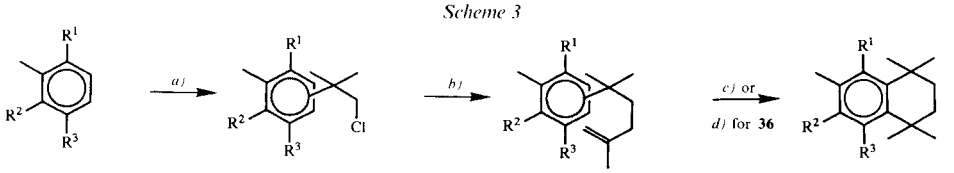
Scheme 2



19 (40%) (12%) **20** **21** **22**

In order to further favor the intramolecular reaction, we next examined the possibility of a stepwise alkylation sequence in which the cyclization is effected on a tetraalkylbenzene intermediate of type **H** *(Scheme 1)*. Alkylation of **20** with methallyl chloride and a catalytic amount of H_2SO_4 [12] [13] afforded chloride **23** as a mixture of regioisomers in 85% yield. Subsequent conversion of **23** to its *Grignard* reagent and coupling with methallyl chloride produced olefin **24** in 90% yield, and H_2SO_4-catalyzed cyclization of

Scheme 3



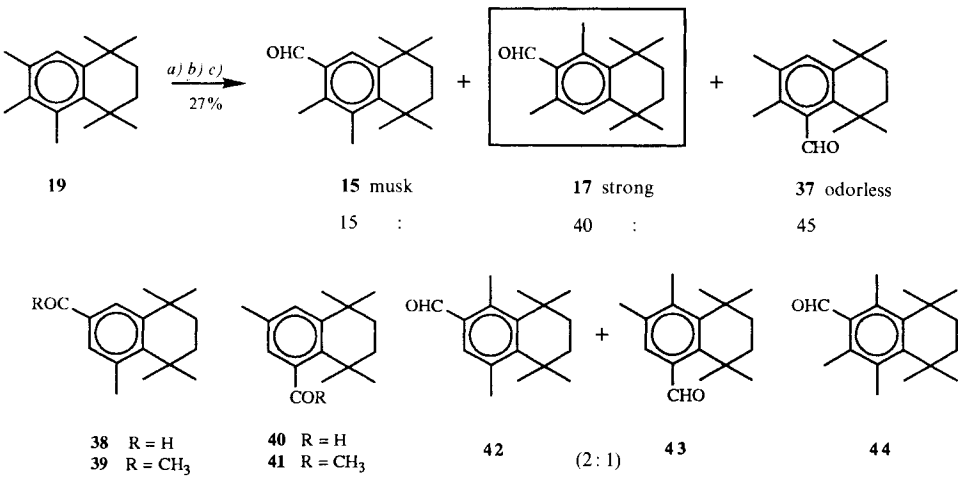
20 R^1 = H, R^2 = R^3 = CH_3 **23** R^1 = H, R^2 = R^3 = CH_3 (85%) **24** R^1 = H, R^2 = R^3 = CH_3 (90%) **19** R^1 = H, R^2 = R^3 = CH_3 (83%)
25 R^1 = R^3 = H, R^2 = CH_3 **26** R^1 = R^3 = H, R^2 = CH_3 (68%) **27** R^1 = R^3 = H, R^2 = CH_3 (67%) **28** R^1 = R^3 = H, R^2 = CH_3 (94%)
29 R^1 = R^2 = H, R^3 = CH_3 **30** R^1 = R^2 = H, R^3 = CH_3 (56%) **31** R^1 = R^2 = H, R^3 = CH_3 (88%) **32** R^1 = R^2 = H, R^3 = CH_3 (93%)
33 R^1 = R^3 = CH_3, R^2 = H **34** R^1 = R^3 = CH_3, R^2 = H (57%) **35** R^1 = R^3 = CH_3, R^2 = H (87%) **36** R^1 = R^3 = CH_3, R^2 = H (77%)

a) CH_2=C(CH_3)CH_2Cl, H_2SO_4 (cat.), 20°. *b)* Mg (1.2 equiv.), THF, then CH_2=C(CH_3)CH_2Cl (1.5 equiv.), 75°. *c)* H_2SO_4 (cat.), petroleum ether (30–50°), 5–10°. *d)* TsOH (cat.), toluene, 110°.

24 afforded **19** in 83% yield *(Scheme 3)*. Application of the same sequence to *o*-xylene (**25**), *m*-xylene (**29**), and 1,2,4-trimethylbenzene (**33**) for the synthesis of the corresponding tetralins **28**, **32**, and **36** (*via* **26** and **27**, **30** and **31**, and **34** and **35**, resp.) further demonstrates the synthetic and industrial value of this new annulation procedure which avoids the use of *Lewis* acids (*cf.* [12] [14–16]).

Hydrocarbon **19** was converted in three conventional steps (bromination with *N*-bromosuccinimide (NBS), hydrolysis [17], and oxidation with pyridinium chlorochromate (PCC), see *Scheme 4*) into a mixture of aldehydes **15**, **17**, and **37** (*ca.* 15:40:45)[7]).

Scheme 4



a) NBS (1.15 equiv.), CCl_4, 77°. *b)* 1-Methylpyrrolidin-2-one, H_2O, 100°. *c)* PCC (1.6 equiv.), CH_2Cl_2, 20°.

Chromatographic separation of this mixture was difficult, and **15** could be isolated only in trace amounts. In addition, formylation of **32** (Cl_2CHOCH_3, $TiCl_4$, CH_2Cl_2 [18]) allowed a selective unequivocal synthesis of **17**. The aldehydes **15** and **17** have a typical strong musk odor, whereas **37** is odorless. Ketone **18**, prepared from **17** *via* a two-step transformation (*a)* MeLi; *b)* PCC, 74%) was found to be odorless.

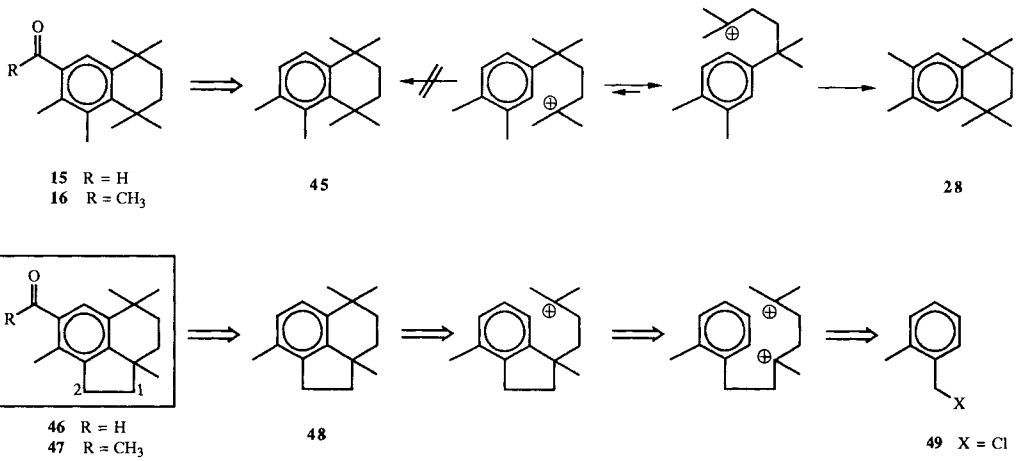
We have also prepared the new but weak musk compounds **38–41** (from **32**), **42**/**43** (from **36**), and **44** (from **36**)[8]).

Synthesis of **46** *and* **47***: Bicyclization* via *Double Intramolecular Alkylation.* The efficient annulation sequence described above allowed ready access to **17**. However, this route proved inappropriate for the synthesis of **15** and **16**, as benzylic oxidation of **19** afforded **15** only in minor amounts *(Scheme 4)*. On the other hand, introduction of a formyl or acetyl group by *Friedel-Crafts* acylation would require precursor **45** *(Scheme 5)* which, for steric reasons, is not accessible from *o*-xylene (**25**) by an intramolecular alkylation sequence, tetralin **28** being formed exclusively *via* a strain-free cyclization (see *Scheme 3*). We, therefore, extended our project to the synthesis of the tricyclic musks **46**

[7]) Direct oxidation of **19** with $Ce(NH_4)_2(NO_3)_6$ afforded also a mixture of aldehydes **15**, **17**, and **37**.

[8]) Compounds **42** and **43** were not separated and are not described in the *Exper. Part.*

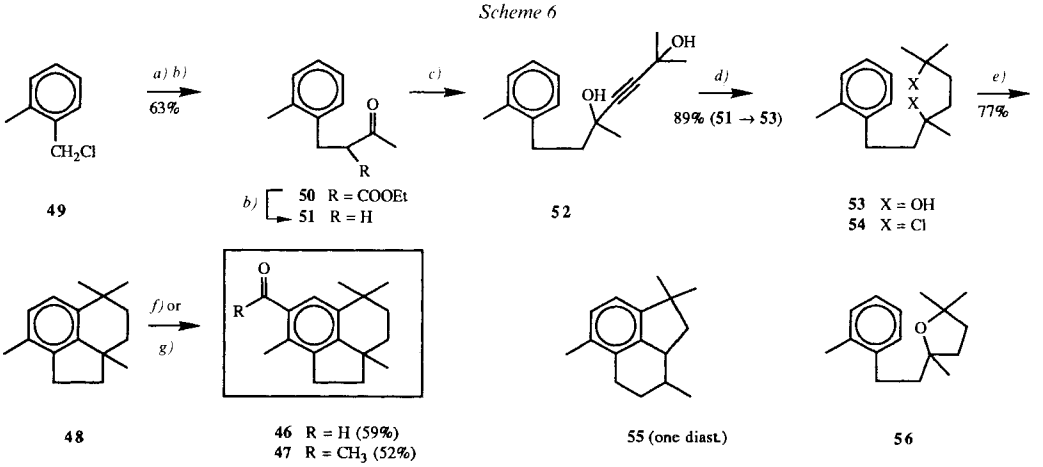
Scheme 5



and **47** whose new bridge linking the atoms C(1) and C(2) only slightly alters the shape of the molecule whilst maintaining the 'closely packed structure' required. Retrosynthetically, access to the precursor tetralin **48** would thus be envisaged *via* a novel strategy starting from **49** and involving two consecutive intramolecular alkylations *(Scheme 5)*. Subsequent acylation would then afford **46** and **47**.

Alkylation of ethyl acetoacetate with chloride **49** afforded ketoester **50** which was deethoxycarbonylated [19] to ketone **51** *(Scheme 6)*. Addition of 2-methylbut-3-yn-2-ol to **51** gave the acetylenic diol **52** which was hydrogenated [15] without prior purification to afford diol **53**. Cyclization of **53** or the corresponding dichloride **54** (*cf.* [15]) to **48**

Scheme 6

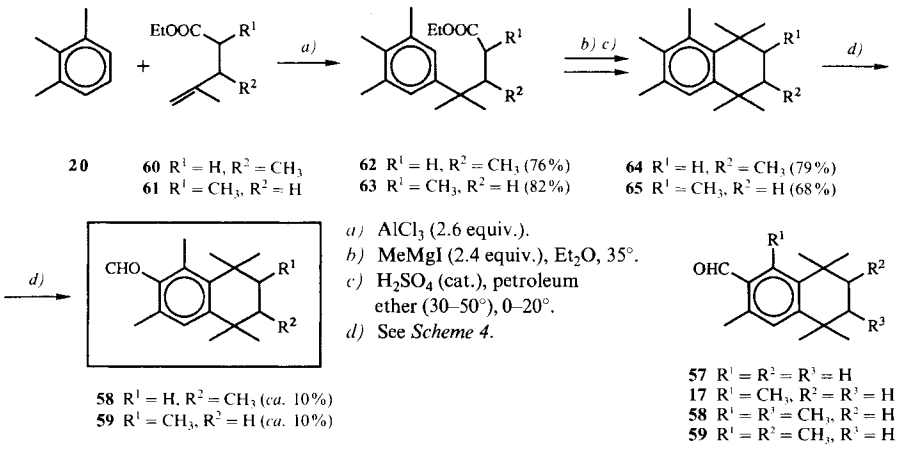


a) $CH_3C(O)CH_2COOEt$ (1 equiv.), K_2CO_3 (3 equiv.), toluene, 100°. *b)* NaCl (cat.), DMSO, H_2O, 160°. *c)* $CH{\equiv}CC(CH_3)_2OH$ (1.3 equiv.), EtMgBr (2.6 equiv.), Et_2O, 0–20°, then addition of **51**, 35°. *d)* *Raney*-Ni (cat.), H_2, MeOH, 70°, 50 atm, 4 days. *e)* **53** → **48**: $TiCl_4$ (3.16 equiv.), CH_2ClCH_2Cl, 4°. *f)* **48** → **46**: Cl_2CHOCH_3 (1 equiv.), $TiCl_4$ (1.67 equiv.), CH_2Cl_2, 0°. *g)* **48** → **47**: CH_3COCl (1.1 equiv.), $AlCl_3$ (1.2 equiv.), CH_2ClCH_2Cl, 5–10°.

proved to depend critically on the reaction conditions. When diol **53** was treated with an excess of $TiCl_4$ (3.16 mol-equiv.) in 1,2-dichloroethane, cyclization to **48** occurred in 77% yield. Dichloride **54**, in the presence of catalytic amounts of $TiCl_4$ (0.2 mol-equiv.), also underwent smooth cyclization, but in addition to **48**, minor amounts of an undesired rearrangement product **55** were obtained (**48**/**55** 4:1). Treatment of **53** with conc. H_2SO_4 afforded predominantly **55** (**55**/**48**/**56** 8:1:1). This latter result is not surprising in view of the known competition under these conditions between indane cyclization *via* a tertiary carbenium ion *vs.* tetralin formation *via* a secondary carbenium ion [14] [15]. Conversely, reaction of **53** with $AlCl_3$ (0.2 mol-equiv.), $SnCl_4$ (3 mol-equiv.), $BF_3 \cdot Et_2O$ (5 mol-equiv.), or 90% H_2SO_4 in petroleum ether (30–50°) at 0° furnished tetrahydrofuran **56** as main product. Finally, acylation of **48** afforded **46** and **47**, both possessing a fairly strong musk odor[9]) as expected.

Synthesis of **58** *and* **59**. In comparison with aldehyde **57**, a known, moderately strong musk, its methyl homolog **17** has a noticeably stronger and more persistent odor. We, therefore, next examined the influence of two additional Me groups added to both the aromatic and cyclohexane ring. The synthesis of **58** (from **20** and **60** *via* **62** and **64**) and **59** (from **20** and **61** *via* **63** and **65**) represents a combination of the strategy applied to **17** *(vide supra)* and a known 'cyclodehydration' procedure [12] *(Scheme 7)*. The new heptamethylated aldehydes **58** and **59** are strong musk odorants. As expected, the corresponding methyl ketones are odorless.

Scheme 7[10])



Synthesis of **66** *and* **67**. We next extended our study to the target molecules **66** and **67** which – with respect to **57** – have two additional CH_3 groups in the *alicyclic* part of the molecule. We expected that the regularly distributed CH_3 groups in **66** and **67** would lead to a compact spherical structure which perfectly fulfills the criteria for musk odor; in addition, the increased lipophilicity of the lipophilic part of the molecule was also expected to be beneficial *(vide infra)*.

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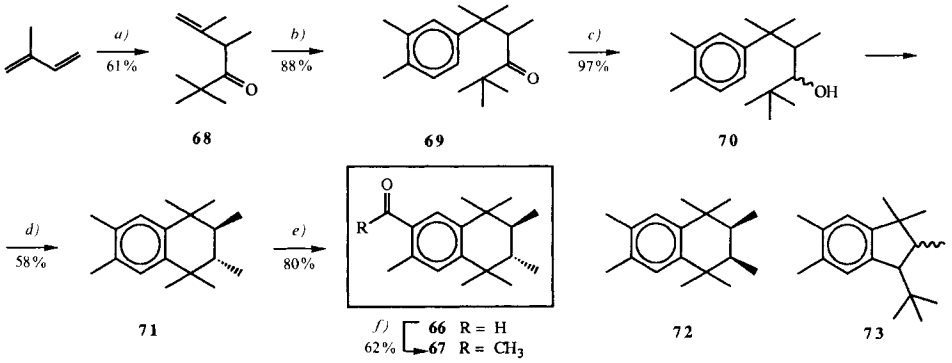
[9]) The formylation product of **55** is nearly odorless.

[10]) The synthesis of **58** and **59** is described in a patent [20].

Scheme 8



a) $CH_2=C(CH_3)CH=CH_2$ (1.1 equiv.), PrMgBr (1 equiv.), Cp_2TiCl_2 (cat.), Et_2O, 20°; then $(CH_3)_3COCl$ (1 equiv.), −10°. *b)* $AlCl_3$ (1.17 equiv.), *o*-xylene (excess), 0–10°. *c)* $LiAlH_4$ (0.49 mol-equiv.), Et_2O, 20°. *d)* MsOH (1.42 equiv.), cat. P_2O_5, 40°. *e)* $Ce(NH_4)_2(NO_3)_6$ (9.4 equiv.), MeOH, 50°. *f)* MeLi (1 equiv.), Et_2O, 20°, then PCC (1.6 equiv.), CH_2Cl_2, 20°.

Our successful approach is outlined in *Scheme 8*. Bis(cyclopentadienyl)titanium dichloride (Cp_2TiCl_2) catalyzed (1 mol-%) hydromagnesiation of isoprene using PrMgBr [21] and addition of the resultant organometallic reagent to pivaloyl chloride in Et_2O afforded ketone **68** in 61% yield[11])[12]). *Friedel-Crafts* alkylation of **68** (*o*-xylene, $AlCl_3$) led to **69** (88% yield) whose reduction with $LiAlH_4$ gave **70** in 97% yield as a 94:6 diastereoisomeric mixture[13]). The most favorable conditions (58% yield) for the cyclization **70** → **71** with concomitant CH_3 migration involved the use of P_2O_5/MsOH[14]). The side products are diastereoisomer **72**[15]) (*ca.* 15%) and minor amounts of **73** (< 10%, tentative assignment). Ce(IV)-mediated oxidation [22] of one of the two identical benzylic CH_3 groups then smoothly afforded **66** in 80% yield. Addition of MeLi to **66** and oxidation of the resultant secondary alcohol with PCC gave **67**[16]). Aldehyde **66** possesses a very powerful musk odor which is much stronger and more persistent than that of *Tonalid*® and thus, up to now, is probably the strongest nitro-free aromatic musk. In comparison to **66**, ketone **67** has a weaker musk odor but is still stronger than *Tonalid*®. Aldehyde **74** (see below, *Scheme 10*), obtained by oxidation of a mixture of **71** and **72**, has also a strong musk odor whose intensity is nevertheless inferior to that of its diastereoisomer **66**.

Structure Determination of **71**. The NMR spectra (^1H and ^{13}C) of **71** and **72** are similar, and due to the C_2 symmetry of **71** and the C_s symmetry of **72**, every resonance is the result

---

[11]) A related procedure for 'acyldemetallation of Ti(III) π-allylic complexes' requires stoichiometric amounts of Cp_2TiCl_2 [23].

[12]) For a less satisfactory synthesis of **68**, see [24].

[13]) The major diastereoisomer has probably the (3*RS*,4*RS*) configuration.

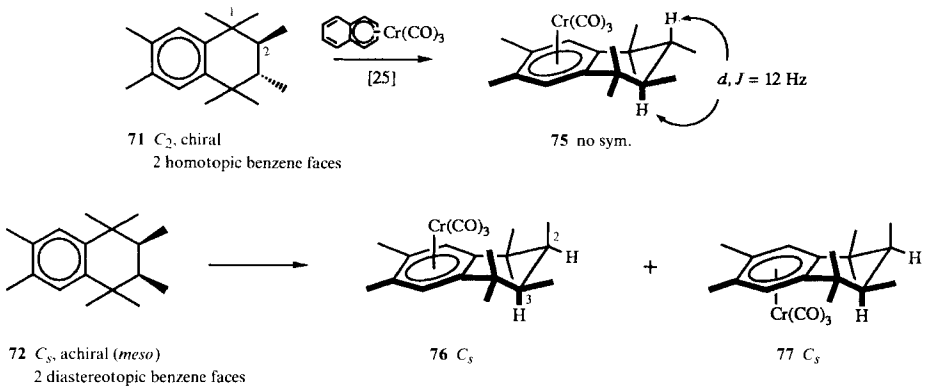
[14]) Unfavorable reagents tested: HCOOH, HCl, H_2SO_4, $KHSO_4$, TsCl, $AlCl_3$, and Al(i-PrO)$_3$.

[15]) For the assignment of configuration **71** to the major diastereoisomer, *vide infra*.

[16]) More directly, **67** was also prepared by *Friedel-Crafts* acylation of the corresponding heptamethylated hydrocarbon.

of two degenerate absorptions[17]). As **71** is chiral, whereas **72** is achiral *(meso)*, one might envisage the application of chiral shift reagents to distinguish between these two possibilities; however, due to the lack of functionality, this method has little chance of success. A more rational approach consists in taking advantage of the different topicity of the aromatic faces in **71** and **72**. As the two benzene faces of **71** are homotopic, reaction with [$Cr(CO)_3$naphthalene] must lead to one $Cr(CO)_3$ complex **75**, whereas **72** with two diastereotopic benzene faces would be expected to give two diastereoisomeric [$Cr(CO)_3$arene] complexes **76** and **77** *(Scheme 9)*.

Scheme 9



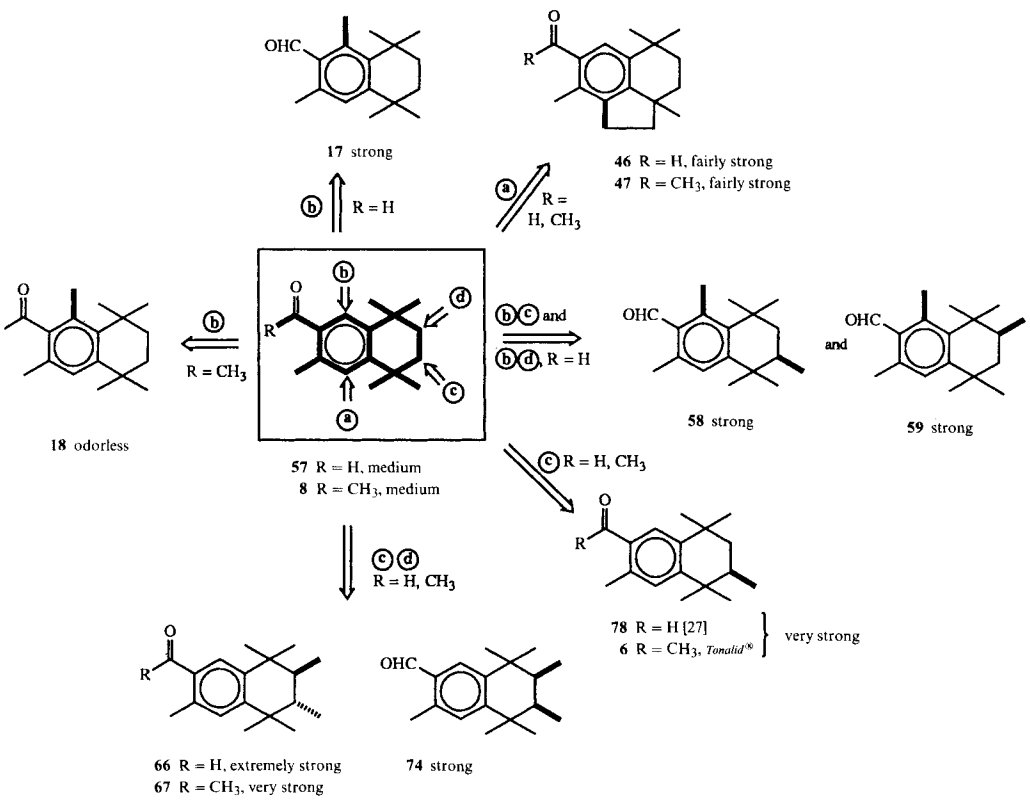
In the event, when the purified major diastereoisomer obtained from the mixture **71**/**72** was treated with [$Cr(CO)_3C_{10}H_8$] [25], only one Cr complex was formed whose structure was unambiguously assigned to **75**, and thus the structure of the starting hydrocarbon to **71**. Due to the loss of symmetry, the number of peaks in the ^{1}H-NMR spectrum of **75** are doubled with respect to **71**, and H–C(2) and H–C(3) show a characteristic vicinal coupling constant of 12 Hz[18]). This correlation was confirmed by decoupling experiments. Our configurational assignment of **71** and **72** is also in agreement with analogous cases [26] (^{1}H-NMR of **71** and **72**: 1.58 and 1.88 ppm (H–C(2, 3))).

Discussion. – In the course of this study, we have found several compounds which possess a strong musk odor. Our hypothesis that increasing the lipophilicity of a known musk compound (*e.g.* **57**) can lead to new compounds of stronger odor intensity has thus been confirmed, exemplified by **17** which possesses an additional CH_3 group at position ⓑ *(Scheme 10)*. This is in contradiction with the generally accepted concept of a sterically unhindered C=O group [2–5] [10b]; but, as expected, the corresponding methyl ketone **18** is odorless. We conclude, therefore, that for a musk odorant, the carbonyl system should not be prevented from adopting coplanarity with the aromatic ring; nevertheless, from the musk compounds known hitherto, nothing can be deduced about the most favorable conformation of the polar group for a strong interaction with a

[17]) *E.g.* H–C(2) and H–C(3) of **71** (or of **72**) are equivalent with each other and, therefore, no vicinal coupling can be observed.

[18]) Due to conformational mobility, H–C(2) and H–C(3) in **76** and **77** are expected to be equivalent (in analogy to **72**).

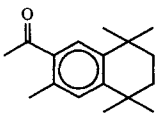
Scheme 10



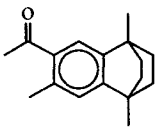
receptor site. Recently [11], a deviation of the C=O group of *ca.* 55° from the π-plane was postulated for an efficient H-bonding between a C=O lone pair and a hypothetical H-donor on the basis of the fact that **7** (*cf. Introduction*) possesses no musk odor, whereas **8** has typical musk character. This hypothesis merits comment. Firstly, several musks are known where the C=O group is part of a cyclic system. These cases clearly show that both coplanar orientations are compatible with musk odor (*cf.* **11**, **12**, *Introduction*)[4]). Secondly, replacement of the C=O group by a nitrile (sp lone pair) does not generally provoke extinction of the musk odor [9], and thirdly, **5** *(cf. Introduction)* possesses medium musk odor although the *ortho* positions of the ketone are not methylated.

Thus, small changes in molecular shape, even in the lipophilic part (*cf.* **5** and **7**), can cause dramatic changes in its organoleptic properties. Indeed, in our study, the most powerful nitro-free aromatic musk known up to now, aldehyde **66**, was obtained by increasing the lipophilicity of the lipophilic part of the molecule. Whereas the effect of the polar group and its environment (accessibility, orientation) on biological activity has been extensively studied (see *e.g.* [28]), the importance of the lipophilic character of a molecule has attracted little attention (for another example, see compounds **14** and **1** cited

in [29]). With the recent discovery of odorant-binding proteins in the *mucosa* of bovines and rats [30], this situation may soon rapidly change. As these odorant-binding proteins seemingly carry or concentrate odorants, it is plausible that a more efficient transport through an aqueous medium is assured for molecules having, at least locally, pronounced lipophilic character. Compounds **57**, **78**, and **66** *(Scheme 10)* which are similar both topologically and stereoelectronically possess increasingly strong musk odors. The additional CH_3 groups in **78** and **66** only slightly alter the outer molecular envelope, but essentially fill the inner sphere of the molecule in a quasi symmetrical manner. Indeed, the musk odor of **74** is less powerful than that of **66**. Nonetheless, to illustrate the complexity



8



79

of structure-activity relationships, ketone **79**[19]), having a highly symmetrical disposition of alkyl substitution, is odorless, whereas the analogous bicyclic ketone **8** has typical musk character! Apparently, the compressed bicyclo[2.2.2]octane system has diminished the volume of the lipophilic part of the molecule below the critical size.

In conclusion, combination of empirical semi-quantitative SAR arguments coupled with synthetic considerations has allowed the discovery of several new strong musks and the development of efficient, new annulation procedures (*Schemes 3, 6,* and *8*).

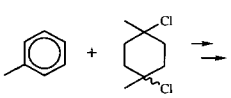
We greatly acknowledge the collaboration of Prof. *E. P. Kündig,* Mrs. *C. Grivet-Linder,* and Mr. *E. Wenger,* Université de Genève, for the preparation of the [$Cr(CO)_3$ arene] complex **75**.

Experimental Part

General. See [31].

1,2,3,4-Tetrahydro-1,1,4,4,5,6,7-heptamethylnaphthalene (**19**) *from* **20** *and* **21**. $TiCl_4$ (15.02 g, 0.079 mol) was added at 0–5° to a soln. of 2,5-dichloro-2,5-dimethylhexane [15] (**21**; 172.8 g, 0.944 mol) in 1,2-dichloroethane (900 ml). Then, 1,2,3-trimethylbenzene (**20**; 113.28 g, 0.944 mol) was slowly added (8 h) at 20° to the mechanically stirred red-brown soln. The mixture was then poured into ice-cold H_2O and filtered through *Celite*®. The phases were separated and the org. phase washed with 10% aq. NaOH and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The crude product was treated with hot EtOH and separated from an insoluble white precipitate (25.9 g, presumably **22**) by filtration. Repeated crystallization from EtOH at 0° afforded white crystals of **19** (35.3 g, 16%). The mother liquors (185 g) represent a complex mixture containing 30% of **19** (by GC). Total yield of **19** (including mother liquors), *ca.* 40%. M.p. 79–82°. IR ($CDCl_3$): 2920, 1455, 1395, 1380. ^{1}H-NMR (60 MHz): 1.27 (*s*, 6H); 1.41 (*s*, 6H); 1.65 (*s*, 4H); 2.12 (*s*, 3H); 2.27 (*s*, 3H); 2.38 (*s*, 3H); 7.01 (*s*, 1H). MS: 230 (22, $M^{+\cdot}$), 216 (15), 215 (100), 174 (11), 173 (73), 171 (14), 159 (41), 141 (10), 128 (10), 57 (16).

5-(2-Chloro-1,1-dimethylethyl)-1,2,3-trimethylbenzene (**23a**) *and 1-(2-Chloro-1,1-dimethylethyl)-2,3,4-trimethylbenzene* (**23b**). At 20°, 2-methylallyl chloride (426.0 g, 4.71 mol) was slowly added (2 h) to a mechanically stirred mixture of **20** (1582 g, 13.18 mol) and H_2SO_4 (84.0 g) (*cf.* [12] [13]). After 3 h, the H_2SO_4 layer was separated

[19]) Synthesis (unpublished): 

and the org. phase successively washed with H_2O, sat. aq. $NaHCO_3$ and sat. aq. NaCl soln. Excess of **20** (1100 g) was recovered by distillation (70°/70 – 20 Torr). The concentrate was distilled *i.v.* to afford **23** (726.0 g, 85% based on **20**; **23a**/**23b** 4:6). B.p. 97–100°/0.02 Torr.

Data of **23a**: IR ($CDCl_3$): 2950, 1485, 1390. ^{1}H-NMR (60 MHz): 1.38 (*s*, 6 H); 2.13 (*s*, 3 H); 2.27 (*s*, 6 H); 3.59 (*s*, 2 H); 7.01 (*s*, 2 H). MS: 210 (8, $M^{+\cdot}$), 174 (7), 161 (100), 133 (28), 121 (34), 115 (14), 105 (16), 91 (19), 77 (14).

Data of **23b**: ^{1}H-NMR (60 MHz): 1.50 (*s*, 6 H); 2.17 (*s*, 3 H); 2.27 (*s*, 3 H); 2.38 (*s*, 3 H); 3.82 (*s*, 2 H); 6.96 (*d*, J = 8, 1 H); 7.13 (*d*, J = 8, 1 H). MS: 210 (10, $M^{+\cdot}$), 174 (12), 161 (100), 144 (14), 133 (56), 121 (34), 115 (19), 105 (22), 91 (27), 77 (19).

5-(1,1,4-Trimethylpent-4-enyl)-1,2,3-trimethylbenzene (**24a**) *and 1-(1,1,4-trimethylpent-4-enyl)-2,3,4-trimethylbenzene* (**24b**). A mechanically stirred suspension of Mg (41.0 g, 1.71 mol) in THF (100 ml) was heated at reflux and treated with 10 ml of a soln. of **23** (300.0 g, 1.43 mol) in THF (200 ml). Once the reaction had started, the turbid suspension was diluted with THF (300 ml), and the totality of **23** in THF added (75 min). The mixture was stirred at 75° for 30 min, then 2-methylallyl chloride (193.0 g, 2.13 mol) was added at reflux temp. (20 min). Precipitation of $MgCl_2$ led to a heavy, but stirrable mixture. After 30 min, the cooled (10°) mixture was hydrolyzed by addition of H_2O (400 ml). The aq. phase was extracted with Et_2O and the combined org. phase washed with sat. aq. NaCl soln. and evaporated. Distillation *i.v.* afforded **24** (294.0 g, 90%). B.p. 130–135°/2 Torr. The colorless oily mixture (^{1}H-NMR (60 MHz): 4.65 (br. *s*, C=CH_2)) was directly used for cyclization to **19**.

1,2,3,4-Tetrahydro-1,1,4,4,5,6,7-heptamethylnaphthalene (**19**) *from* **24**. Hydrocarbon **24** (288.0 g, 1.25 mol) was added within 1 h to a mixture of petroleum ether (30–50°; 100 ml) and H_2SO_4 (7.0 g) at 5–10° (*cf.* [12] [13]). After 30 min, the separated org. phase was washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln. Recrystallization from EtOH (1.1 l) afforded **19** (240.0 g, 83%), identical with the product obtained before *(vide supra)*.

4-(2-Chloro-1,1-dimethylethyl)-1,2-dimethylbenzene (**26**). Proceeding as above (see **23**), the reaction of *o*-xylene (**25**; 489.7 g, 4.62 mol), 2-methylallyl chloride (150.0 g, 1.65 mol), and H_2SO_4 (30.0 g) afforded **26**[20]) (221.2 g, 68%). B.p. 75–80°/0.05 Torr. IR (neat): 2950, 1445, 1390. ^{1}H-NMR (60 MHz): 1.38 (*s*, 6 H); 2.24 (*s*, 3 H); 2.27 (*s*, 3 H); 3.60 (*s*, 2 H); 7.10 (*s*, 3 H). MS: 196 (8, $M^{+\cdot}$), 160 (10), 147 (100), 145 (29), 119 (44), 115 (16), 107 (27), 91 (23), 77 (12).

4-(1,1,4-Trimethylpent-4-enyl)-1,2-dimethylbenzene (**27**). Proceeding as above (see **24**), **26** (10.0 g, 51.0 mmol) afforded **27** (7.40 g, 67%). B.p. 115°/2 Torr. IR (neat): 2930, 1445. ^{1}H-NMR (60 MHz): 1.29 (*s*, 6 H); 1.65 (*s*, 2 H); 1.77 (*s*, 5 H); 2.23 (*s*, 3 H); 2.26 (*s*, 3 H); 4.63 (br. *s*, 2 H); 7.07 (*s*, 3 H). MS: 216 (3, $M^{+\cdot}$), 147 (100), 119 (28), 107 (14), 91 (14).

1,2,3,4-Tetrahydro-1,1,4,4,6,7-hexamethylnaphthalene (**28**). Proceeding as above (see **19** from **24**), **27** (1.00 g, 4.63 mmol) afforded **28** (0.94 g, 94%). B.p. 130°/1 Torr (bulb-to-bulb dist.). Spectra are identical with those reported [12].

1-(2-Chloro-1,1-dimethylethyl)-2,4-dimethylbenzene (**30**). Proceeding as above (see **23**), the reaction of *m*-xylene (**29**; 490.0 g, 4.62 mol), 2-methylallyl chloride (150.0 g, 1.65 mol), and H_2SO_4 (30.0 g) gave **30**[21]) (182.8 g, 56%). B.p. 80°/0.2 Torr. IR (neat): 2950, 1460, 1390, 1300. ^{1}H-NMR (60 MHz): 1.46 (*s*, 6 H); 2.19 (*s*, 3 H); 2.49 (*s*, 3 H); 3.80 (*s*, 2 H); 6.90 (*m*, 2 H); 7.20 (*d*, J = 8, 1 H). MS: 196 (8, $M^{+\cdot}$), 147 (100), 128 (12), 119 (76), 115 (19), 107 (26), 91 (31), 77 (17), 41 (11).

1,2,3,4-Tetrahydro-1,1,4,4,5,7-hexamethylnaphthalene (**32**). Proceeding as above (see **24**), **30** (100.0 g, 0.509 mol) afforded *1-(1,1,4-trimethylpent-4-enyl)-2,4-dimethylbenzene*[21]) (**31**; 97.0 g, 88%). B.p. 75–78°/0.05 Torr. ^{1}H-NMR (60 MHz): 4.62 (br. *s*, C=CH_2).

Cyclization of **31** (86.9 g, 0.402 mol) as above (see **19** from **24**) gave **32** (80.6 g, 93%). B.p. 120°/0.2 Torr. IR (neat): 2910, 1600, 1455, 1390, 1375. ^{1}H-NMR (60 MHz): 1.24 (*s*, 6 H); 1.35 (*s*, 6 H); 1.66 (*s*, 4 H); 2.23 (*s*, 3 H); 2.49 (*s*, 3 H); 6.75 (br. *s*, 1 H); 7.00 (br. *s*, 1 H). MS: 216 (33, $M^{+\cdot}$), 201 (100), 159 (67), 145 (29), 141 (13), 128 (11), 115 (10).

1-(2-Chloro-1,1-dimethylethyl)-2,4,5-trimethylbenzene (**34**). Proceeding as above (see **23**), the reaction of 1,2,4-trimethylbenzene (**33**; 672 g, 5.6 mol), 2-methylallyl chloride (181 g, 2 mol), and H_2SO_4 (35.3 g) gave **34**[22]) (254.3 g, 91% pure, 57%). B.p. 40–50°/10 Torr. IR (neat): 2950, 1510, 1460, 1390, 1365. ^{1}H-NMR (60 MHz): 1.49 (*s*, 6 H); 2.20 (*s*, 3 H); 2.23 (*s*, 3 H); 2.45 (*s*, 3 H); 3.80 (*s*, 2 H); 6.90 (br. *s*, 1 H); 7.10 (br. *s*, 1 H). MS: 210 (8, $M^{+\cdot}$), 161 (100), 133 (48), 121 (32), 105 (18), 91 (21), 77 (17).

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[20]) Containing 4% of its regioisomer.

[21]) Containing 10% of a regioisomer.

[22]) No regioisomer detected by GC.

1,2,3,4-Tetrahydro-1,1,4,4,5,6,8-heptamethylnaphthalene (**36**). Proceeding as above (see **24**), **34** (200 g, max. 0.95 mol) afforded **35** (190.8 g, 87%). B.p. 94–96°/0.03 Torr. ^{1}H-NMR (60 MHz): 4.63 (br. *s*, 2 H).

A soln. of **35** (69.0 g, 0.30 mol), TsOH (5.2 g, 30.0 mmol), and toluene (400 ml) was heated at reflux[23]). After 5 h, H_2O was added and the org. layer washed with sat. aq. $NaHCO_3$ soln., evaporated, and distilled *i.v.*: 65.1 g (*ca.* 82% pure, 77%) of **36**. B.p. 88–105°/0.1 Torr. Recrystallization from EtOH gave **36** (31.2 g, 96% pure). M.p. *ca.* 40°. Retreatment of the mother liquors (containing **35**/**36**) with TsOH (2.0 g) and crystallization afforded a second crop of **36** (18.0 g, 96% pure). IR ($CHCl_3$): 3000, 2930, 1460, 1365. ^{1}H-NMR (60 MHz): 1.40 (*s*, 6 H); 1.44 (*s*, 6 H); 1.64 (*s*, 4 H); 2.14 (*s*, 3 H); 2.36 (*s*, 3 H); 2.50 (*s*, 3 H); 6.83 (*s*, 1 H). MS: 230 (23, $M^{+\cdot}$), 215 (85), 185 (11), 173 (100), 159 (62), 141 (19), 128 (23), 115 (19), 91 (20), 77 (21), 57 (56).

5,6,7,8-Tetrahydro-3,4,5,5,8,8-hexamethylnaphthalene-2-carbaldehyde (**15**), *5,6,7,8-Tetrahydro-1,3,5,5,8,8-hexamethylnaphthalene-2-carbaldehyde* (**17**), *and 5,6,7,8-Tetrahydro-2,3,5,5,8,8-hexamethylnaphthalene-1-carbaldehyde* (**37**) *from* **19**. NBS (5.56 g, 31.2 mmol) was added to a soln. of **19** (6.25 g, 27.2 mmol) in CCl_4 (70 ml). The stirred suspension was irradiated with a 100-W lamp, thus bringing the mixture to reflux. After 45 min, the cooled (20°) mixture was poured into H_2O and extracted (Et_2O). The org. phase was washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The crude mixture of benzylic bromides (10.5 g) containing *ca.* 15% of unreacted **19**[24]) was dissolved in 1-methylpyrrolidin-2-one (70 ml) and H_2O (10 ml) and heated at reflux for 1 h [17]. The cooled soln. (20°) was extracted (Et_2O) and the org. layer washed with H_2O (3×), sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated (7.65 g). Chromatography (SiO_2 (200 g), cyclohexane/Et_2O 98:2) afforded an apolar fraction of alcohol A (1.30 g) and a polar fraction containing alcohols **B** and C (1.86 g, B/C 4:1). Combined yield of A–C: 3.16 g (47%). A soln. of **B**/C (4:1; 1.55 g, 6.3 mmol) in CH_2Cl_2 (5 ml) was added at 20° to a stirred soln. of PCC (2.18 g, 10.1 mmol) in CH_2Cl_2 (15 ml). After 2 h, the dark brown mixture was filtered (SiO_2 (20 g), CH_2Cl_2), evaporated, and crystallized from MeOH to afford crystalline **17** and **15** (501 mg, **17**/**15** 9:1) and mother liquors (439 mg containing 85% of **17**/**15**). Combined yield: 57%. A sample of **15** containing 10% of **17** could be obtained by prep. GC[25]). Application of the same PCC treatment to alcohol A (1.30 g, 5.29 mmol) gave **37** (456 mg), m.p. 74–78°, and mother liquors (426 mg, 80% pure). Estimated yield: 61%.

^{1}H-NMR (360 MHz) of **15**[26]): 1.33 (*s*, 6 H); 1.47 (*s*, 6 H); 1.68 (*s*, 4 H); 2.42 (*s*, 3 H); 2.53 (*s*, 3 H); 7.67 (*s*, 1 H); 10.26 (*s*, 1 H).

Data of **17**: IR ($CDCl_3$): 2975, 2940, 2850, 1685, 1600, 1385. ^{1}H-NMR (360 MHz): 1.30 (*s*, 6 H); 1.45 (*s*, 6 H); 1.68 (br. *s*, 4 H); 2.47 (*s*, 3 H); 2.70 (*s*, 3 H); 7.07 (*s*, 1 H); 10.58 (*s*, 1 H). MS: 244 (50, $M^{+\cdot}$), 229 (100), 187 (19), 173 (22), 159 (56), 145 (13), 128 (10).

Data of **37**: IR ($CDCl_3$): 2990, 2955, 2890, 1705, 1470, 1380. ^{1}H-NMR (360 MHz): 1.28 (*s*, 6 H); 1.36 (*s*, 6 H); 1.61–1.72 (*m*, 4 H); 2.16 (*s*, 3 H); 2.26 (*s*, 3 H); 7.20 (*s*, 1 H); 10.83 (*s*, 1 H). MS: 244 (23, $M^{+\cdot}$), 229 (100), 211 (40), 196 (18), 185 (15), 169 (17), 159 (29), 141 (17), 128 (15), 115 (15).

Selective, Unequivocal Synthesis of **17** *from* **32** *and of* **37** *from* **28**. Following a known procedure [18], a mixture of **32** (5.00 g, 23.2 mmol) and $TiCl_4$ (7.32 g, 38.8 mmol) in CH_2Cl_2 (40 ml) was treated with Cl_2CHOCH_3 (2.66 g, 23.2 mmol) in CH_2Cl_2 (5 ml) at 0° for 20 min. The dark red mixture was allowed to attain 20° (20 min), poured into ice-cold H_2O, and extracted with Et_2O. The org. phase was washed with 10% aq. NaOH soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. Recrystallization from MeOH afforded **17** (4.06 g, 72%). M.p. 92–93°.

The same reaction with **28** afforded **37**, identical with the product obtained before.

1-(5,6,7,8-Tetrahydro-1,3,5,5,8,8-hexamethylnaphth-2-yl)ethan-1-one (**18**). MeLi (2.54 ml 1.6M in Et_2O, 4.06 mmol) was added (10 min) to a soln. of **17** (1.00 g, 4.06 mmol) in Et_2O (25 ml) at 25–30°. After 30 min (temp. 25°), the reaction was quenched with sat. aq. NH_4Cl soln., extracted with Et_2O, and the org. extract washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated (0.912 g). The crude product was oxidized with PCC (1.19 g, 5.53 mmol) in CH_2Cl_2 (*cf.* **15**, **17**, and **37** from **19**) to afford recrystallized (EtOH/H_2O) **18** (0.61 g, 58%). M.p. 82–83°. IR ($CDCl_3$): 2950, 2920, 1685, 1350, 1260. ^{1}H-NMR (60 MHz): 1.26 (*s*, 6 H); 1.40 (*s*, 6 H); 1.68 (*s*, 4 H); 2.16 (*s*, 3 H); 2.36 (*s*, 3 H); 2.47 (*s*, 3 H); 7.03 (*s*, 1 H). MS: 258 (25, $M^{+\cdot}$), 243 (100), 201 (19), 187 (13), 159 (40), 145 (14), 43 (58).

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[23]) Cyclization with H_2SO_4 (see **19** from **24**) gave only minor amounts of **36** together with CH_3-migration product **19**.

[24]) In order to prevent formation of dibromides, the reaction was stopped before completion.

[25]) As both **15** and **17** represent distinct musk tonalities, the fairly strong musk odor of **15** can not be imputed to remaining traces of **17**.

[26]) IR and MS: same as for **17**. The constitution was assigned on the basis of ^{1}H-NMR NOE measurements (between arom. CH_3's and CH=O).

5,6,7,8-Tetrahydro-4,5,5,8,8-pentamethylnaphthalene-2-carbaldehyde (**38**) *and 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethylnaphthalene-1-carbaldehyde* (**40**). Proceeding as above (**15**, **17**, and **37** from **19**), **32** (30.0 g, 138 mmol) and NBS (23.5 g, 132 mmol) gave a mixture of unpurified bromides (44.4 g). Hydrolysis with 1-methylpyrrolidin-2-one (300 ml) and H_2O (45 min) afforded, after chromatographic purification (SiO_2, cyclohexane/AcOEt 95:5), an apolar fraction containing essentially alcohol A (10.75 g) and a polar fraction containing essentially alcohol B (3.70 g). Taking into account the intermediate fractions (3.14 g), the yield of A + B was 17.28 g (55%). Alcohols B (3.70 g, 15.95 mmol) and A (10.65 g, 46.0 mmol) were separately oxidized with PCC (5.60 g (26.0 mmol) for B; 15.85 g (74.0 mmol) for A) to afford, after crystallization from MeOH, **38** (2.23 g, 61%) and **40** (8.95 g, 85%).

Data of **38**: M.p. 58–61°. IR ($CDCl_3$): 2950, 2920, 2855, 1685, 1600, 1460, 1360. ^{1}H-NMR (60 MHz): 1.30 (*s*, 6 H); 1.40 (*s*, 6 H); 1.67 (*s*, 4 H); 2.57 (*s*, 3 H); 7.40 (*d*, *J* = 2, 1 H); 7.68 (*d*, *J* = 2, 1 H); 9.86 (*s*, 1 H). MS: 230 (15, M^+), 215 (60), 173 (28), 159 (64), 145 (100), 131 (34), 115 (17), 105 (15), 91 (12), 57 (28).

Data of **40**: M.p. 60–62°. IR ($CHCl_3$): 2950, 2925, 2855, 1675, 1600, 1455, 1390, 1360, 1245. ^{1}H-NMR (360 MHz): 1.30 (*s*, 6 H); 1.52 (*s*, 6 H); 1.69 (br. *s*, 4 H); 2.33 (*s*, 3 H); 7.35 (*d*, *J* = 2, 1 H); 7.52 (*d*, *J* = 2, 1 H); 10.90 (*s*, 1 H). MS: 230 (10, M^+), 215 (100), 197 (37), 182 (10), 173 (13), 159 (17), 155 (18), 145 (47), 131 (16), 128 (15), 115 (13).

The assignment of constitution was verified by decarbonylation of a sample of **40** with $[RhCl(PPh_3)_3]$ in refluxing toluene [32], thus affording 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene which was also prepared from toluene and dichloride **21** [12].

5,6,7,8-Tetrahydro-1,3,4,5,5,8,8-heptamethylnaphthalene-2-carbaldehyde (**44**). Proceeding as above (**17** from **32**), **36** (5.00 g, 21.7 mmol) was converted into **44**. After crystallization of the crude product (5.55 g) from EtOH, white crystals of **44** (4.02 g, 72%) were obtained, M.p. 104–106°. IR ($CHCl_3$): 2920, 1685, 1455, 1360. ^{1}H-NMR (360 MHz): 1.47 (*s*, 6 H); 1.48 (*s*, 6 H); 1.73 (br. *s*, 4 H); 2.24 (*s*, 3 H); 2.40 (*s*, 3 H); 2.58 (*s*, 3 H); 10.60 (*s*, 1 H). MS: 258 (28, M^+), 243 (73), 215 (10), 201 (11), 187 (33), 173 (100), 159 (54), 143 (15), 128 (15), 115 (11), 91 (11), 57 (18), 41 (12).

4-(2-Methylphenyl)butan-2-one (**51**). A mixture of 2-methylbenzyl chloride (**49**; 140.6 g, 1.0 mol), ethyl 2-acetylacetate (130.0 g, 1.0 mol), K_2CO_3 (414 g, 3.0 mol), and toluene (800 ml) was heated at 100° for 20 h. The cooled (20°) suspension was treated with H_2O (500 ml), the org. phase washed with sat. aq. NaCl soln., dried (Na_2SO_4), evaporated (269.6 g), and distilled *i.v.* to give *ethyl 2-acetyl-3-(2-methylphenyl)propanoate* (**50**; 163 g, 70%). B.p. 120–125°/0.05 Torr. The distillate was mixed with NaCl (16.4 g, 0.28 mol), DMSO (150 ml), and H_2O (25 ml) and heated in a steel autoclave at 160° for 7 h (*cf.* [19]). The cooled mixture was extracted with petroleum ether (30–50°), washed 5 times with sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and distilled *i.v.* to afford **51** (102 g, 63% from **49**). B.p. 65–70°/0.1 Torr. IR (neat): 2925, 1705, 1490, 1350, 1160. ^{1}H-NMR (60 MHz): 2.10 (*s*, 3 H); 2.28 (*s*, 3 H); 2.65–3.00 (*m*, 4 H); 7.07 (*s*, 4 H). MS: 162 (2, M^+), 144 (100), 129 (50), 119 (52), 105 (83), 91 (45), 77 (28), 65 (18), 43 (58).

7-(2-Methylphenyl)-2,5-dimethylheptane-2,5-diol (**53**). At 0–5°, 2-methylbut-3-yn-2-ol (47.0 g, 0.56 mol) was added (30 min) to a soln. of EtMgBr (1.12 mol) in Et_2O (300 ml). The heterogeneous, grey mixture was stirred at 20° for 30 min and at reflux for 1 h, treated with **51** (69.7 g, 0.43 mol) at 20°, and heated at reflux for 1 h. The mixture which became homogeneous was hydrolyzed with sat. aq. NH_4Cl soln./ice, extracted with Et_2O, washed with sat. aq. NaCl soln., dried, and evaporated to give crude oily *7-(2-methylphenyl)-2,5-dimethylhept-3-yne-2,5-diol* (**52**; 107.9 g). IR (neat): 3350. ^{1}H-NMR (60 MHz): 1.50 (*s*, 9 H); 1.70–2.03 (*m*, 2 H); 2.30 (*s*, 3 H); 2.63–2.94 (*m*, 2 H); 2.94 (br. *s*, 2 H); 7.13 (*s*, 4 H).

Diol **52** was hydrogenated in an autoclave (*Raney*-Ni (3.0 g)) in MeOH (80 ml) at 70° and 50 atm of H_2 (*cf.* [15]). After 4 days, the suspension was filtered and the filtrate evaporated and distilled to give **53** (96.0 g, 94% pure, 89%). B.p. 125°/0.05 Torr. IR (neat): 3350, 2930, 1455, 1370. ^{1}H-NMR (60 MHz, +D_2O): 1.22 (2*s*, 9 H); 1.60 (*s*, 4 H); 1.50–1.90 (*m*, 2 H); 2.30 (*s*, 3 H); 2.45–2.85 (*m*, 2 H); 7.12 (*s*, 4 H). MS: 158 (10), 143 (18), 113 (72), 105 (100), 95 (20), 91 (11), 77 (13), 59 (18), 43 (57).

1,2,2a,3,4,5-Hexahydro-2a,5,5,8-tetramethylacenaphthylene (**48**). $TiCl_4$ (28.5 g, 150 mmol) was added dropwise (30 min) to a cold (4°) soln. of **53** (12.4 g, 94% pure, 47.5 mmol) in 1,2-dichloroethane (150 ml). After 30 min, a sat. aq. NaCl soln. (50 ml) was added dropwise (temp. →30°). The org. phase (GC: **48**/**55** ≥ 96:4) was separated, washed with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and distilled *i.v.* to afford **48** (7.76 g, 77%). B.p. 130°/0.02 Torr. IR (neat): 2920, 1485, 1445, 1360. ^{1}H-NMR (360 MHz): 1.12 (2*s*, 6 H); 1.38 (*s*, 3 H); 1.60–1.85 (*m*, 4 H); 2.02 (*m*, 2 H); 2.22 (*s*, 3 H); 2.68 (*m*, 1 H); 2.97 (*m*, 1 H); 6.94 (*d*, *J* = 8, 1 H); 7.01 (*d*, *J* = 8, 1 H). MS: 214 (15, M^+), 199 (100), 157 (18), 143 (14).

1,2,2a,3,4,5-Hexahydro-1,1,3,6-tetramethylacenaphthylene (**55**) *and 2,3,4,5-Tetrahydro-2,2,5-trimethyl-5-[2-(2-methylphenyl)ethyl]furan* (**56**). Stirred **53** (7.20 g, 28.8 mmol) in petroleum ether (30–50°; 60 ml) was treated at 20° with 95% H_2SO_4 (10 ml). After 30 min, the mixture was poured into ice and extracted with Et_2O *(vide supra)* to

afford, after bulb-to-bulb dist. (150°/0.1 Torr), **55**/**48**/**56** (8:1:1; 4.87 g, 79%). Pure **55** (one diastereoisomer) and **56** were obtained by prep. GC.

Data of **55**: IR (neat): 2940, 2850, 1450. ^{1}H-NMR (360 MHz): 1.06 (*d*, *J* = 7, 3 H); 1.21 (*s*, 3 H); 1.32 (*s*, 3 H); 1.30–1.40 (*m*, 1 H); 1.41–1.58 (*m*, 2 H); 1.97 (*m*, 1 H); 2.13 (*dd*, *J* = 10, 7, 1 H); 2.19 (*s*, 3 H); 2.47–2.67 (*m*, 2 H); 2.77 (*dd*, *J* = 17, 7, 1 H); 6.89 (*d*, *J* = 7, 1 H); 6.97 (*d*, *J* = 7, 1 H). MS: 214 (18, $M^{+\cdot}$), 199 (100), 157 (30), 143 (15).

Data of **56**: IR (neat): 2950, 2860, 1490, 1450, 1365. ^{1}H-NMR (360 MHz): 1.27 (*s*, 3 H); 1.29 (*s*, 3 H); 1.31 (*s*, 3 H); 1.63–2.02 (*m*, 6 H); 2.32 (*s*, 3 H); 2.57–2.76 (*m*, 2 H); 7.12 (*m*, 4 H). MS: 232 (1, $M^{+\cdot}$), 158 (10), 143 (17), 113 (100), 105 (47), 95 (22), 77 (10), 43 (50).

Tetrahydrofuran **56** could be obtained selectively (**56**/**55** 9:1), when a cooled (0°) soln. of **53** (1.00 g, 4.00 mmol) in petrolcum ether (30–50°; 10 ml) was treated (1 min) with 90% H_2SO_4 (1.2 ml) and stirred for 20 min. Usual workup and bulb-to-bulb dist. (100°/0.02 Torr) afforded **56**/**55** (9:1; 802 mg, 86%).

1,2,6,7,8,8a-Hexahydro-3,6,6,8a-tetramethylacenaphthylene-4-carbaldehyde (**46**). Proceeding as above (**17** from **32**), **48** (4.71 g, 22.0 mmol) was converted into **46** (3.14 g, 59%). M.p. 84–88°. IR ($CDCl_3$): 2950, 2855, 1680, 1590, 1450. ^{1}H-NMR (60 MHz): 1.15 (*s*, 6 H); 1.41 (*s*, 3 H); 1.65–2.30 (*m*, 6 H); 2.52 (*s*, 3 H); 2.70–3.15 (*m*, 2 H); 7.60 (*s*, 1 H); 10.23 (*s*, 1 H). MS: 242 (18, $M^{+\cdot}$), 227 (100), 199 (20), 165 (10), 157 (36), 143 (25), 128 (17), 115 (14), 92 (12), 69 (11).

1-(1,2,6,7,8,8a-Hexahydro-3,6,6,8a-tetramethylacenaphthylen-4-yl)ethan-1-one (**47**). A soln. of **48** (1.28 g, 6.00 mmol) in 1,2-dichloroethane was added dropwise at 5–10° to a suspension of $AlCl_3$ (960 mg, 7.20 mmol) in 1,2-dichloroethane (10 ml). AcCl (518 mg, 6.60 mmol) was then added to the orange suspension. After 30 min, H_2O was added and the product extracted with Et_2O. The org. phase was washed with sat. aq. $NaHCO_3$ soln., then sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The residue was purified by chromatography (SiO_2, cyclohexane/AcOEt 95:5): **47** (0.80 g, 52%). IR ($CHCl_3$): 2920, 2850, 1675, 1445, 1345, 1290, 1245. ^{1}H-NMR (360 MHz): 1.13 (*s*, 3 H); 1.15 (*s*, 3 H); 1.40 (*s*, 3 H); 1.58–1.85 (*m*, 4 H); 1.98–2.09 (*m*, 2 H); 2.37 (*s*, 3 H); 2.56 (*s*, 3 H); 2.74 (*m*, 1 H); 2.99 (*m*, 1 H); 7.43 (*s*, 1 H). MS: 256 (11, $M^{+\cdot}$), 241 (87), 199 (20), 153 (10), 43 (100).

2,2,4,5-Tetramethylhex-5-en-3-one (**68**). Freshly distilled isoprene (30.0 g, 44.0 ml, 440 mmol) was treated at 20° under stirring with PrMgBr (213 ml, 1.88N, 400 mmol; prepared from PrBr (54.2 g, 40 ml, 440 mmol), Mg (12.7 g, 528 mmol), and Et_2O (200 ml)) and Cp_2TiCl_2 (*Fluka*, 1.0 g). No exothermicity was observed. The mixture became immediately red and, after 5 min, dark brown [21]. After 15 h at 20°, the soln. was transferred *via* canula into a cooled (−10°), stirred flask containing pivaloyl chloride (48.2 g, 49.2 ml, 400 mmol) and Et_2O (100 ml). The mixture was stirred at −10° for 1 h, poured into sat. aq. NH_4Cl soln., and extracted with Et_2O. The org. phase was vigorously shaken with 5% aq. NaOH soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated in a distillation apparatus at 1 atm and the product distilled *i.v.*: 39.2 g (96% pure, 61%) of **68**. B.p. 50°/10 Torr. IR ($CDCl_3$): 3050, 1700, 1640, 1470, 1360, 990. ^{1}H-NMR (60 MHz): 1.12 (*s*, 9 H); 1.17 (*d*, *J* = 7, 3 H); 1.74 (br. *s*, 3 H); 3.71 (*q*, *J* = 7, 1 H); 4.80 (*s*, 2 H). MS: 154 (3, $M^{+\cdot}$), 85 (32), 69 (14), 57 (100), 41 (34).

5-(3,4-Dimethylphenyl)-2,2,4,5-tetramethylhexan-3-one (**69**). A soln. of **68** (37.2 g, 96% pure, 232 mmol) in *o*-xylene (50 ml) was added dropwise at 0° to a suspension of $AlCl_3$ (36.2 g, 271.4 mmol) in *o*-xylene (380 ml). The mixture was warmed at 10° (30 min), poured into H_2O, and extracted with Et_2O. The org. phase was washed with sat. aq. Na_2CO_3 soln. and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and distilled *i.v.* to afford **69** (54.4 g, 97% pure, 88%). B.p. 120°/1 Torr. IR ($CDCl_3$): 2950, 1690, 1470, 1360, 990. ^{1}H-NMR (60 MHz): 0.95 (*d*, *J* = 7, 3 H); 0.96 (*s*, 9 H); 1.37 (*s*, 3 H); 1.46 (*s*, 3 H); 2.22 (*s*, 3 H); 2.26 (*s*, 3 H); 3.27 (*q*, *J* = 7, 1 H); 7.05 (br. *s*, 3 H). MS: 260 (1, $M^{+\cdot}$), 147 (100), 131 (8), 119 (17), 91 (10), 57 (12), 41 (10).

5-(3,4-Dimethylphenyl)-2,2,4,5-tetramethylhexan-3-ol (**70**). A soln. of **69** (54.4 g, 97% pure, 203.4 mmol) in Et_2O (50 ml) was added dropwise (1 h) under stirring at 20° to a suspension of $LiAlH_4$ (3.80 g, 100 mmol) in Et_2O. The cooled (10°) mixture was carefully treated under stirring with H_2O (4 ml), then 5% aq. NaOH soln. (4 ml) and H_2O (12 ml). Filtration of the white cake, concentration of the filtrate, and distillation *i.v.* afforded **70** (51.5 g, 98% pure, 97%), b.p. 130–140°/1.5 Torr, as a 94:6 diastereoisomeric mixture. IR (neat): 3600, 2980, 1480, 1370, 1010. ^{1}H-NMR (360 MHz, +D_2O): 0.81 (*s*, 9 H); 1.05 (*d*, *J* = 7, 3 H); 1.20 (*s*, 3 H); 1.46 (*s*, 3 H); 2.01 (*q*, *J* = 7, 1 H); 2.02 (*s*, 3 H); 2.04 (*s*, 3 H); 3.09 (*d*, *J* = 7.5, 1 H); 7.07 (*d*, *J* = 7.5, 1 H); 7.14 (br. *d*, *J* = 7.5, 1 H); 7.18 (*s*, 1 H). MS: 244 (trace, $M^{+\cdot}$ − 18), 187 (7), 173 (7), 147 (100), 131 (8), 119 (17), 107 (9), 91 (10), 57 (8), 41 (13).

(2RS,3RS)-1,2,3,4-Tetrahydro-1,1,2,3,4,4,6,7-octamethylnaphthalene (**71**) *and (2RS,3SR)-1,2,3,4-Tetrahydro-1,1,2,3,4,4,6,7-octamethylnaphthalene* (**72**). Alcohol **70** (41.6 g, 98% pure, 155.7 mmol) was added under stirring to a mixture of methanesulfonic acid (21.25 g, 14.3 ml, 221 mmol) and P_2O_5 (8.5 g), maintaining the temp. at 40° with occasional cooling. The mixture was then heated at 40° for 4 h, cooled to 20°, diluted with CH_2Cl_2 (10 ml), and poured into H_2O/ice. Extraction with Et_2O, washing of the org. layer with 5% aq. NaOH and sat. aq. NaCl soln., drying (Na_2SO_4), and evaporation afforded a 4:1 mixture **71**/**72** (37.8 g). Crystallization from EtOH, distillation of the mother liquors (110°/1 Torr), and crystallization of the distillation fractions afforded **71** (16.7 g,

98% pure, 43%), m.p. 132–138°, and an oil consisting of **71**/**72** (20.5 g, 57% pure, **71**/**72** *ca.* 1:1). Estimated yield: **71**/**72**, 72%; **71**, 58%.

Data of **71**: IR ($CHCl_3$): 2990, 1500, 1450, 1400, 1370. ^{1}H-NMR (360 MHz): 0.96 (*d*, *J* = 6, 6 H); 1.09 (*s*, 6 H); 1.31 (*s*, 6 H); 1.58 (*m*, 2 H); 2.23 (*s*, 6 H); 7.12 (*s*, 2 H). ^{13}C-NMR (360 MHz): 143.1 (2 *s*); 133.6 (2 *s*); 128.2 (2 *d*); 39.5 (2 *d*); 37.5 (2 *s*); 29.6 (2 *q*); 25.7 (2 *q*); 19.5 (2 *q*); 13.9 (2 *q*). MS: 244 (7, $M^{+\cdot}$), 229 (24), 187 (43), 173 (100), 157 (12), 145 (23), 128 (11), 91 (8), 57 (38), 41 (9).

Data of **72**: ^{1}H-NMR (360 MHz): 0.95 (*d*, *J* = 7, 6 H); 1.25 (*s*, 6 H); 1.26 (*s*, 6 H); 1.88 (br. *q*, *J* = 7, 2 H); 2.23 (*s*, 6 H); 7.08 (*s*, 2 H). ^{13}C-NMR (360 MHz): 142.0 (2 *s*); 133.6 (2 *s*); 127.9 (2 *d*); 41.4 (2 *d*); 37.1 (2 *s*); 33.7 (2 *q*); 27.7 (2 *q*); 19.4 (2 *q*); 13.3 (2 *q*). MS: 244 (7, $M^{+\cdot}$), 229 (24), 187 (41), 173 (100), 159 (10), 145 (23), 128 (9), 91 (6), 57 (38), 41 (9).

*Tricarbonyl[(2*RS,*3*RS*)-1,2,3,4-tetrahydro-1,1,2,3,4,4,6,7-octamethylnaphthalene]chromium* (**75**). Degassed **71** (45 mg, 0.18 mmol), tricarbonyl(naphthalene)chromium [25], (50 mg, 0.19 mmol), and Et_2O/THF 9:1 (0.5 ml) were added successively into a *Pyrex* tube (diameter, 5 mm). The tube was sealed and heated at 70° for 17 h. The cooled (20°) mixture was filtered through *Celite*®, washed with Et_2O, and evaporated. The dark brown residue was dissolved in hexane, filtered through *Celite*®, and purified by chromatography (SiO_2, hexane/Et_2O 9:1): 11.5 mg (18%) of **75**. ^{1}H-NMR (360 MHz, C_6D_6): 0.65 (*d*, *J* = 7, 3 H); 0.71 (*d*, *J* = 7, 3 H); 0.79 (*s*, 3 H); 0.90 (*s*, 3 H); 1.10 (*s*, 3 H); 1.21 (*dq*, *J* = 7, 12, 1 H); 1.26 (*s*, 3 H); 1.68 (*s*, 3 H); 1.70 (*s*, 3 H); 1.78 (*dq*, *J* = 7, 12, 1 H); 4.94 (*s*, 1 H); 5.16 (*s*, 1 H).

*(6*RS,*7*RS*)-5,6,7,8-Tetrahydro-3,5,5,6,7,8,8-heptamethylnaphthalene-2-carbaldehyde* (**66**). During 8 h, 16 portions of $Ce(NH_4)_2(NO_3)_6$ (16 × 16 g = 256 g, 467 mmol) dissolved in MeOH (16 × 100 ml) were added at 50° to a soln. of **71** (14.4 g 98% pure, 57.7 mmol) in MeOH (700 ml). The cooled (20°) soln. was poured into sat. aq. NaCl soln. and extracted with petroleum ether (30–50°). The combined org. phase was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated[27]) and the residue crystallized from EtOH to afford **66** (12.1 g, 98.5% pure, 80%). M.p. 133–136°. IR ($CDCl_3$): 2960, 1680, 1600, 1450, 1360, 1205. ^{1}H-NMR (360 MHz): 0.99 (*d*, *J* = 6, 6 H); 1.12 (*s*, 6 H); 1.33 (*s*, 3 H); 1.35 (*s*, 3 H); 1.59 (*m*, 2 H); 2.61 (*s*, 3 H); 7.21 (*s*, 1 H); 7.80 (*s*, 1 H); 10.19 (*s*, 1 H). MS: 258 (24, $M^{+\cdot}$), 243 (58), 201 (30), 187 (100), 173 (40), 159 (34), 141 (18), 131 (23), 115 (15), 57 (12), 43 (47).

*(6*RS,*7*SR*)-5,6,7,8-Tetrahydro-3,5,5,6,7,8,8-heptamethylnaphthalene-2-carbaldehyde* (**74**). Oxidation of **71**/**72** (mother liquors) afforded **66**/**74**. A sample of pure **74** was obtained by prep. GC. IR ($CDCl_3$): 2960, 1680, 1600, 1450, 1360, 1205. ^{1}H-NMR (360 MHz): 0.95 (*d*, *J* = 7, 6 H); 1.28 (2 *s*, 6 H); 1.31 (*s*, 3 H); 1.32 (*s*, 3 H); 1.92 (*m*, 2 H); 2.62 (*s*, 3 H); 7.18 (*s*, 1 H); 7.76 (*s*, 1 H); 10.20 (*s*, 1 H). MS: 258 (24, $M^{+\cdot}$), 243 (58), 201 (30), 187 (100), 173 (40), 159 (34), 141 (18), 131 (23), 115 (15), 57 (12), 43 (47).

*(6*RS,*7*RS*)-1-(5,6,7,8-Tetrahydro-3,5,5,6,7,8,8-heptamethylnaphth-2-yl)ethan-1-one* (**67**). In analogy to **18** (see above), **66** (7.0 g, 98.5% pure, 26.8 mmol) was treated with MeLi in Et_2O (or MeMgCl in THF) and the crude alcohol oxidized with PCC in CH_2Cl_2. Ketone **67** was crystallized from EtOH: 4.3 g (95% pure, 62%). A sample was recrystallized. M.p. 75–77°. IR ($CDCl_3$): 2960, 1670, 1440, 1350, 1220. ^{1}H-NMR (60 MHz): 0.91 (*d*, *J* = 6.5, 6 H); 1.06 (*s*, 6 H); 1.30 (*s*, 6 H); 1.58 (*m*, 2 H); 2.40 (*s*, 3 H); 2.45 (*s*, 3 H); 7.20 (*s*, 1 H); 7.73 (*s*, 1 H). MS: 272 (7, $M^{+\cdot}$), 257 (22), 215 (14), 201 (40), 173 (23), 159 (16), 141 (16), 128 (17), 115 (12), 57 (13), 41 (100).

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[27]) In certain experiments, it proved necessary to treat the crude product with 5% aq. HCl soln. in THF prior to crystallization (hydrolysis of acetal side product).

REFERENCES

[1] B.D. Mookherjee, R.A. Wilson, in 'Fragrance Chemistry', Ed. E.T. Theimer, Academic Press, New York, 1982, p. 433.

[2] M.G.J. Beets, 'Structure-Activity Relationships in Human Chemoreception', Applied Science Publishers Ltd., London, 1978, p. 207.

[3] T.F. Wood, in 'Fragrance Chemistry', Ed. E.T. Theimer, Academic Press, New York, 1982, p. 509.

[4] T.F. Wood, 'Chemistry of the Aromatic Musks', Givaudan Corporation Publisher, Geneva, 1968, p. 1.

[5] E.T. Theimer, J.T. Davies, *J. Agric. Food Chem.* **1967,** *15,* 6.

[6] A. Baur, *Chem. Ber.* **1891,** *24,* 2836; German Patents 47, 599, Appl. July 3, 1888, and 62,362, Appl. Aug. 14, 1891.

[7] M.S. Carpenter, W.M. Easter, Jr., US Patent 2,450,878, 1948; M.S. Carpenter, W.M. Easter, Jr., *J. Org. Chem.* **1951,** *16,* 618.

[8] L.G. Heeringa, M.G.J. Beets, US Patent 3,360,530, 1967.

[9] K. Kulka, US Patent 3,910,853, 1975.

[10] a) A.I. Stuper, W.E. Brügger, P.C. Jurs, 'Computer Assisted Studies of Chemical Structure and Biological Function', Wiley-Interscience, New York, 1979; P.C. Jurs, C.L. Ham, W.E. Brügger, in 'Odor Quality and Chemical Structure', Eds. H.R. Moskowitz and C.B. Warren, *ACS Symp. Ser.* **1981,** *148,* 143; b) J.N. Narvaez, B.K. Lavine, P.C. Jurs, *Chem. Senses* **1986,** *11,* 145.

[11] M. Chastrette, D. Zakarya, *C. R. Acad. Sci., Ser. 2* **1988,** *307,* 1185.

[12] T.F. Wood, M.W. Easter, Jr., M.S. Carpenter, J. Angiolini, *J. Org. Chem.* **1963,** *28,* 2248.

[13] F.C. Whitmore, C.A. Weisgerber, H.C. Shabica, Jr., *J. Am. Chem. Soc.* **1943,** *65,* 1469; W.T. Smith, Jr., J.T. Sellas, *Org. Synth.* **1952,** *32,* 90.

[14] R.O. Roblin, Jr., D. Davidson, M.T. Bogert, *J. Am. Chem. Soc.* **1935,** *57,* 151.

[15] H.A. Bruson, J.W. Kroeger, *J. Am. Chem. Soc.* **1940,** *62,* 36.

[16] B.M. Trost, M.R. Ghadiri, *J. Am. Chem. Soc.* **1984,** *106,* 7260.

[17] R.O. Hutchins, I.M. Taffer, *J. Org. Chem.* **1983,** *48,* 1360.

[18] B. Sullivan, P. Djura, D.E. Mc Intyre, D.J. Faulkner, *Tetrahedron* **1981,** *37,* 979.

[19] A.P. Krapcho, *Synthesis* **1982,** *805,* 893.

[20] C. Fehr, Swiss Patent Appl., prior. 30.6.1989.

[21] F. Sato, H. Ishikawa, M. Sato, *Tetrahedron Lett.* **1980,** *21,* 365.

[22] L. Syper, *Tetrahedron Lett.* **1966,** 4493; S. Torii, H. Tanaka, T. Inokuchi, S. Nakane, M. Akada, N. Saito, T. Sirakawa, *J. Org. Chem.* **1982,** *47,* 1647.

[23] A.N. Kasatkin, A.N. Kulak, G.A. Tolstikov, *J. Organomet. Chem.* **1988,** *346,* 23.

[24] J. Collonge, K. Mostafavi, *Bull. Chem. Soc. Fr.* **1939,** 335.

[25] E.P. Kündig, C. Perret, S. Spichiger, G. Bernardinelli, *J. Organomet. Chem.* **1985,** *286,* 183.

[26] H. Peters, R.A. Archer, H.S. Mosher, *J. Org. Chem.* **1967,** *32,* 1382.

[27] *Polak's Frutal Works Inc.*, Fr. 1,392,804, 1963 (*CA:* **1965,** *63,* 6781d).

[28] B. Winter, *Helv. Chim. Acta* **1989,** *72,* 1278.

[29] K.H. Schulte-Elte, W. Giersch, B. Winter, H. Pamingle, G. Ohloff, *Helv. Chim. Acta* **1985,** *68,* 1961.

[30] J. Pevsner, P.B. Sklar, S.H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.* **1986,** *83,* 4942.

[31] C. Fehr, J. Galindo, R. Perret, *Helv. Chim. Acta* **1987,** *70,* 1745.

[32] J. March, 'Advanced Organic Chemistry', J. Wiley, New York, 1985, p. 655.