

## New Woody and Ambery Notes from Cedarwood and Turpentine Oil<sup>1)</sup>

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The development of a new product in the chemical industry is still driven by needs like technical properties, price/performance ratio, biodegradability, or product safety. However, in terms of improving more and more on ecological criteria, summarized under such catchphrases as *sustainable development* or *green chemistry*, another important aspect is to use renewable resources as starting materials. This is not significantly new in fragrance chemistry, and there are a lot of raw materials in the perfume oils that are derived from molecules of renewable resources. Two commonly used materials are: *longifolene* (from turpentine oil) and *cedrene* (from cedarwood oil). These compounds are very suitable for the synthesis of *woody* and *ambery* notes, and even though it seemed that all possibilities were exhausted, it is actually still feasible to discover new molecules with excellent olfactory properties such as *Ambrocenide*<sup>®</sup> (**50a**), which is available in three steps from *α*-cedrene. Some of these molecules will be treated in this review, both with respect to synthesis as well as structural and sensory aspects.

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**Introduction.** – In the chemical industry, many companies have introduced rules and programs under the generic term *responsible care*. All efforts towards *green chemistry* can be seen as an important step in this direction. One of the mental fathers of *green chemistry*, Paul Anastas, has defined this term by means of twelve principles [1]. This review focuses on one of these principles and demonstrates how fragrance chemists, involved in the discovery of new odorants could contribute to this subject.

The principle we are referring to is: ‘Use renewable resources as raw materials wherever it is possible’. This is not significantly new in the domain of fragrance chemistry. Perfumery on the whole has its origin in the utilization of natural resources such as essential oils and natural extracts. But, after a triumphant progress in the area of synthetic fragrant substances, natural ingredients are nowadays used only to a relatively small extent, *e.g.*, in fine-fragrance perfumery. However, several natural raw materials consist mainly of hydrocarbons that are not suitable as smelling substances *per se*. These hydrocarbons often possess complex carbon skeletons, which are difficult to synthesize, but offer excellent possibilities for functionalization with oxygen-containing groups – transformations that often lead to interesting new fragrant materials. Some examples of naturally occurring raw materials that are especially useful in the synthesis of *woody* and *ambery* materials are depicted in *Fig. 1*.

Sclareol (**1**) is recovered from clary sage oil (*Salvia sclarea*) by solvent extraction [2]. The same technique is used for the isolation of manool (**2**) from the coniferous tree *Dacrydium biforme* [3]. Although both compounds are already functionalized, they represent the starting materials for two of the most-important ambery notes

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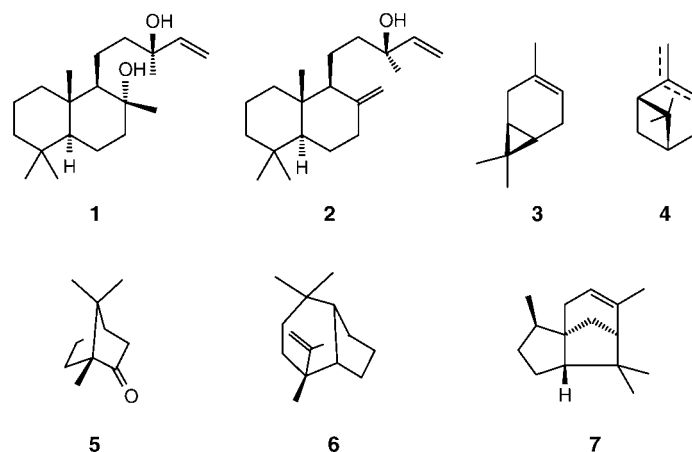


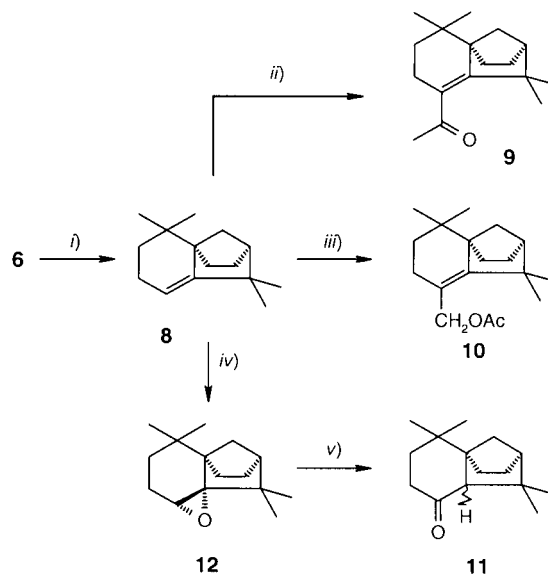
Fig. 1. Naturally occurring raw materials for the synthesis of fragrances with woody and ambery notes

(ambroxide (**52**) and amberketal (**47**); see below). Further examples include the cyclopropyl-monomer carene (**3**), a major ingredient of turpentine oil (*Pinus silvestris*; content: 40%), and, from the same essential oil,  $\alpha$ - and  $\beta$ -pinene (**4**). These compounds are produced by steam distillation of the plant material, followed by fractional distillation of the resulting oil. Camphor (**5**) is produced from camphor oil (*Ho oil*, content: ca. 50%) by crystallization. As the two most-promising starting materials in the search for new woody and ambery odorants, we chose longifolene (**6**), which is obtained from turpentine oil (*Pinus longifolia*; content: 5–10%) [4], and  $\alpha$ -cedrene (**7**), which is obtained from cedarwood oil (*Juniperus chinensis*; content: 20–46%) [5]. Woody and ambery notes play a decisive role in modern perfumery. They form the foundation of a lot of perfumes, and it is difficult to imagine a perfume without any woody or ambery notes.

**Fragrance Raw Materials from Longifolene.** – The synthesis of nearly all fragrant substances derived from longifolene (**6**) commences with an acid-catalyzed rearrangement of **6** to isolongifolene (**8**), *Brønsted* and *Lewis* acids working equally well (*Scheme 1*).

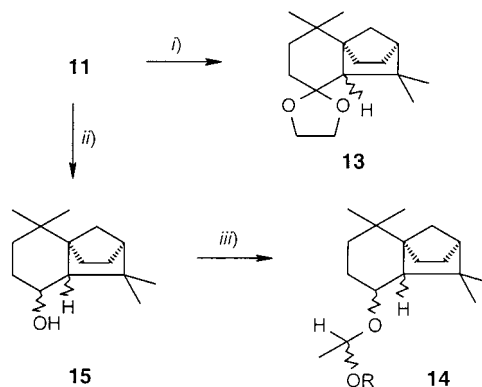
A simple derivatization of the first-generation product **8** is, e.g., the acetylation to acetylisolongifolene (**9**; *Capinone*<sup>®</sup>), which is described as *woody* (*Scheme 1*). Chemists from *Bush, Boake & Allen* investigated the *Prins* reaction of **8** with formaldehyde already in the 1970s [6], and commercialized **10**, which possesses *ambery, cedarwood- and vetiver-like aspects*, as *Amborylacetate*<sup>®</sup>. Vetiver oil is also a natural product of the woody family, though it is not obtained from wood, but from the roots of the grass *Vetiveria zizanioides*.

The most-important smelling substance from isolongifolene (**8**) up to the mid 1990s was isolongifolanone (**11**), which is synthesized by oxidation with a peracid, providing epoxide **12** (*Scheme 1*), which was commercialized under the name of *Folenox*<sup>®</sup>. The latter can easily be converted to **11** (*Piconia*<sup>®</sup>) in the presence of a *Lewis* acid, is being produced in hundreds of tons annually, and possesses a *pleasant warm woody smell* [7].

Scheme 1. First-Generation Products from Longifolene (**6**; see also Scheme 4)

*i*)  $\text{H}^+$  or Lewis acid. *ii*)  $\text{Ac}_2\text{O}$ , Lewis acid. *iii*)  $\text{CH}_2\text{O}$ ,  $\text{H}^+$ . *iv*) Peracid. *v*) Lewis acid.

Isolongifolanone (**11**) was the starting point of our research activities in the early 1990s. To improve the performance, we systematically synthesized acetals of **11**, and, at last, discovered *Ysamber K*<sup>®</sup> (**13**), the ethyleneglycol acetal of (**11**) (Scheme 2) [8].

Scheme 2. Acetals Derived from Isolongifolanone (**11**)

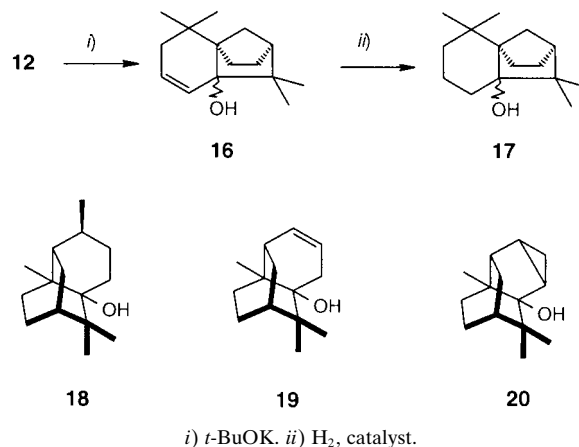
*i*)  $\text{HO}(\text{CH}_2)_2\text{OH}$ ,  $\text{H}^+$ . *ii*)  $\text{NaBH}_4$ ,  $\text{NaOH}$ . *iii*)  $\text{MeHC}(\text{OR})_2$ ,  $\text{H}^+$  ( $\text{R}=\text{Me}$ ,  $\text{Et}$ ).

*Ysamber K*<sup>®</sup> (**13**) has a powerful woody smell, and combines harmoniously *ambery* and *woody* elements. The importance of the acetal structure is discussed later, but the success of *Ysamber K*<sup>®</sup> (**13**) inspired us to look for other acetals, and we decided to investigate noncyclic acetals. Therefore, a number of linear formaldehyde- and

acetaldehyde-based acetals **14** were synthesized (*Scheme 2*) [9], which are easily available on  $\text{NaBH}_4$  reduction of **11** to **15**, followed by transacetalization. The new substances emanated an *interesting woody smell with herbaceous side notes*.

Some years ago, a sudden shortage of patchouli oil, a highly popular natural woody ingredient in perfumery, produced from the dried leaves of *Pogostemon cablin*, drove our attention to isolongifolenol (**16**). It is obtained by reaction of the epoxide **12** with *t*-BuOK (*Scheme 3*) [10].

Scheme 3. *Synthesis of Isolongifolenol (16) and Its Derivative 17. Compounds 18–20 are the so-called patchouli alcohols.*

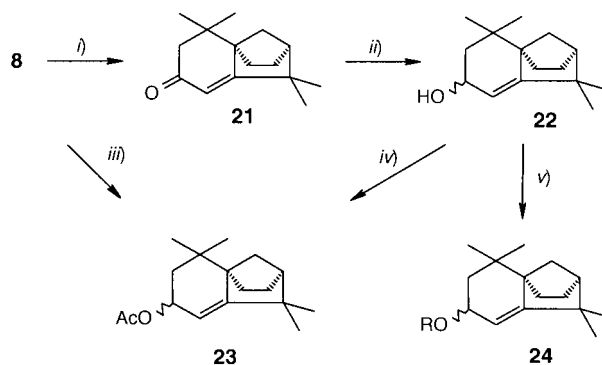


The unsaturated tertiary alcohol **16** possesses a *woody smell combined with strong earthy, patchouli-type aspects*. Hydrogenation of the C=C bond afforded the saturated alcohol **17** (*Scheme 3*), which is not so distinctly earthy as **16**. Indeed, both **16** and **17** show similarities to the structures of the alcohols occurring in patchouli oil, which are patchoulol (**18**) [11], *nor*-patchoulenol (**19**) [12], and *nor*-patchoulol (**20**) [13]. In combination with other *patchouli-like* smelling materials, isolongifolenol (**16**) has shown promising results in attempts for the reconstitution of this highly desired oil in perfumery.

The synthesis of another important commercial longifolene-derived first-generation product started with allylic oxidation of isolongifolene (**8**). Subsequent  $\text{NaBH}_4$  reduction of the resulting ketone **21**, followed by esterification of **22**, yielded isolongifolyl acetate (**23**), (*Scheme 4*). The latter possesses a *woody smell with vetiver-like nuances*, and is reported to combine well with vetiveryl acetate, a material synthesized from vetiver oil. Researchers from *Bush, Boake & Allen* published a one-step synthesis of this compound in the early 1970s, employing  $\text{AcOH}$ ,  $\text{CuCl}$ , and di(*tert*-butyl) peroxide [14].

We used the unsaturated isolongifolenol (**22**) to synthesize ethers like **24**, because the ether function is another frequently occurring structural element in woody and ambery materials (*cf.* ambroxide (**52**) below). And, indeed, simple substitution of the ester group with an ether function shifted the scent to an ambery direction and, what really surprised us, with musky side notes [15].

Scheme 4. First-Generation Products from Isolongifolene (8)



i) AcOH, Cr<sup>6+</sup>. ii) NaBH<sub>4</sub>. iii) O<sub>2</sub>, CuCl, (t-BuO)<sub>2</sub>. iv) Ac<sub>2</sub>O. v) Me<sub>2</sub>SO<sub>4</sub>, NaOH.

As described above, most products derived from longifolene (6) are synthesized *via* isolongifolene (8). However, other isomers are also useful for the creation of amber molecules, as described in reference [16], and according to this publication, the *allo*-isolongifolene ketone **25** does also exhibit an *amber-like* odor (Fig. 2).

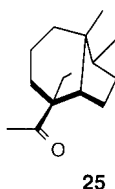


Fig. 2. Structure of *allo*-isolongifolene ketone, an amber-like odorant

**Fragrance Raw Materials from  $\alpha$ -Cedrene.** –  $\alpha$ -Cedrene (7) is a major constituent of the sesquiterpene fraction of cedarwood oil. Two other ingredients are  $\beta$ -cedrene (26) and thujopsene (27) (Fig. 3). By far, the commercially most-important cedrene-derived perfumery materials are produced by acylation of the sesquiterpene fraction of cedarwood oil, and are sold under the names of *Lignofix*<sup>®</sup>, *Vertofix*<sup>®</sup>, *MCK*<sup>®</sup>, and *methyl cedryl ketone*, to name just the most-important ones. The industrial syntheses basically make use of acetic anhydride (Ac<sub>2</sub>O) and polyphosphoric acid (H<sub>3</sub>PO<sub>4</sub>) as acetylating agents. Numerous investigations have been carried out to identify the compounds responsible for the *attractive warm and woody smell*. Today, it is generally accepted that the acetylated thujopsene isomer **29** is the principal odorant of the commercial mixture, the formation of which is detailed in *Scheme 5*, according to *Kitchens* and co-workers [17].

A series of *Wagner–Meerwein* rearrangements results in the unsaturated tricyclic compound **28**, which was coined *isomer B*. Acetylation of **28** then affords *isomer G* (**29**) in a highly unselective reaction, accompanied by numerous other compounds. The acetylation products of  $\alpha$ -cedrene (7) and  $\beta$ -cedrene (26) were also identified in the reaction mixture, but do not have any significant impact on the overall smell of the

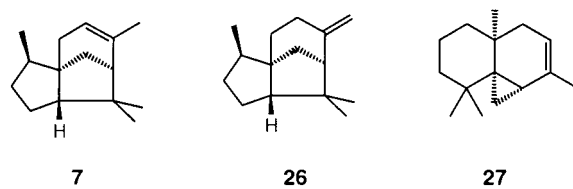
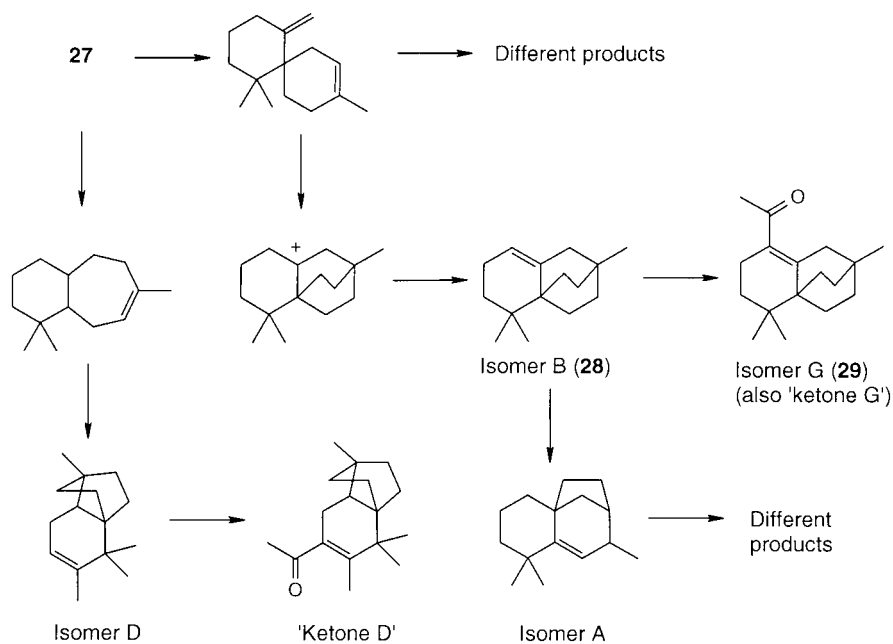
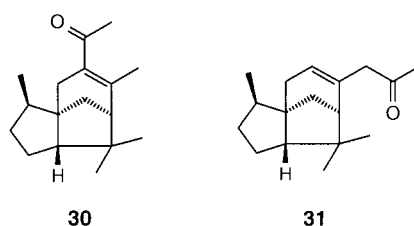


Fig. 3. Main constituents of the sesquiterpene fraction of cedarwood oil

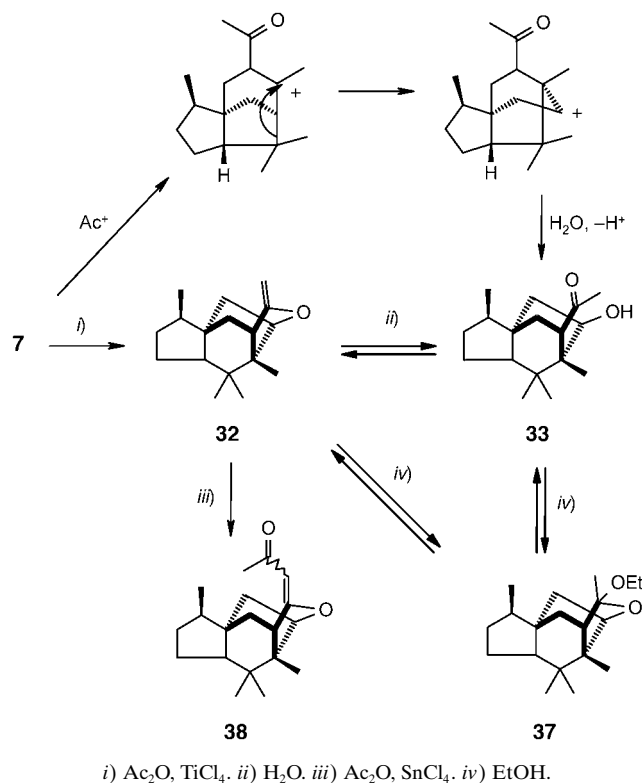
Scheme 5. Acetylation Products of Thujopsene (**27**)

mixture, as verified by olfactory evaluation of the pure substances. The acetylated  $\alpha$ -cedrene **30** possesses a *warm woody smell* [18], while the acetylated  $\beta$ -cedrene **31** is very weak in smell (Fig. 14) [19].

Fig. 4. Acetylation products of  $\alpha$ - and  $\beta$ -cedrene

Much effort was put into getting a more-definite picture of the acylation products of the sesquiterpene fraction of cedarwood oil. In 1973, *Sell* and co-workers [20] reported on the acetylation of  $\alpha$ -cedrene (**7**) in the presence of *Lewis* acids; they isolated and identified a compound of the new and unexpected structure **32**, an enol ether with a tetracyclic skeleton (*Scheme 6*). Upon hydration, the ring was opened, and hydroxy ketone **33** was obtained, which is *nearly odorless*, while **32** has a *weak, cedarwood-like odor*. In the initial step, the C=C bond of **7** is protonated, and the resulting *tertiary* carbocation undergoes a *Wagner–Meerwein* rearrangement prior to nucleophilic attack by a H<sub>2</sub>O molecule to afford **33** (*Scheme 6*). This unusual structure has not yet been found in nature, but the cyclic form **32** shows some structural similarity to the unnatural khusimone-like compound **34**, which was reported by *Büchi* [21] in 1978 (*Fig. 5*).

Scheme 6. Acetylation Products of  $\alpha$ -Cedrene (**7**), and Mechanism for the Formation of the Unexpected Product **33**



Khusimone (**35**) and  $\beta$ -vetivone (**36**) are responsible for the typical scent of vetiver oil [22]. When we synthesized the enol ether **32** to study its odor, we noticed that it emanates a *surprisingly strong and woody odor* when dissolved in EtOH. This was due to the acetal **37** (*Scheme 6*), which, indeed, exhibits a *powerful woody scent* [23]. The

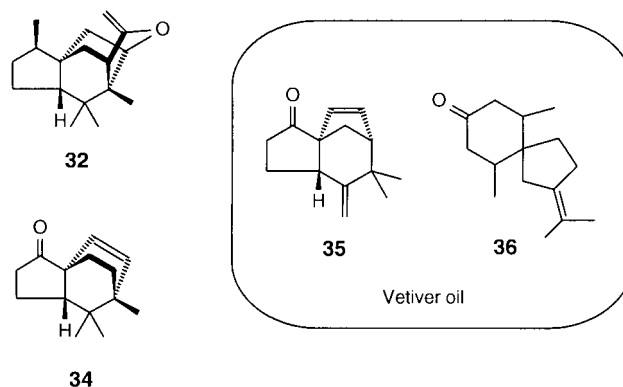


Fig. 5. *Khusimone* (**35**) and  $\beta$ -vetivone (**36**), constituents of vetiver oil, and structural relationship between the *khusimone*-like compounds **32** and **34**

usage of **37** in perfume formulations is, however, limited owing to its instability to heat and  $H_2O$ . Yet, in the course of our investigations on the acylation of  $\alpha$ -cedrene (**7**), we isolated some other compounds with interesting structures such as the vinylogous ester **38**, which is formed by acylation of **32** (Scheme 6), but possesses only a weak odor [24].

As in the case of isolongifolene, other commercial cedrene-derived first-generation products include the epoxide **39**, the tertiary alcohol **40**, the acetate **41**, and the very popular methyl ether **42**, which was commercialized as *Cedramber*<sup>®</sup> (Fig. 6). Their industrial syntheses are commonly known and, thus, not detailed here.

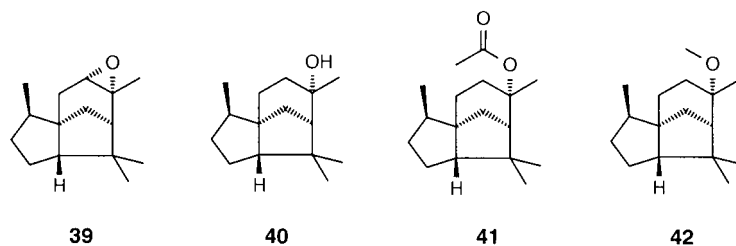


Fig. 6. Structures of commercial cedrene-derived products

Woody and ambery molecules have especially challenged fragrance chemists to investigate their structure–activity relationship (SAR). The main reason is probably that these molecules show great structural diversity and possess relatively similar scents. Until the beginning of the 1990s, the two most-important theories in this domain were *Ohloff's triaxial rule* [25] and *Vlad's ambergris triangle* [26]. The *triaxial rule* describes the relative position of three Me groups in a *trans*-decalin system. These should be in an *axial* position if the molecule smells ambery. The *ambergris triangle* specifies a range of distances of an O-atom to two adjacent H-atoms for an amber odorant.

In the mid 1980s, acetals became popular structural elements in the synthesis of woody and ambery odorants. Some examples, delineated in Fig. 7, include *Spirambrene*<sup>®</sup> (**43**), which is synthesized from carene (**3**) [27], *Karanal*<sup>®</sup> (**44**) [28], *Okoumal*<sup>®</sup>



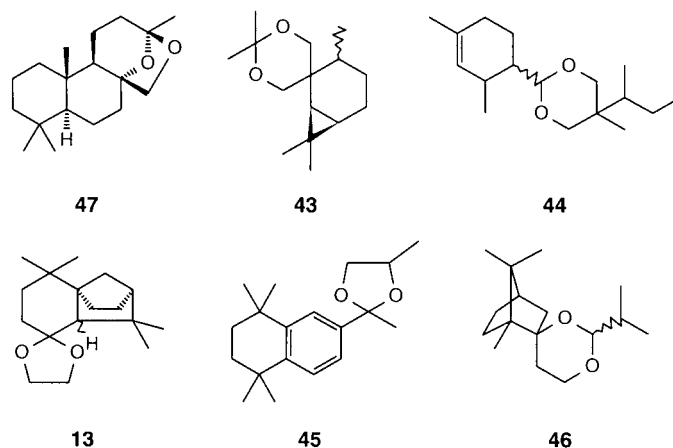
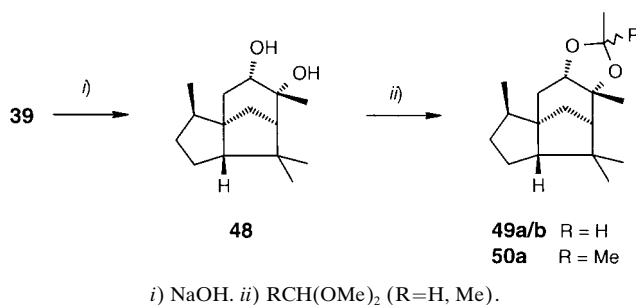


Fig. 7. Structures of woody- and ambery-smelling, acetal-based molecules

(**45**) [29], *Ysamber K*<sup>®</sup> (**13**), and *Belambre*<sup>®</sup> (**46**), which is synthesized from camphor (**5**) [30]. Known for a long time is, in addition, amberketal (**47**) [31], which is also synthesized from a renewable source, namely manool (**2**).

With this in mind, we decided to synthesize acetals possessing an  $\alpha$ -cedrene (**7**) skeleton. Starting material was the epoxide **39**, and, after ring opening of **39** to the diol **48**, we first obtained the acetaldehyde acetal **49a/b**, which, indeed, possesses a *woody, ambery smell*, with an odor threshold of 50 ppb in H<sub>2</sub>O (*Scheme 7*). The odor threshold of a new substance is a very interesting and important figure in addition to the sensory properties. The real breakthrough was, however, the synthesis of the corresponding acetone acetal, which led to the new captive *Ambrocenide*<sup>®</sup> (**50a**) [32]. The olfactory properties of **50a** differ not so significantly from that of **49a/b**, but the odor threshold, 0.06 ppb in H<sub>2</sub>O, is extremely low. The molecular weight of **50a** (278 g/mol) is very high compared to other fragrant chemicals, and very rarely do so large molecules possess such a low odor threshold, making **50a** very substantive in applications. Careful structural analysis confirmed that the diol moiety of **50a** is *syn*-configured, as shown in the calculated structure [33] depicted in *Fig. 8*.

Scheme 7. Synthesis of Acetals with  $\alpha$ -Cedrene Skeleton



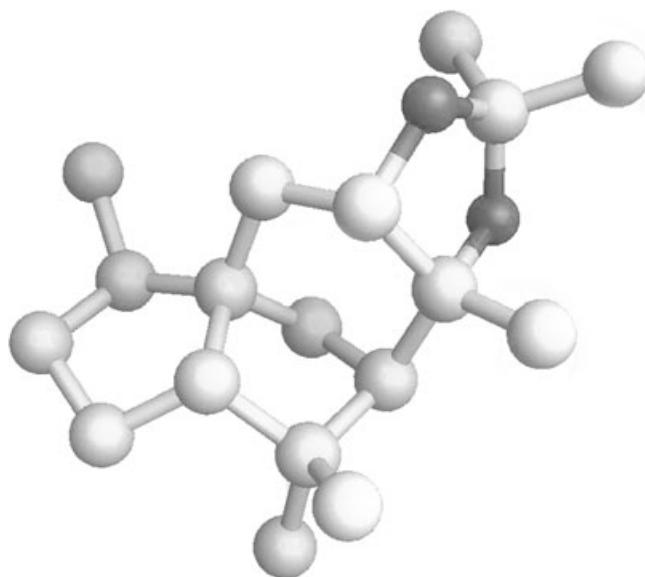


Fig. 8. 'Ball-and-stick' representation of Ambrocenide® (**50a**). Molecular structures and relative energies were calculated by means of the MAB all-atom force field without additional constraints, as implemented in MOLOC. Due to the rigid system of fused rings, only a few conformers had to be taken into account. Interatomic distances  $d$  are given in Å for the conformer of the lowest internal energy.

To further improve the odor threshold and, thus, the strength of Ambrocenide® (**50a**), we systematically varied its structure (Fig. 9). But neither the stereoisomers nor the *nor*-analogs did possess lower thresholds than the parent compound **50a**. In an additional attempt, we wanted to employ molecular-modeling techniques. Recently, three new theories were published on the structure–odor correlation of ambery

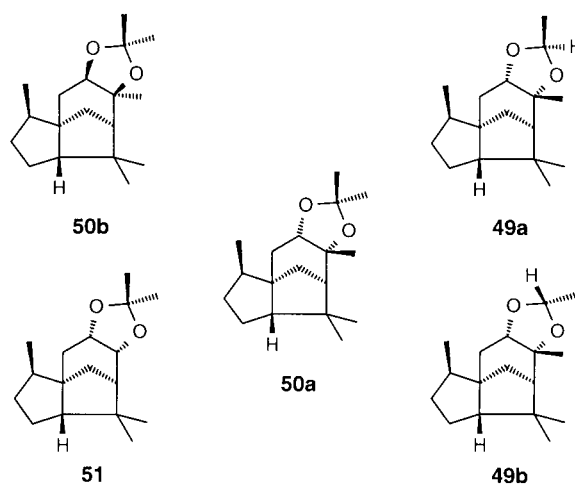


Fig. 9. Structural variations of Ambrocenide® (**50a**)

odorants: 1) Gorbachov and Rossiter [34] defined an ‘active amber-fragment, which consists of one oxygen and three carbon atoms which show certain atom partial charges in characteristic distances to each other’; 2) Bajgrowicz and Frank [35] introduced ‘a hypothesis generated from a special software, which is composed of one oriented hydrogen-bond-acceptor (HBA) function and four hydrophobic function’; and 3) Buchbauer and co-workers [36] followed ‘a combinatorial QSAR-approach, which considers all possible independent models and different descriptor collection’.

In our own SAR calculations [33], we followed the general approach of Gorbachov and Rossiter [34]. We first determined the distances of the designated atoms in the Ambroxide® (52) molecule (Fig. 10), and then calculated the distances of the respective atoms in the hypothetical, THF-fused molecules 53 and 54 (Fig. 11). The interatomic distances of 53 and 54 were compared to those of 52. Thereby, the data for 54 corresponded better with those of Ambroxide® (52) (Table).

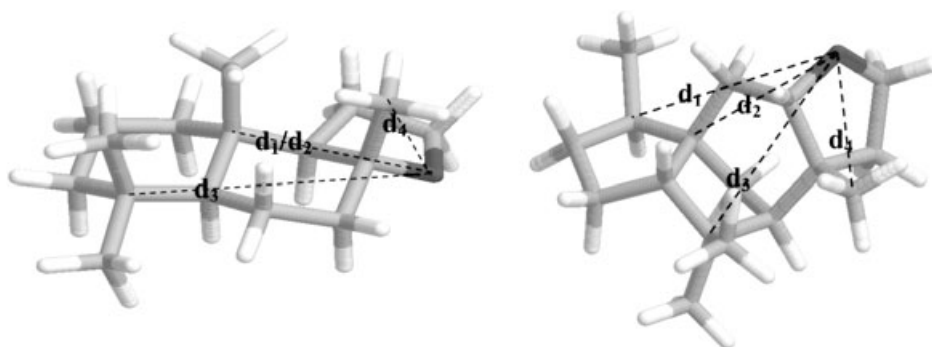


Fig. 10. Calculated structures and selected interatomic distances of 52 (left) and 53 (right). For experimental details, see the Table and the legend to Fig. 8.

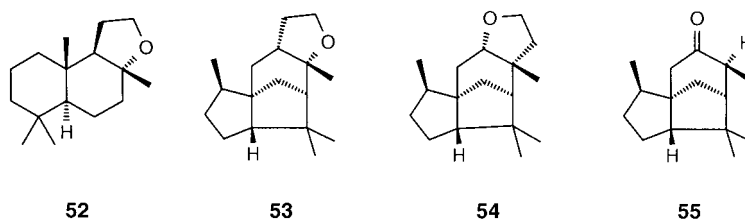


Fig. 11. Structures of Ambroxide® (52) and of the two new, analogous compounds 53 and 54, which were (incorrectly) anticipated to be ambery odorants (see text). Compound 54 was synthesized from cedranone (55).

Table. Comparison of Selected Interatomic Distances (see Fig. 10) of Compounds 52–54

Distance [Å]	Ambroxide® (52)	Analog 53	Analog 54
$d_1$	3.72 (0.10)	5.03 (0.10)	4.91 (0.10)
$d_2$	3.72 (0.10)	3.76 (0.05)	3.56 (0.05)
$d_3$	5.73 (0.10)	4.56 (0.10)	3.89 (0.10)
$d_4$	2.41 (0.05)	3.04 (0.05)	2.37 (0.05)

Compound **54** was readily synthesized from commercially available cedrane (**55**), [37]. However, contrary to our expectations, **54** showed neither the ambery odor characteristics and strength of *Ambrocenide*<sup>®</sup> (**50a**) nor of *Ambroxide*<sup>®</sup> (**52**), being not only much weaker, but with *dominating cedar and woody notes*. This finding shows that odor predictions on the basis of SAR theories still seem to be difficult.

In summary, we have shown that longifolene (**6**) and  $\alpha$ -cedrene (**7**) are still attractive starting materials for the synthesis of new woody and ambery fragrant substances. *Ambrocenide*<sup>®</sup> (**50a**) seems to be the best currently available molecule from these two resources. Predictions with existing SAR theories on the ambery odor of a given compound seem, however, to be difficult.

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