PERFUMER & FLAVORIST

Sesquiterpenoids: The Lost Dimension of Perfumery

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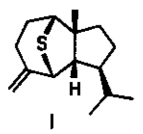
Over the last forty years, the isolation and characterization of sesquiterpenes has become an increasingly straightforward task for the organic chemist. Early successes in establishing the structures of hydrocarbons such as caryophyllene and longifolene paved the way to the solution of more difficult structural problems such as patchouli alcohol and β-vetivone. But even today new and interesting sesquiterpenoid structures are still being established as evidenced by mint sulphide [**1**] in peppermint residues and the pungent tamariscol [**2**] from the liverwort *Frullania tamarisci*.



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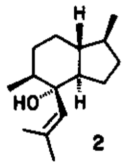
fresh, earthy, green



2

pungent

From the organic chemist's point-of-view, one of the more significant developments has been the classification of these structures into 18 groups based on proven or suspected biogenetic relationships involving the cyclization of cis- or trans-farnesyl pyrophosphate. An interesting question is how the compounds in these groups are perceived and used by the creative perfumer.

Sesquiterpenes, by definition, contain 15 carbon atoms which places them among the less volatile perfumery ingredients. Nevertheless, there exists considerable diversity in

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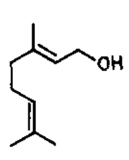

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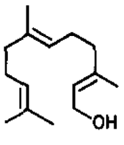

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floral

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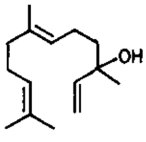

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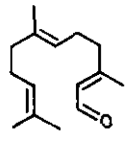
floral



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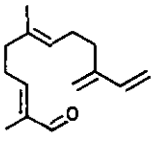

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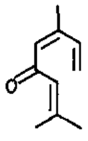

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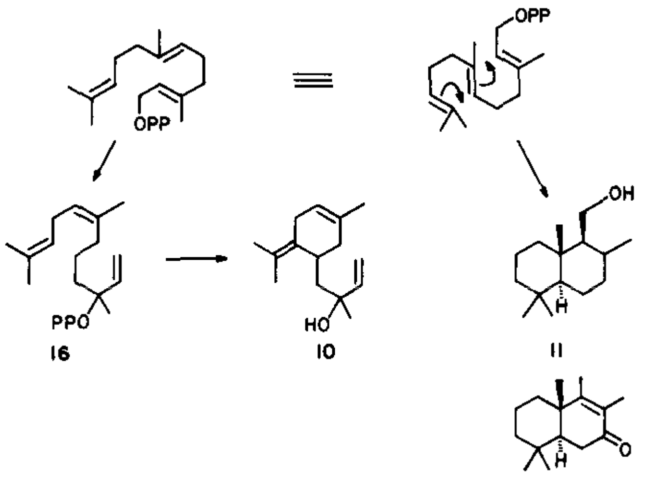
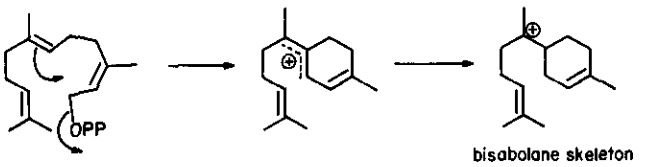
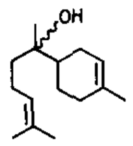
Group 1



Group 2





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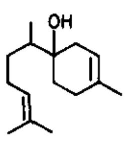
floral



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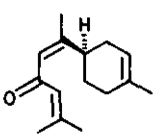
floral



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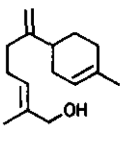

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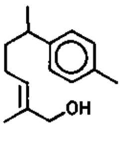

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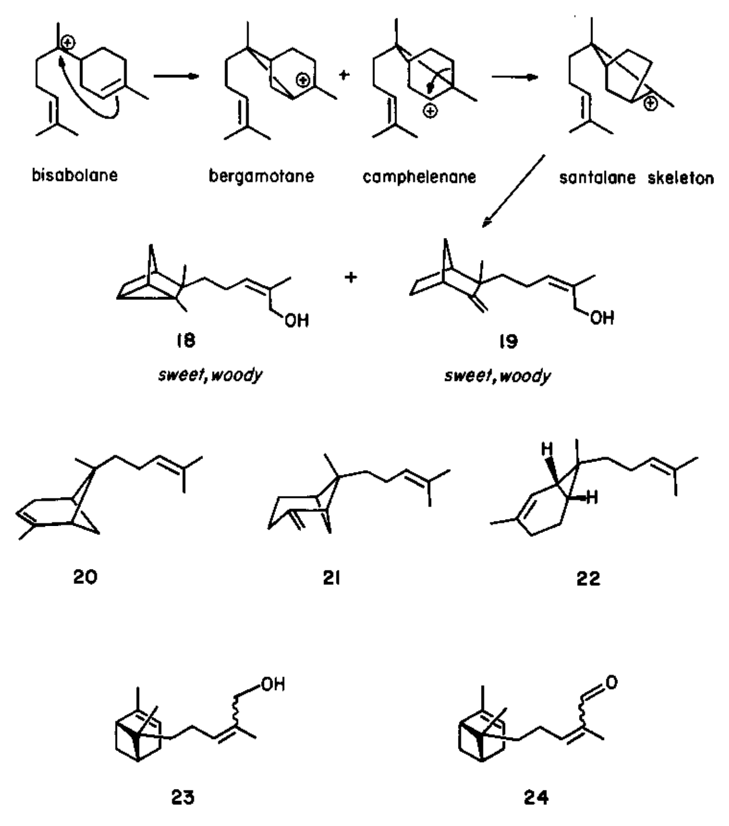
Group 3

physical properties between sesquiterpene hydrocarbons such as germacrene D and sesquiterpenoid alcohols, some of which are crystalline solids when isolated in a pure state. These mono-ols particularly play an important role in the base and fixative notes of the perfume; however, more polar materials with two or more functional groups are generally insufficiently volatile to be of perfumery interest.

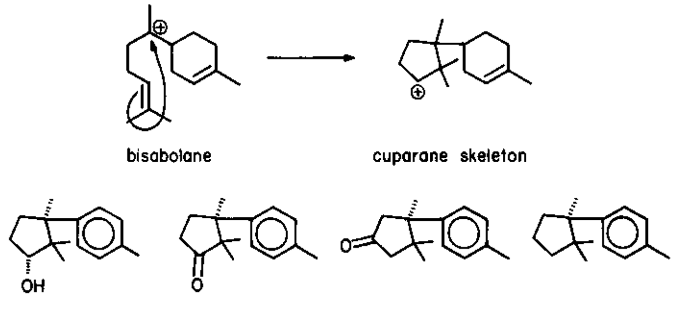
Group 1

The first group, the farnesane group, encompasses the sesquiterpene analogues of geraniol [**3**] and linalool [**5**]—farnesol [**4**] and nerolidol [**6**].

Synthetic farnesol and nerolidol are readily available intermediates to vitamin A and have a steady if modest use in perfumery for their tenacious mild floral odors. In addition, nerolidol [**6**] is accessible



Group 4



Group 5

as the major component of Cabreuva oil (*Myrocarpus rondosus*) and one or two other oils. Farnesal [**7**], the oxo analogue of farnesol, has little utility but the aldehyde with the functionality at the other end of the chain, sinensal [**8**], is a character impact component of Chinese orange oil.

Rather surprising, however, is the nullibiety of the sesquiterpene analogues of, for example, tagetone [**9**] oxygenated at a non-terminal position.

Group 2

In complete contrast, the mono- and bicyclo-farnesanes (Group 2), exemplified by humbertiol [**10**] and drimenol [**11**], have never become materials of perfumery commerce. The latter is often present in liverworts. Other oxygen-containing derivatives bearing the drimane skeleton are tobacco constituents, such as drimenone [**12**].

Group 3

The third group, the bisabolanes, although formally a sub-group of the monocyclofarnesanes, have a much longer history in both chemistry and perfumery. While many of this group's hydrocarbons (such as zingiberenes and curcumenes) are used as components of ginger oil (*Zingiber officinale*), the most important member of the group is the tertiary alcohol α-bisabolol [**13**], a component of oil of chamomile (*Matricaria chamomilla*), used not only for its delicate floral odor but also for its anti-inflammatory activity. Interestingly enough, β-bisabolol [**14**] is another naturally occurring alcohol for which a floral odor has been mentioned in literature, but its synthetic access is much more difficult. α-Atlantone [**15**] is a major component of Atlas and Himalaya cedarwood oils.

A contrast is provided by lanceol [**16**], the major component of *Santalum lanceolatum*, known since 1928 but never achieving real perfumery interest since the oil is not produced commercially. The corresponding aromatic alcohol nuciferol [**17**] appears not to have excited any attention either.

Group 4

The molecular rearrangements of the sesquiterpene skeleton begin to demonstrate themselves in the santalane molecules (Group 4). Sandalwood oil, produced by the steam distillation of the heartwood and roots of *Santalum album*, is used extensively for its powerful long-lasting sweet woody fragrance and contains as its major odoriferous components the polycylic alcohols α- and β-santalol [**18,19**]. Acetylation of an alcohol-rich fraction of the oil provides the important santalyl acetate, which possesses a sweet, woody odor of excellent tenacity.

Parenthetically, it is noteworthy that the cis-form of the aforementioned lanceol, and nuciferol are minor components of sandalwood oil.

Despite substantial efforts by synthetic chemists, sandalwood oil remains the preferred source of the important and valuable materials of Group 4. Included in this group, but based on a different cyclization of the bisabolyl cation, are α- and β-bergamotene [**20,21**] and sesquicarene [**22**], the sesquiterpene analogues of α- and β-pinene and carene. Whereas the hydrocarbons [**20** and **21**] are relatively spread constituents of essential oils used in perfumery, oxygenated derivatives like bergamotol [**23**] and bergamotenal [**24**] are rather rare natural components of specific oils (sandalwood and costus oils, respectively).

Group 5

The cuparanes (Group 5), exemplified by such compounds as α-cuparenol [**25**] and α- and β-cuparenone [**26,27**], are materials of perfumery indifference despite the availability of the parent hydrocarbon cuparene [**28**] in some cedarwood oil fractions, an obvious starting material for synthesis.

Group 6

Providing an excellent foil are the chamigrane class (Group 6) which includes α- and β-chamigrene [**29,30**], unusual natural products in having a central spiro-carbon atom. Further rearrangement leads to the tertiary alcohol widdrol [**31**], and most importantly to thujopsene [**32**] which incorporates a cyclopropane ring in its structure.

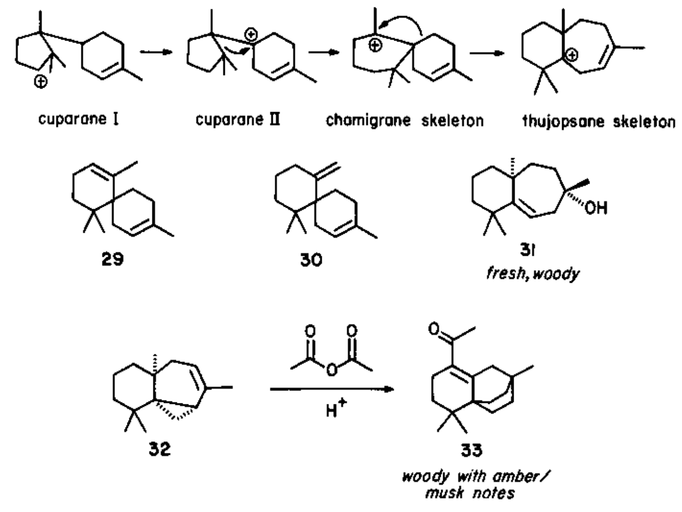
This hydrocarbon is the starting material for such products as Lixetone and Vertofix. The acetylated and rearranged thujopsene derivative [**33**] is the key odoriferous component of these important commodities, manufactured in hundreds of tons each year.

Group 7

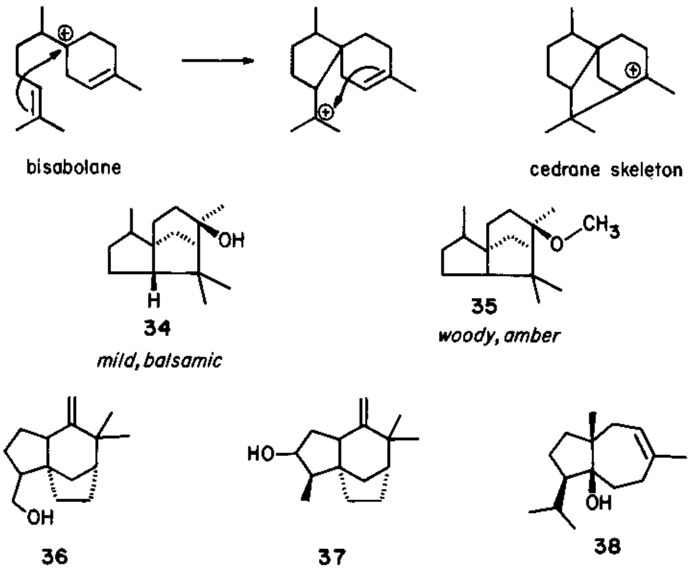
As well as being the principal component of hibawood oil (*Thuja dolabrata*), thujopsene is a major component of many cedarwood oils. The most important oxygenated component of these oils, however, is the crystalline tertiary alcohol cedrol [**34**], the 'parent' of the cedranes (Group 7). Cedrol is well-known and well established in the perfumery industry both in its own right as a mild balsamic odorant and as a source of such specialties as Cedramber [**35**] which is used for its woody odor with an amber undertone. Cedryl acetate is also used for its woody, leathery notes.

Other members of this group such as tricyclovetivenol (also known as khusenol or, more misleadingly as khusimol) [**36**], zizanol [**37**] and related carboxylic acids are known to perfumery only as components of vetiver oil. However, khusimyl acetate is now considered to be an important odor-bearing component of the speciality vetiveryl acetate.

Also included within Group 7 is carotol [**38**], the odor-character component of carrot seed oil (*Daucus carota*).



Group 6

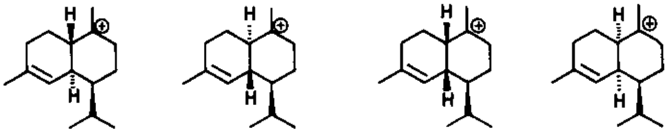


Group 7

Group 8

The cadinanes which are structures of much less complexity and generally based on the octalin skeleton, are found in Group 8. This group includes the cationic precursors to bulgarene [**39**], cadinene [**40**], muurolene [**41**] and amorphene [**42**], differing only in stereochemical details.

The cadinanes themselves form the largest group, and are widely distributed in nature. Bulgarenes in contrast are



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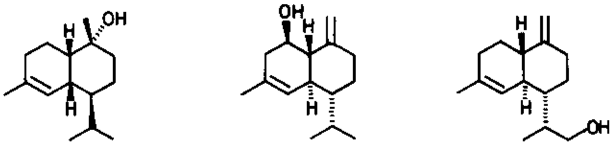

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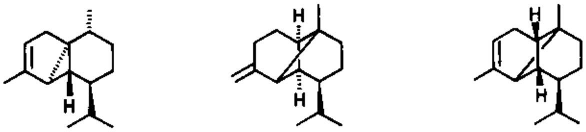

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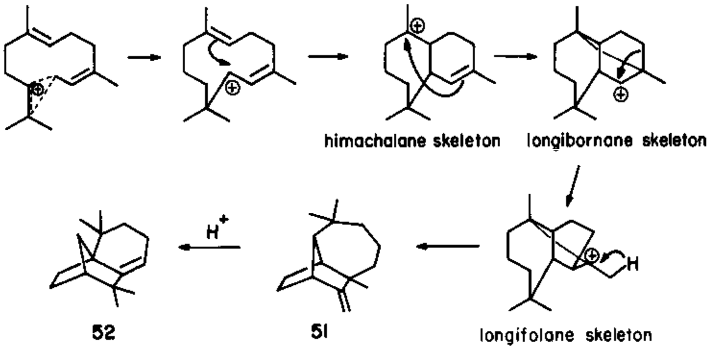
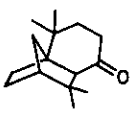
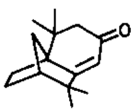
Group 8





53
woody, amber



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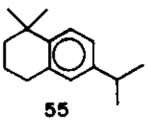
woody, cedar



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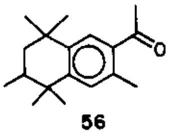

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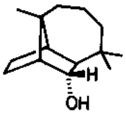


57
woody, mossy

Group 9

widerelatively uncommon, the earliest isolated one found in *Mentha piperita* of Bulgarian origin. Muurolenes are found in Swedish sulphate turpentine while amorphenes with very unusual isocyanide (-NC) and isothiocyanate groups (-N=C=S) are limited to marine sponges.

Their oxygenated counterparts such as torreyol [**43**], khusimol [**44**] and khusol [**45**] have no individual usage, merely finding their way into perfumes as essential oil components. The aromatic hydrocarbons calamenene [**46**] and α- or β-calacorenes [**47**] are also naturally occurring materials. The first [**46**] calls for a certain interest in view of its spicy-peppery odor notes and synthetic access to this material has been studied. Perfumers have shown no interest in other materials from this group such as cubebene [**48**], ylangene [**49**] and copaene [**50**], all of these with the complexity of an additional carbocyclic ring.

Group 9

Much greater interest is evident in the himachalanes (Group 9), primarily in their cyclized form of longifolene [**51**]. The chemistry of this complex hydrocarbon, readily and cheaply available from higher boiling fractions of Indian turpentine, has been particularly actively studied in that subcontinent. From either longifolene or its acid-catalyzed rearrangement product, isolongifolene [**52**], have come a number of perfumery products such as isolongifolanone [**53**] and isolongifolenone [**54**]; however, their use remains modest. In contrast to the acetylation of cedrene/thujopsene, acetylation of longifolene or isolongifolene provides no product of value.

When longifolene or isolongifolene is treated with a Lewis acid (e.g., zinc chloride) 1,1-dimethyl-7-isopropyltetralin [**55**] is formed, an obvious intermediate to musk-smelling odorants analogous to the well-known acetylhexamethyltetralin (Tonalid) [**56**]. The commercial exploitation of longifolene remains an obvious target for the research chemist. Longiborneol [**57**], which has been isolated from *Cedrus deodara*, has an interesting mossy-woody aroma.

Group 10

Equally readily available is caryophyllene [**58**], the parent hydrocarbon of Group 10. From *Eugenia caryophyllata*, used in its own right as clove oil, come the important phenolic ingredient eugenol (80%) and the bicyclic hydrocarbon caryophyllene (15%). Its structure and ready rearrangement under acid-catalyzed conditions provided organic chemistry with a host of problems in the 1950s. Indeed, it is this last property that has generated perfumery interest—in β-caryophyllene alcohol (caryolanol) [**59**] and its esters, the alcohol having a warm earthy-mossy odor with some woody character and the acetate a tenacious mild fruity-woody odor.

Caryophyllene epoxide [**60**] occurs in a great number of essential oils useful in perfumery. In its own right, it seems to be a valuable aroma chemical in reconstituted oils. An internal tricyclic oxide, caryophyllane-2,6β-oxide [**61**] has been mentioned in the literature as a constituent of verbena oil (*Kippia citriodora* Kunth.)

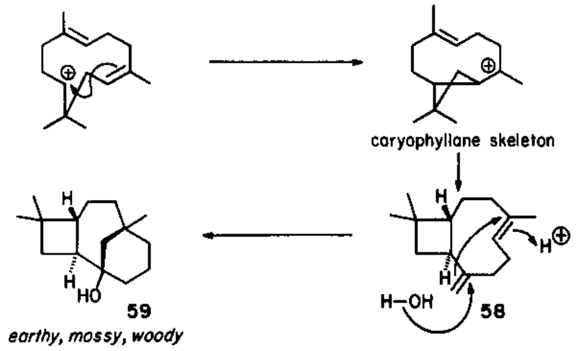
Group 11

Humulene [**62**] (Group 11), the third most common component of clove oil at 5%, and structurally akin to an uncyclized caryophyllene, has only one perfumery material developed from it—α-caryophyllene alcohol [**63**]. Like the β-isomer, α-caryophyllene alcohol has a formidably rearranged skeleton. Gymnomitrol [**64**], a liverwort metabolite, displays this unusual ring structure.

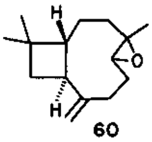
Group 12

Chemical knowledge of the germacranes (Group 12) is of a much younger vintage: due largely to the high reactivity of their diene functionality in the ten-membered ring, the germacrenes react readily to form cadinene and its stereoisomers. Consequently the isolation and structural identification of germacrenes A, B, C and D [**65-68**] was only completed as late as 1970. They are surprisingly ubiquitous and are found as quite major components in essential oils such as ylang-ylang and cananga.

Oxygenated analogues such as hedycaryol [**69**] and germacrone [**70**] exhibit similar high reactivity, so it is unlikely that members of this group will achieve commercial importance. Nevertheless, the latter is a major component of Bulgarian zdravetz oil (*Geranium macrorhizum*), and its odor has been described as sweet-woody, somewhat herbaceous, and of great tenacity.



earthy, mossy, woody



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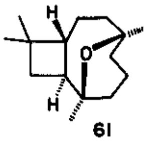

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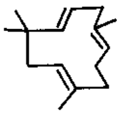
Group 10



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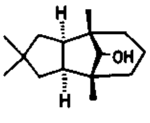

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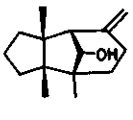

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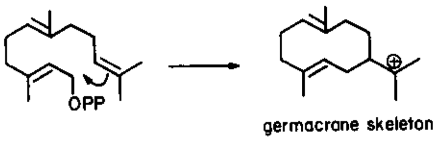
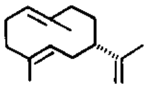
Group 11





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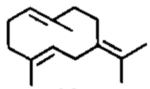

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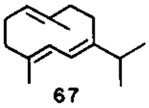

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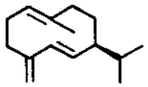

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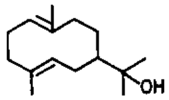

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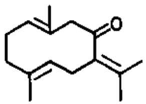


70

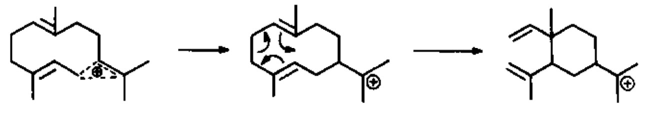
sweet, woody, herbaceous

Group 12

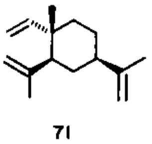
Group 13

As a group, the germacranes rearrange thermally via a Cope rearrangement to the elemanes, typical examples of which are β- and δ-elemene [**71,72**] (Group 13). Compounds of this type are the major components of elemi and amyris oils used for their fresh lemony/peppery and woody/balsamic odors respectively. However, their exceptionally wide provenance suggests that in some cases they are artefacts formed during isolation procedures.

Both elemi and amyris oils contain substantial quantities of hydrocarbons such as α- and β-elemene [**73,71**] which should be capable of elaboration to more useful and powerful odoriferous materials such as occidenol [**75**] and shyobunone [**76**]. Crystalline monocyclic α-elemol [**77**] is also readily available as an isolate from amyris oil, the so-called West Indian sandalwood oil (*Amyris balsamifera*); it has a faint sweet-woody odor.



elemane skeleton



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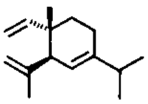

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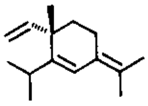

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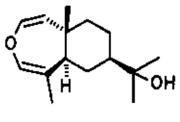

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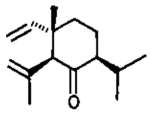

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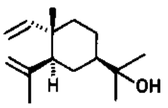

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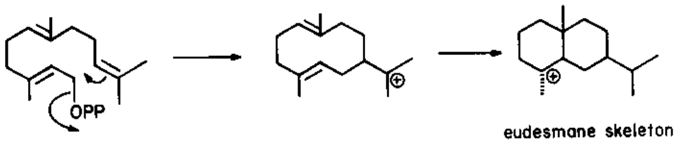
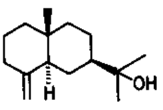
sweet, woody

Group 13



eudesmane skeleton



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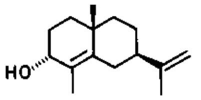
herbal, woody



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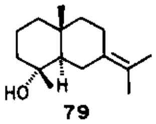

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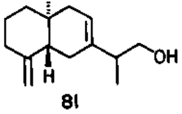
minty, woody



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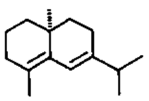

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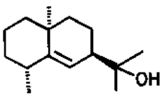

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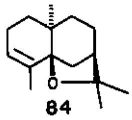

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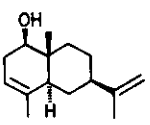

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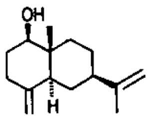

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Group 14

Group 14

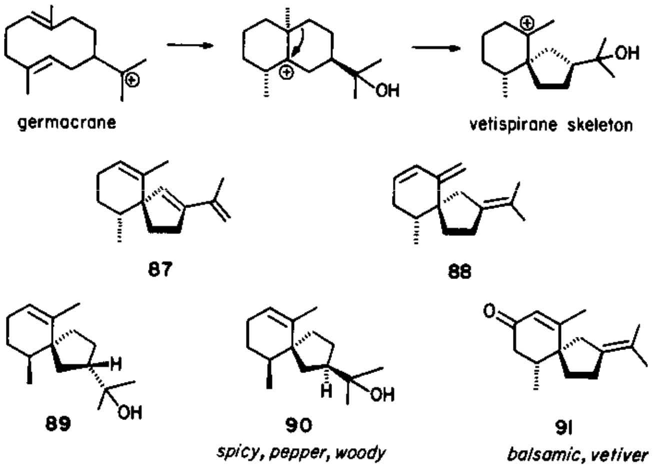
With the eudesmanes (Group 14), we revert back to a group of materials that became familiar to organic chemists more than a century ago, comparable therefore in many ways to the cadinanes. (Both groups produce substituted naphthalenes on dehydrogenation.) Oxygen substitution is found at numerous positions round the rings as demonstrated in β-eudesmol [**78**], juniper camphor [**79**], cyperol [**80**] and vetiselinenol [**81**]. These compounds are seldom used as individual materials, instead just as components of essential oils—β-eudesmol [**78**], for instance, is a common component of many eucalyptus oils and juniper camphor [**79**] is a crystalline component of juniperberry oil. β-Eudesmyl acetate is of interest for its linalyl acetate notes combined with improved intensity.

The availability of suitable selinene hydrocarbons (e.g. [**82**]) makes materials like rosifoliol [**83**] and α-agarofuran [**84**] attractive and realizable targets. The alcohols, α- and β-dictyopterol [**85,86**] have been detected in the essential oil of the brown algae *Dictyoptelis divaricata*; algae remain an unusual and underutilized source of sesquiterpenoid material.

Group 15

Vetiselinenol [**81**], mentioned above, is a more recently identified vetiver oil (*Vetiveria zizanoides*) component, and provides a link with the 15th group, the vetispiranes, the majority of examples being components of that extremely important fragrance oil. Accurate structure elucidation within this group has been a long and difficult task and misidentification has led to confusion and misnaming. Typical examples of this genre are α- and β-vetispirene [**87,88**]; the tertiary alcohols agarospirol [**89**] and hinesol [**90**], the latter having spicy-pepper and woody notes; and of course β-vetivone [**91**]—generally accepted as one of the key odoriferous components of vetiver oil.

Academic syntheses of these materials have been achieved but the partial synthesis from the hydrocarbon analogues has been little explored due to the difficulty of obtaining substantial quantities in a pure state. The alcohol-rich fraction of the oil (vetiverol) is often acetylated to produce the established perfumery specialty, vetiveryl acetate, produced under a variety of trade names, noted for its exceptionally tenacious woody odor.

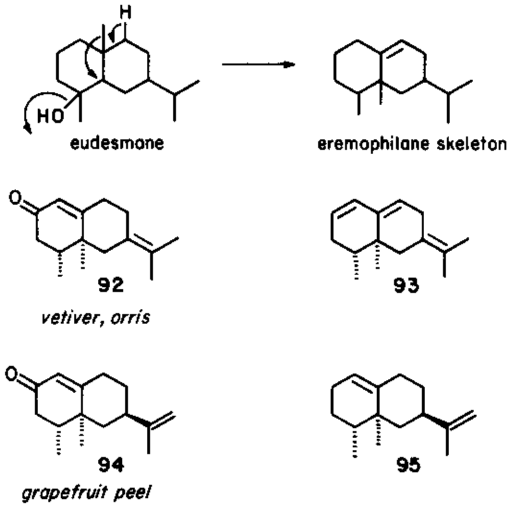


87 88 89 90 91

90 *spicy, pepper, woody*

91 *balsamic, vetiver*

Group 15



92 *vetiver, orris*

93

94 *grapefruit peel*

95

Group 16

Group 16

Vetiver components are also prominent among the eremophilanes (Group 16), rare among terpenoids in having methyl groups on contiguous carbon atoms. Typical examples are α-vetivone [**92**], another character-impact component of vetiver oil and β-vetivenene [**93**]. Closely related to the former compound is nootkatone [**94**], an important component of grapefruit odor and flavor, available synthetically from the hydrocarbon valencene [**95**], present in orange peel oil.

Group 17

Earlier it was pointed out that cyclization of a germacrene intermediate led to the six-membered-ring eudesmane group. An alternative mode of cyclization producing five- and seven-membered rings gives the guaiane skeleton (Group 17), which on subsequent rearrangement and internal cyclization provides the pseudoguaiane, patchoulane and seychellane sub-classes, typical members of which are displayed [**96-98**].

From a historical perspective the guaiane skeleton is of particular interest since the intensely blue hydrocarbon guaiazulene [**99**], a component of chamomile oil, has had an important bearing on the development of the theory of chemical aromaticity. More normal compounds in this class are the patchoulenes [**100,101**] of patchouli oil, and guaia-6,9-diene [**102**], the characteristic sesquiterpene hydrocarbon of geranium bourbon oil. It is easy to derive two other constituents with interesting structural features from compound [**102**] by oxidative cleavage of a double bond in the seven-membered ring or by additional ring closure: furopelargone A [**103**] and β-bourbonene [**104**] represent sesquiterpenes for the first time detected in the same oil which has a great importance in fragrancing soaps.

Oxygenated compounds are better known, the isomeric tertiary alcohols guaiol [**105**] and bulnesol [**106**] being widely distributed in nature; the former is used as the source of a variety of speciality esters with woody, floral odors, and of the cyclic oxide guaioxide [**107**], of possible utility in the perfumery industry.

Key components in important patchouli oil are pogostol [**108**] and patchouli alcohol [**109**], the latter's structure having posed severe chemical problems until the position was resolved by Büchi. From an olfactive point-of-view the more recently isolated norpatchoulenol [**110**] may be another important constituent. Unusual components of patchouli oil are the sesquiterpene alkaloids patchoulipyridine [**111**] and epiguaipyridine [**112**].

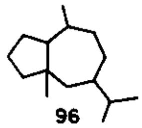
Group 18

Finally Group 18, a somewhat diffuse group, encompasses members of the last two classes in which the isopropyl side-chain has cyclized to produce an additional three-membered ring. Typical examples are aromadendrene [**113**], α-gurjunene [**114**] and aristoladiene [**115**]. This group also includes a particularly wide range of alcohols: globulol [**116**], ledol [**117**], spathulenol [**118**], viridiflorol [**119**] and palustrol [**120**]; while they have excited the talents of the synthetic chemist, they have not caught the imagination of the perfumer, despite the fact that they possess generally woody odors buttressed by other characteristic notes such as amber, balsamic, earthy and orris.

Conclusions

What conclusions then can we reach? The natural products chemist has elicited a formidable array of structures over the last forty years; new compounds are still being isolated and their structures identified, particularly fruitful


germacrane → guaiane skeleton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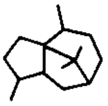
pseudoguaiane skeleton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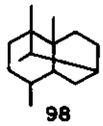
patchoulane skeleton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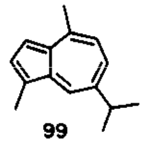
seychellane skeleton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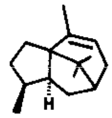
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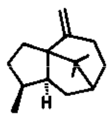
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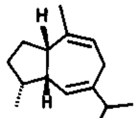
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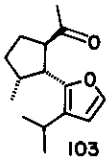
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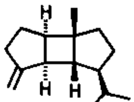
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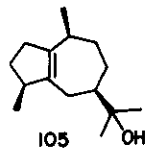
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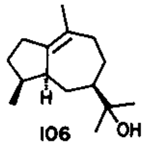
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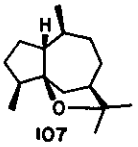
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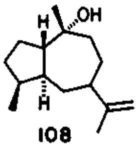
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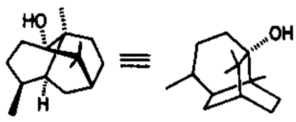
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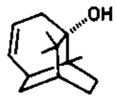
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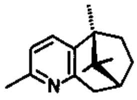
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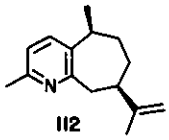
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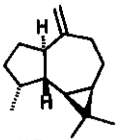
Group 17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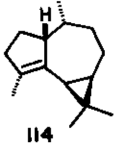
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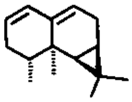
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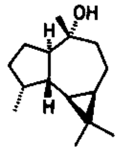
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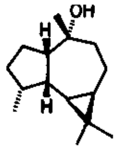
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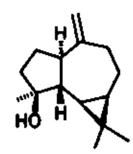
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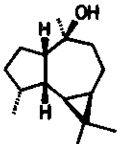
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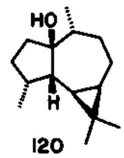
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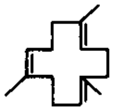
Group 18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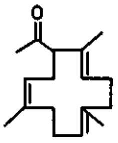
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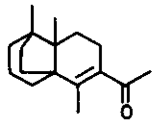
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areas currently being those derived from algae and other aquatic material. The perfumery industry has been slow to use this knowledge and these new materials, for the most part being content in the use of the essential oils that have been familiar for the last century. What can be achieved by cooperation of organic chemist and perfumer is well demonstrated by the development of 1,5,9-trimethylcyclododecatriene [**121**].

This totally synthetic sesquiterpene hydrocarbon, prepared by the trimerization of isoprene, with no analogues in nature (at least not yet), has been acetylated under mild conditions to yield an acetylated trimethylcyclododecatriene [**122**] (marketed as Trimofix O) and under more vigorous conditions to produce an isomeric acetylated tricyclic ketone [**123**], both of which have achieved commercial success.

Further opportunities for the positive interaction of technical and creative personnel to produce attractive new products in the sesquiterpene field are, I believe, manifold.

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References

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Sesquiterpene chemistry is regularly reviewed in the Royal Society of Chemistry's "Natural Product Reports," ed. BM Fraga, *Nat Prod Rep* **1** 61 (1990); **5** 497 (1988)