Translated from *Uspekhi Khimii*, 51 1129-1156 (1982) U.D.C. 547.596/599 + 665.53.091

The Chemistry of Perfumes Based on Labdane Diterpenoids

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The advances in the synthesis of C_{14}-C_{19} perfumes derived from bicyclic labdane diterpenoids and their enantiomers as well as data concerning the sources of the starting materials are presented. The dependence of the odour of the above compounds on their structure and stereochemistry and the questions arising in the manufacture of some of them and their practical applications are considered.
The bibliography includes 242 references

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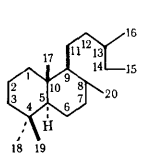
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I. INTRODUCTION

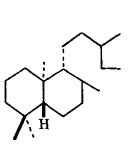
Derivatives of labdane (I) [1-4] occupy an important place among diterpenoids. They are stable biosynthetic intermediates in the conversion of aliphatic compounds into cyclic compounds, including kauranoids, which are precursors of gibberellins[5]. Derivatives of both labdane and *enantio*-labdane (II) (eneruane) are widely distributed in nature[3]. In certain plants they are present in large amounts, can be readily isolated, and have therefore been known for a long time. Labdanoids have frequently been used as the starting materials in syntheses (including biomimetic syntheses) of tricyclic and tetracyclic diterpenoids[6]. All these factors led to the accumulation of extensive factual data on the chemistry of these compounds.

An important stimulus for the development of the chemistry of labdanoids proved to be the discovery among their transformation products of substances with an intense smell of ambergris[7,8]—full substitutes of ambergris, which is a product of the metabolism of sperm whales and is one of the most valuable types of raw material for perfumery[9]. Its odour is due to the products of the autoxidation of the main component—ambrein (3) (a triterpene)[10,11]. Simultaneously with the elucidation of the chemical nature of the perfume components of ambergris, it was noted[7] that the products of the oxidation of the labdanum glycol sclareol (4), isolated from the muscat sage, also have the odour of ambergris. These observations gave rise to a series of studies on the resolution of sclareol[8,12,13], which culminated in the preparation of a series of interesting compounds with the ambergris odour.

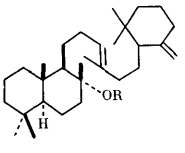
Subsequently such substances were obtained also from other labdanoids. The majority of these contain 16–18 carbond atoms and have effective fixative properties.



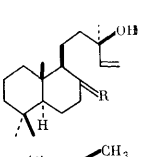
(1)



(2)



(3) R=H
(137) R = THP



(4) R = $\swarrow^{CH_3}_{OH}$
(5) R = CH_2

The industrial manufacture of perfumes based on readily available labdane diterpenoids was begun in the 1950's[14-20]. These include sclareol, isolated from the waste products of the essential oil industry[21-29], and manool (V), isolated from the wood of the yellow pine[30,31]. The main raw materials for the manufacture of sclareol are in the USSR. Our perfume industry manufactures on its basis two products with the odour of ambergris—ambrial[19,32-34] and ambroxide[20,32].

During the last 10–15 years, there has been a considerable growth of interest in the perfumes obtained from labdanoids, as shown by the numerous publications. The reason for this is the continually growing demand for these substances throughout the world and the continuously decreasing number of sperm whales.

Another cause of the intensification of this research is the study of the dependence of odour on the structure of substances, a problem which is far from being solved[35]. The rigid *trans*-decalin skeleton, the possibility of obtaining enantiomeric compounds, as well as the extensive factual data which have accumulated make perfumes based on labdane diterpenoids a convenient model for tracing the dependence of odour on structure.

The intensification of studies on labdanoids was also promoted by the fact that large amounts of these substances as well as their cleavage products are present in tobacco[36-44], imparting to it valuable organoleptic properties. The addition of these compounds to various kinds of tobacco improves its quality[45-48].

The majority of the perfumes considered have been obtained from labdanoids. Several oxides of the *enantio*-labdane series, which also proved to have the odour of ambergris, have been synthesised quite recently[49,50].

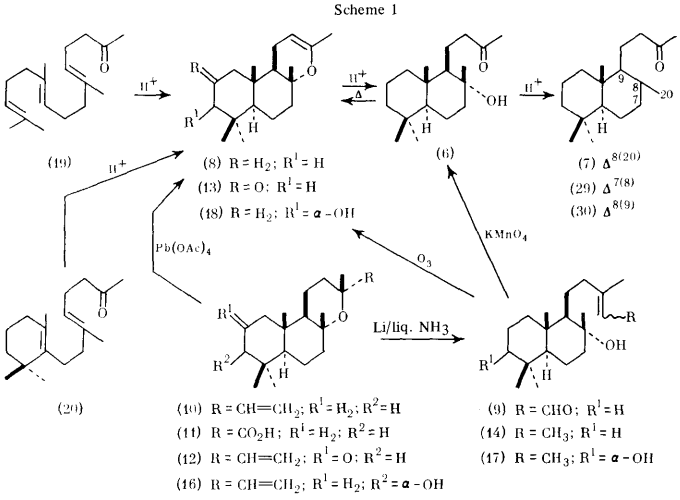
The present review surveys data on the chemistry of perfumes obtained from labdane diterpenoids and published up to 1981. Certain reviews[51-53] and monographs[3,54] devoted to other problems include isolated information concerning the topic under consideration, but there have been no systematic surveys. We have used the system of numbering of carbon atoms in labdane proposed by Kocker and Halsall[1].

II. 14,15-BISNOR-13-LABDANONES—IMPORTANT INTERMEDIATES IN THE SYNTHESIS OF PERFUMES

When labdanoids are cleaved to C_{15}-C_{18} compounds, derivatives of 14,15-bisnor-13-labdanone are always formed. 8α-Hydroxy-14,15-bisnor-13-labdanone (6) and 14,15-bisnorlabd-8(20)-en-13-one (7) are of greatest interest for the synthesis of perfumes. The hydroxyketone (6) was

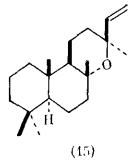
obtained on oxidising sclareol[55–57]. It is unstable and is converted into the oxide (8) on standing or heating (Scheme 1).

Scheme 1



(19) (8) R = H_2; R^1 = H (6) (7) $\Delta^{8(20)}$
(13) R = O; R^1 = H (29) $\Delta^{7(8)}$
(18) R = H_2; R^1 = α-OH (30) $\Delta^{8(9)}$
(20) (10) R = CH=CH_2; R^1 = H_2; R^2 = H (9) R = CHO; R^1 = H
(11) R = CO_2H; R^1 = H_2; R^2 = H (14) R = CH_3; R^1 = H
(12) R = CH=CH_2; R^1 = O; R^2 = H (17) R = CH_3; R^1 = α-OH
(16) R = CH=CH_2; R^1 = H_2; R^2 = α-OH

The melting point indicated for this compound therefore varies from 90° to 122 °C.[55,58–60] The reverse reaction, involving the opening of the oxide (8), takes place on treatment with acids or semicarbazide[56,58]. By altering the conditions, the sclareol oxidation reaction can be directed preferentially towards the formation of substances (6) or (8), which have been obtained also on oxidation of certain sclareol transformation products, for example the aldehyde (9):[58,60]



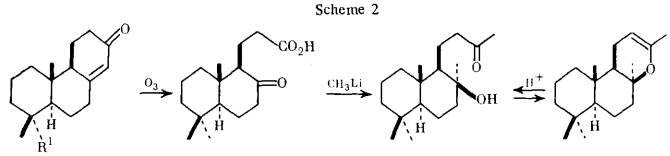
(15)

The enol ester (8) has also been synthesied from manoyl oxide (10) as a result of its oxidation with the acid (11) [61] and the decarboxylation of the latter[62]. The keto-oxide (13) has been obtained similarly from 2-oxomanoyl oxide (12) [63] (see Scheme 1). 2-Oxomanoyl oxide can also be reduced quantitatively to manoyl oxide without isolating it from the pine resin[63]. On a preparative scale, a different method of converting the oxide (10) into the hydroxyketone (6) is more convenient: the hydrogenolysis of the oxide to dihydroabienol (14) [64] and its oxidation [the yield of the hydroxyketone (6) was 94%]. The hydroxyketone (6) can be obtained in this way also from 13-epimanoyl oxide (15). The hydrogenolysis of 3α-hydroxymanoyl oxide (16) leads to the product (17), whose ozonisation gives rise to the alcohol oxide (18).[65]

The enol ester (8) has also been synthesised by cyclising *trans, trans*-farnesylacetone (19) [66] or *trans*-β-monocyclofarnesylacetone (20) [67] (see Scheme 1). Its stereoisomers have been obtained analogously[68]. However, the method is complex, since the starting materials are difficult to obtain.

The epimer (21) of the hydroxyketone (6) at the C(8) atom is formed together with the enol ester (22) [58] when methyl-lithium reacts with the ketoacid (23)—the product of the ozonisation of podocarp-8(14)-en-13-one (24). The unsaturated ketone (24) was synthesised from manool[30,69] and neoabietic acid (25) [70] or *m*-methoxyphenylacetylene[58] (see Scheme 2).

Scheme 2

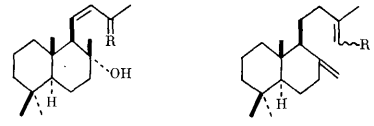


(24) R = O; R^1 = CH_3 (23) (21) (22)
(25) R = iso-Pr; R^1 = CO_2H

The enol ester (8), the hydroxyketone (6), and its dehydro-derivative (26) have been detected in tobacco[39]. Compound (26) was first isolated from the resin of the Siberian larch[71]. It is the product of the autoxidation of neoabienols (27) and (28).[72–75] Its hydrogenation gives rise to the hydroxyketone (6).[71]

14,15-Bisnorlabd-8(20)-en-13-one is a product of the dehydration of the hydroxyketone (6). However, the dehydration of the latter leads to 14,15-bisnorlabd-7-en-13-one (29) [56,58,76] or to a mixture of the isomeric compounds (7), (29), and (30),[77] which has also been obtained in the oxidation of sclareol[78,79]. On dehydration of the stereoisomeric hydroxyketone (21), a mixture of the ketones (29) and (30) is obtained[70].

14,15-Bisnorlabd-8(20)-en-13-one was first obtained in the oxidation of manool with potassium permanganate[30]. The structure was demonstrated by Schenk et al.[80], who modified the method of oxidation described in another communication[81] (see also Ohloff[82] and Demole and Weust[83]).



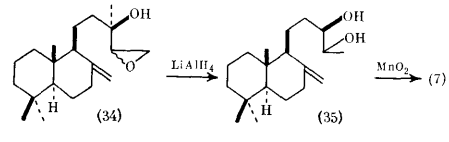
(26) R = O (31) R = CH_2Br
(27) R = $CHCH_3$; Δ^{13}-*cis* (32) R = CHC
(28) R = $CHCH_3$; Δ^{13}-*trans* (33) R = CH_2OAc

The yield of the ketone (7) is 36–40% and does not increase when the oxidation conditions are varied[84–86]. It is also formed in a low yield of (14%) in the ozonisation of manool[84].

Two- and three-stage methods of synthesising the ketone (7) from manool are known. Thus on treatment with certain oxidants[85,87] or via the bromide (31),[88] manool is converted into a mixture of the *cis*- and *trans*-aldehydes (32), which are oxidised to the ketone (7).[85] The acetate (33), which is a product of the substitution of the bromide (31), also gives rise to the ketone (7) on oxidation[88]. Compound (31), in a mixture with its isomers and dibromides, is also formed on bromination of sclareol[88–91], which permits the synthesis of the ketone (7) from sclareol. On the other hand, it is known[82] that sclareol diacetate yields manool acetate on pyrolysis. This reaction can be achieved more simply by heating sclareol with acetic anhydride and calcium carbide[92] or pyridine[93]. In the latter case the product consists of a complex mixture of substances.

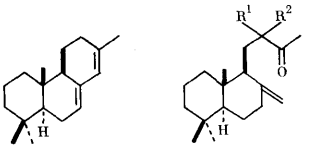
An interesting conversion of manool into the ketone (7) in 90–95% yields, involving its selective epoxidation to a mixture of epoxides (34), the reduction of the latter to a mixture of diols (35), and the cleavage of the latter by various oxidants, the best of which is manganese dioxide, has been described (see Scheme 3)[94]. This series of transformations can be achieved without isolating the intermediates.

Scheme 3



(34) (35)

14,15-Bisnorlabd-8(20)-en-13-one has been detected in tobacco[42] and in certain types of resin[95,96]. In one of them[95] it is present together with its Δ^{11}-dehydro-derivative, formed on dehydration of the hydroxyketone (26).[71] We may note that the ketone (7) is unstable: it undergoes autoxidation on standing[79] and cyclises to the hydrocarbon (36) under the influence of acids[13,97,98].

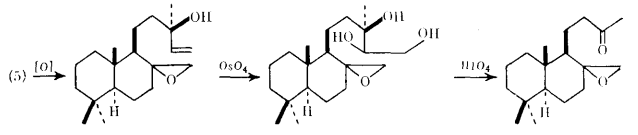


(36) (44) $R^1 + R^2 = CH_2$

(45) $R^1 = CH_2OCH_3$; $R^2 = H$

8,20-α-Epoxy-14,15-bisnor-13-labdanone (37), detected in *Dacrydium kirkii*, is of great importance for the synthesis of perfumes[99]. It was obtained from the manool monoepoxide (38), which is formed together with its steroisomer (39) when manool is oxidised by peracids (see Scheme 4). The ratio of the stereoisomers (38) and (39) varies within wide limits as a function of the reactants and the reaction conditions[91, 99-101]. On interaction with osmic acid, the epoxide (38) gives the epoxytriol (40), which is cleaved by periodic acid to the epoxyketone (37).[100,102] This transformation can be achieved in a single stage, using catalytic amounts of osmic acid[100,102,103]. The same result is obtained when the unsaturated epoxide (38) is ozonised[104].

Scheme 4



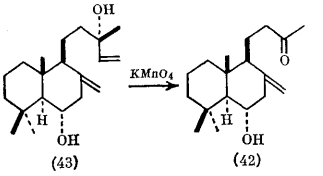
(38) α-epoxy (40) (37) α-epoxy

(39) β-epoxy (41) β-epoxy

Compound (37) and a small amount of its stereoisomer (41) are formed when the ketone (7) is oxidised with *m*-chloroperbenzoic acid[85,100,104]. Monoperphthalic acid leads mainly to its further transformation products[85]. The expoxyketones (37) and (41) have been detected among the sclareol oxidation products[79].

6-α-Hydroxy-14,15-bisnorlabd-8(20)-en-13-one (42)—the product of the oxidation of larixol (43) [105-109] which is one of the main components of the resins of different species of larch[110-115]—is of great interest for the synthesis of perfumes.

The forms of the ketone (7) oxidised in the C(19)-position have been detected in natural sources[116,117].

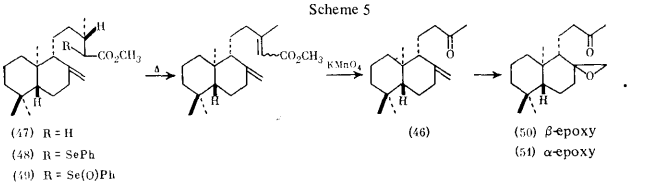


(43) (42)

When the ketone (7) is condensed with formaldehyde, it gives rise to a mixture of C_{19} products (44) and (45), which have also been used to synthesise perfumes[118].

The synthesis of the optical isomer (46) to the ketone (7) via Scheme 5 from the ester of eperuic acid (47) [119] has been achieved recently[49]. The selenium derivatives (48) and (49) are of key importance in this synthesis. Thus the possibility, in principle, of using labdanoids and their optical isomers with a saturated side chain in the syntheses of perfumes has been demonstrated, which makes it possible to extend significantly the range of starting materials for such syntheses.

Scheme 5



(47) R = H (46) (50) β-epoxy

(48) R = SePh (51) α-epoxy

(49) R = Se(O)Ph

When the ketone (46) is epoxidised with *m*-chloroperbenzoic acid, it gives rise to a mixture of the epoxides (50) and (51), in which the former predominates.

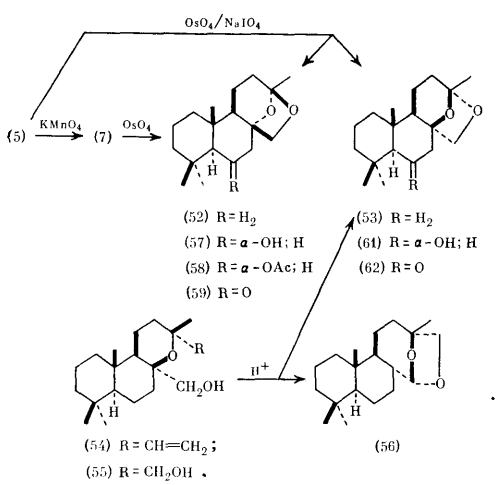
III. THE SYNTHESIS OF PERFUMES FROM LABDANE DITERPENOIDS

1. C_{18} and C_{19} Perfumes

The group of C_{18} perfumes consists mainly of intramolecular ketals. The first of these [compound (52)], which has an intense odour of ambergris, was discovered among the products of the oxidation of manool with permanganate[81] (see Scheme 6). Its structure was confirmed by the fact that it is formed on interaction of the ketone (7) with osmic acids[8,103] and also by NMR and data for its hydrogenolysis[100]. Compound (52) has also been obtained on oxidation of manool with osmic acid and sodium periodate[100] or, together with its diastereoisomer (53), on isomerisation of the epoxyketone (37),[100,102-104] which occurs in the course of its formation on oxidation of the ketone (7) with monoperphthalic acid[86]. It was thought that the ketal (53) also has a powerful odour of ambergris, but, according to the latest data[50], it lacks such an odour.

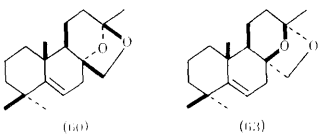
The main method of opening the epoxide ring in compound (37) involves nucleophilic attack by the carbonyl oxygen on the C(8) atom with inversion of configuration, since, for a ratio of the epoxyketones (37) and (41) in the initial mixture of 16 : 1, the content of the ketal (53) in the reaction products changes from 50% [118] to 70%,[100,102-104] depending on the conditions. Partial opening of the epoxide ring occurs also via the S_N1 mechanism, since, in the presence of 6% of the epoxyketone (41) in the initial mixture, the yield of the ketal (52) reaches 25% and, in the isomerisation of the pure epoxyketone (37) under the same conditions, the yield is 10%.[83] If the isomerisation of the mixture of the epoxyketones (37) and (41) is carried out with silicic acid in a heterogeneous medium, then the opening of the opoxide ring in compound (37) takes place preferentially via the S_N1 mechanism and the ketal (52) predominates in the reaction products[83].

Scheme 6



A theoretically interesting method of converting manool into the ketal (53) has been described[120]. Manool monoepoxide is isomerised with an acid to the alcohol oxide (54). Successive ozonisation, reduction, and hydrolysis of its acetate lead to the diol (55), which is converted by acids into a mixture of the ketals (53) and (56) (see Scheme 6).

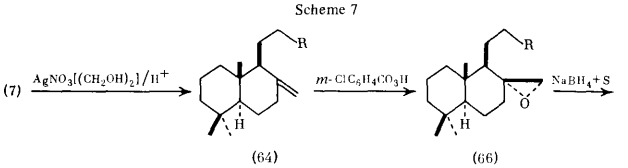
In order to expand the raw material resources for the preparation of the ketals (52) and (53) and their analogues, methods have been developed for their synthesis from other labdanoids. Thus the oxidation of larixol[108] and its acetate[106–110] results in the formation of the hydroxyketal (57) and its acetate (58) respectively. The product of the oxidation of the former—the ketoketal (59)—undergoes the Wolff-Kishner reduction to the ketal (52),[109] which has also been obtained from compound (57) on dehydration of the latter to compound (60) and its subsequent hydrogenation[108, 121]. Only the ketal (60) has an odour. An analogous synthesis of the ketals (53) and (61)–(63) from the hydroxyketone (42) has been described in a patent[121]; one of the products [compound (63)] is a perfume[118]:

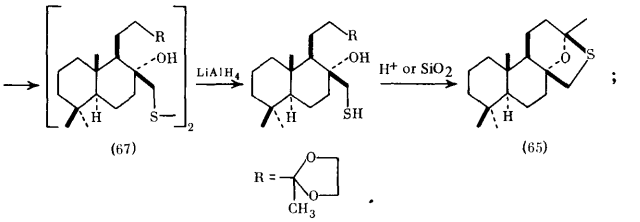


Compounds (52) and (53) have been discovered also among the products of the oxidation of sclareol[122,123].

The thio-analogue (65) of the ketal (52) has been synthesised from the ketal (64) of the ketone (7).[97] The conversion of the ketone (7) into the ketal by treatment with silver nitrate and the formation of the sulphur-containing dimer (67) when the epoxide (66) interacts with the sulphur-treated sodium tetrahydroborate are key stages in the synthesis. The thioketal (65) has a weak woody odour.

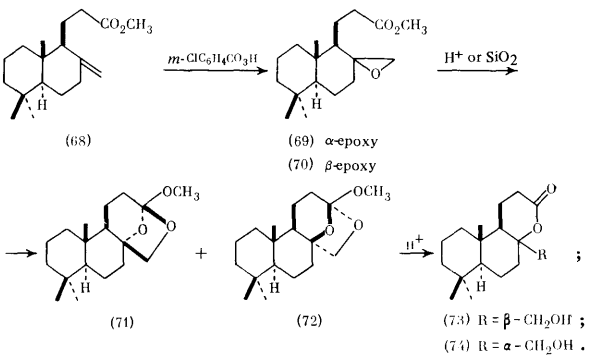
Scheme 7



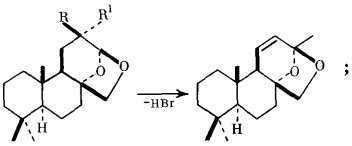


Interesting perfume analogues of the ketals (52) and (53) have been described[83]. The ester (68), which is the product of the oxidation of the ketone (7),[81,85] is oxidised by *m*-chloroperbenzoic acid to an 8 : 1 mixture of the epoxyesters (69) and (70) (Scheme 8), which isomerise on treatment with acid to a mixture of the orthoesters (71) and (72), in which the latter predominates. This conversion of the ester (68) can be achieved in a single stage when the epoxidation is carried out at a higher temperature. When the epoxyester (69) is isomerised with silicic acid, the orthoester (71) predominates in the reaction product, i.e. there is a complete similarity in the behaviour of compounds (37) and (69). The structure and stereochemistry of the orthoesters (71) and (72) have been confirmed by spectroscopic methods and by the formation, following their acid hydrolysis, of the known 20-hydroxyambreinolide (73) and its epimer (74).

Scheme 8

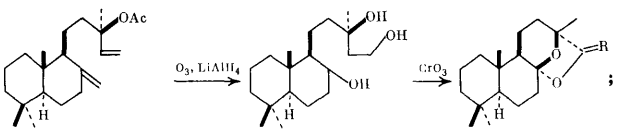


The reaction of the ketal (52) with bromine converts it into a mixture of compounds (75)–(77).[124] The monobromoderivative (75) is resistant to the action of alkalies, while its isomer (76) splits off hydrogen bromide, albeit with difficulty, and is converted into the scented ketal (78):



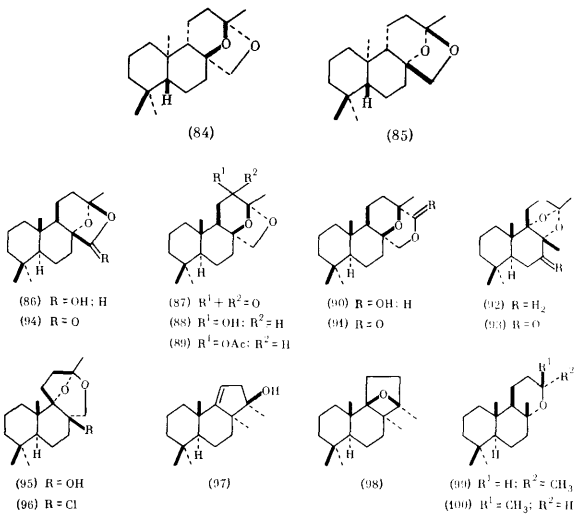
When manool acetate (79) was ozonised, the triol (80), which can be oxidised to the perfume (81), was isolated in a low yield (see Scheme 9)[125]. The ozonisation of manool itself leads to the formation (together with other products) of the hemiacetalketal (82), which has no odour. However its oxidation product, the lactone (83),[126] which can be obtained from manool in a single stage[85], is a perfume.

Scheme 9



(79) (80) (81) R = H_2; (82) R = OH; H; (83) R = O.

The enantiomers (84) and (85) of the ketals (52) and (53), the first substances of the *enantio*-labdane series which also possess the odour of ambergris[50], have been obtained recently[49] by the isomerisation of the epoxyketones (50) and (51):



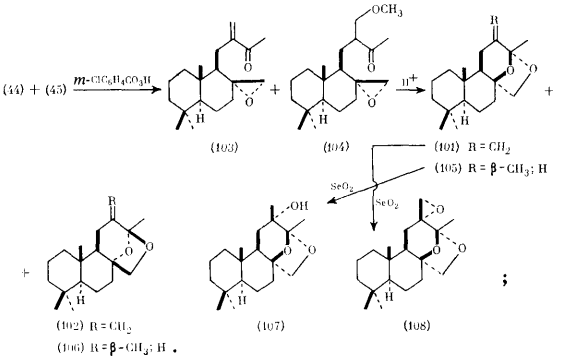
(84) (85) (86) R = OH; H (94) R = O (87) $R^1 + R^2$ = O (88) R^1 = OH; R^2 = H (89) R^1 = OAc; R^2 = H (90) R = OH; H (91) R = O (92) R = H_2 (93) R = O (95) R = OH (96) R = Cl (97) (98) (99) R^1 = H; R^2 = CH_3 (100) R^1 = CH_3; R^2 = H

In the course of the search for perfumes, the intramolecular ketals (86),[124] (87)–(91),[100] (92) [125] (this substance has also been found in tobacco[43]), (93),[80] (94),[85] and (95) and (96) [127] were synthesised, but none of them are scented.

When the ketone (7) is irradiated with ultraviolet light, a mixture of 12 substances is formed, two of which, compounds (97) and (98), have the odour of ambergris[128]. When the enol ester (8) is hydrogenated, a mixture of oxides (99) and (100), which have also been detected in tobacco[43], is produced. The oxide (100) has the odour of ambergris[129].

Few C_{19} perfumes are known. The reason for this is apparently their low volatility owing to their high molecular weights. The scented substances (101) and (102) have been obtained by treating the epoxides (103) and (104), which are the products of the oxidation of the ketones (44) and (45),[118] with acid (see Scheme 10). Simultaneously with isomerisation, the epoxyketone (104) splits off methanol. The products (105) and (106) of the hydrogenation of the ketals (101) and (102) and the products (107) and (108) of the oxidation of the ketals (101) and (105) with selenium dioxide are also scented.

Scheme 10



(102) R = CH_2 (106) R = β-CH_3; H. (103) (104) (101) R = CH_2 (105) R = β-CH_3; H (107) (108)

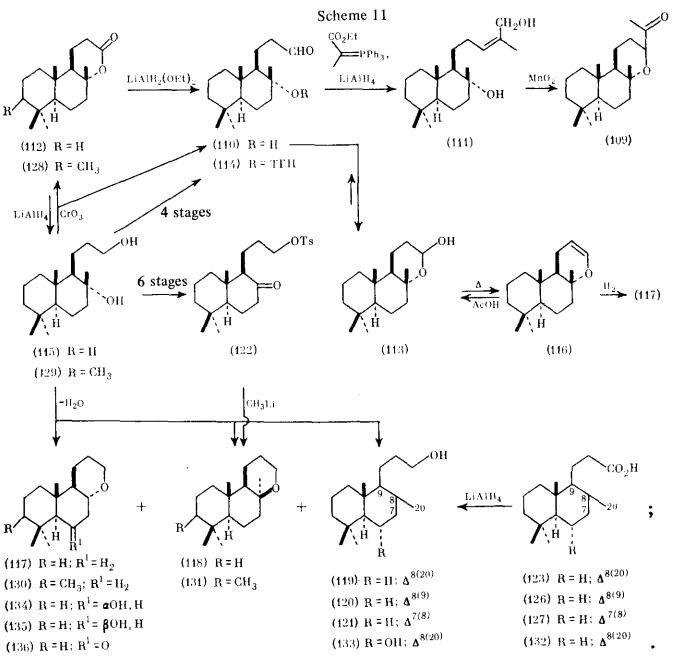
Yet another C_{19} perfume [compound (109)] has been synthesised in accordance with Scheme 11 below from ambreinolal (110). The oxidation of the diol (111) with activated manganese dioxide takes place in an unusual manner with the cleavage of the C–C bond and the formation of a tetrahydropyran ring[130].

2. C_{17} Perfumes

This group of substances includes the perfume components of ambergris. Depending on the conditions, the oxidative cleavage of ambrein leads to the formation of ambreinolal[131–133] or ambreinolide (112).[10,11,131,134] Under natural conditions, this is caused by light and atmospheric oxygen and is catalysed by copper ions[9] and photosensitisers[135]. Ambreinolal exists in the form of the cyclic hemiacetal (113) [131] and its derivatives, for example, the tetrahydropyranyl derivative (114), can be obtained only indirectly from ambrein[136] or ambreinolal (115)—the product of the reduction of ambreinolide[8,131,137].

On vacuum distillation, compounds (113) and (114) are converted into the oxide (116) [131–133,136–141]—the first known derivative of *trans*-decalin with the odour of ambergris, which enters into the composition of the volatile component of ambergris. The reverse hydration of the oxide (116) to the hemiacetal (113) is also possible (Scheme 11).

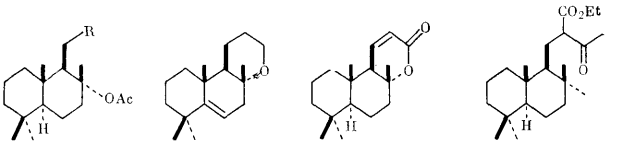
Scheme 11



(112) R = H (128) R = CH_3 (110) R = H (114) R = THH (111) (109) (115) R = H (129) R = CH_3 (122) (113) (116) (117) (117) R = H; R^1 = H_2 (130) R = CH_3; R^1 = H_2 (134) R = H; R^1 = αOH, H (135) R = H; R^1 = βOH, H (136) R = H; R^1 = O (118) R = H (131) R = CH_3 (119) R = H; $\Delta^{8(20)}$ (120) R = H; $\Delta^{8(9)}$ (121) R = H; $\Delta^{7(8)}$ (133) R = OH; $\Delta^{8(20)}$ (123) R = H; $\Delta^{8(20)}$ (126) R = H; $\Delta^{8(9)}$ (127) R = H; $\Delta^{7(8)}$ (132) R = H; $\Delta^{8(20)}$

The hydroxyaldehyde (110) has been obtained in a low yield (~20%) by the reduction of ambreinolide by complex hydrides[130,142] and by the oxidation of the diol (115) by chromium trioxide[136] (see Scheme 11). According to Demole and Wuest[83], ambreinolide is formed in the latter case.

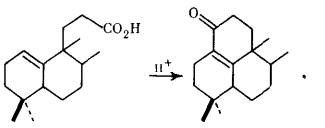
When the oxide (116) is hydrogenated, the dihydro-derivative (117), with a strong odour of ambergris, is formed[133]; it has also been synthesised by the dehydration of ambreinolol (115) by various reagents[8,15,131,137,143]. The stereochemistry of compound (117) follows from the fact that its oxidation yields ambreinolide[137]. Apart from the oxide (117), the dehydration of the diol (115) leads to the formation of the oxide (118) and a mixture of scented alcohols (119)–(121). The stereoselective synthesis of the oxide (118) from the diol (115), in which the key stage is the interaction of the ketotosylate (122) with methyl-lithium, has been achieved recently[50] (see Scheme 11). In contrast to its epimer (117), the product has no odour. The alcohol (119) has also been obtained from the acid (123), synthesised from ambreinolide[144] and the hydroxyacetate (124)—the product of the ozonolysis of the oxide (8),[7] or by the reduction of the acetoxyaldehyde (125), which is also formed when the oxide (8) is ozonised[144]. The last synthesis of the acid (123) constitutes one of the possible ways of converting labdane diterpenoids into C_{17} compounds, a characteristic of which is cleavage to C_{16} compounds. Finally the acid (123) has been synthesised by the hypohalite oxidation of the ketone (7).[80,81] Ambreinolide has also been converted into the isomeric acid (126)[10,145] and into the mixture of the acids (123), (126), and (127)[85,137] and their esters[10], which can be reduced to a mixture of the alcohols (119)–(121). The acid (126) has been detected among the products of the cleavage of the diterpenoid marrubiin[146]. Its most convenient synthesis is the hypohalite oxidation of the ketone (30).[58,77,85] The full multistage synthesis of the racemic acid (126) has been achieved using *m*-methoxyphenylacetylene as the starting material[58]. The synthesis can be greatly simplified by taking into account the fact that the intermediate (8-epi-ambreinolide) can be converted into a mixture of esters of the acids (123), (126), and (127), like ambreinolide, and can be synthesised from podocarp-8-(14)-en-13-one in only two stages[58].



(124) R = CH_2OH
(125) R = CHO
(137) (140) (141)

Scented analogues of the oxides (117) and (118) are known. Thus the product of the reduction of 3-methylambreinolide (128), namely the diol (129), gives rise on dehydration to a mixture of the oxides (130) and (131), which have a fruity smell[147], while the product of the oxidation of the hydroxy-ketone (42), i.e. the hydroxyacid (132), has been reduced to the diol (133), which cyclises with simultaneous epimerisation at C(6) to a mixture of the oxides (134) and (135).[120,148] Like the keto-oxides (136), they are not scented[62], but the oxide (137) obtained on their dehydration has the odour of ambergris[121,148].

On treatment with sulphuric acid, ambreinolide rearranges to the acid (138), which subsequently cyclises to the carbonyl compound (139), with a phenalan structure which has a strong odour of ambergris[137,149]:

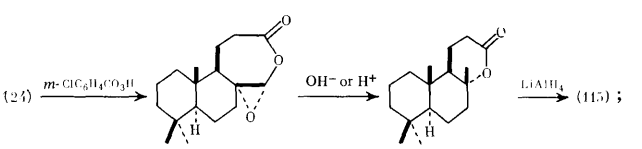


(138) (139)

The above data show that ambreinolide is an important substance for the synthesis of valuable perfumes. Ambreinolide and Δ^{12}-dehydroambreinolide (140) are present in small amounts in tobacco[39], but there are no natural sources with a high content of these substances. The problem therefore arose of the synthesis of ambreinolide. In one of its first syntheses it was obtained from the hydroxyketone (6) (yield 68%)[59,150]. On interaction with diethyl carbonate, it gives rise to the hydroxyketoester (141), the ketone cleavage of which leads to ambreinolide. The latter has also been obtained by the cyclisation of the acid (123)[80] or by the reduction of the product of the epoxidation of its ester (69) to the diol (115) and subsequent oxidation of the latter with chromium trioxide[83]. The isomeric acid (126) also cyclises to ambreinolide[58,85]. In the method of its synthesis described by Bigley et al.[58], the intermediate is podocarp-8-(14)-en-13-one, which was converted into ambreinolol in accordance with Scheme 12.[151]

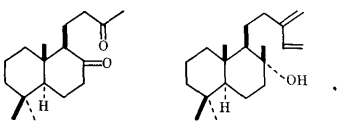
Another pathway leading to the tosylate (144) was mentioned earlier by Demole and Wuest[83].

Scheme 12



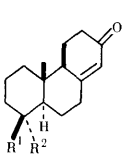
(142)
(143) R = CHO;
(73) R = CH_2OH;
(144) R = CH_2OTs.

The ketone (24) is an important intermediate in the synthesis of many compounds. It is formed on cyclisation of the diketone (145), produced as a result of the oxidation of manool by various oxidants[30,70,80,84,85,151,152]:

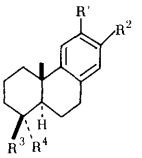


(145) (151)

Podocarpenone (24) and its derivatives with functional groups at the C(18) and C(19) carbon atoms can be obtained relatively simply from readily available substances such as resin acids. Thus neoabietic acid has been converted into the ketoester (146),[153] 13-desisopropyl-13-methoxydehydroabietate (147) has been converted into the hydroxyketone (148),[154] and podocarpic acid (149) has been converted into the hydroxyketone (150).[155] The ketoester (146) has been converted into podocarpenone[70].



(146) $R^1 = CH_3$; $R^2 = CO_2CH_3$
(148) $R^1 = CH_3$; $R^2 = CH_2OH$
(150) $R^1 = CH_2OH$; $R^2 = CH_3$

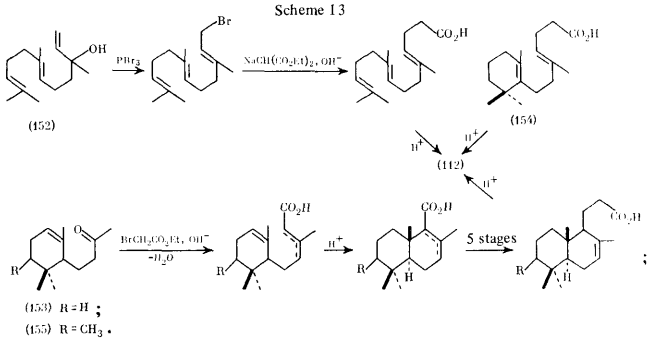


(147) $R^1 = H$; $R^2 = OH$; $R^3 = CH_3$; $R^4 = CO_2CH_3$
(149) $R^1 = OH$; $R^2 = H$; $R^3 = CO_2H$; $R^4 = CH_3$

A convenient method of synthesis of ambreinolide consists in the oxidation of isoabienol (151),[156] which has been synthesised from sclareol[156] and enters into the composition of the resin of the Siberian fir[157,158] and the evergreen cypress[75]. However, isoabienol is difficult to obtain. The situation changed after it was observed[159] that it is contained in a large amount in the needles of the common pine.

Several syntheses of racemic ambreinolide have been developed. They all consist of many stages and the starting materials are difficult to obtain. Scheme 13 shows that nerolidol (152),[160] dihydro-α-ionone (153),[161] or β-monocyclofarnesylacetic acid (154) [162] have been used as the starting materials. 3-Methylambreinolide has been obtained analogously from methyldihydro-α-ionone (155).[147]

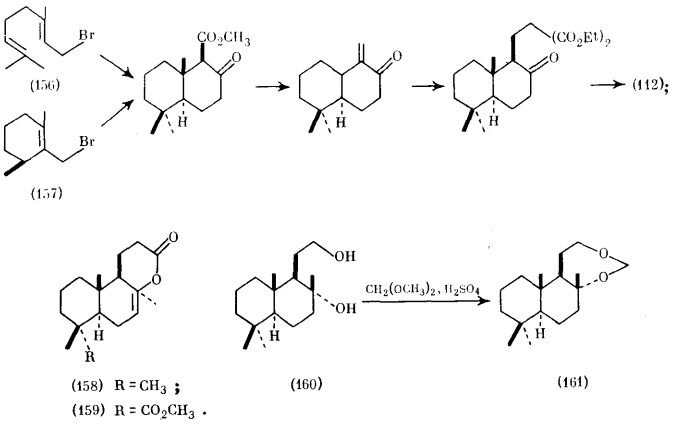
Scheme 13



(153) R = H;
(155) R = CH_3.

A novel synthesis of ambreinolide from geranyl bromide (156) and β-cyclogeranyl bromide (157), the principal stages of which are presented in Scheme 14, has been described[163]. On the whole, very numerous syntheses of ambreinolide have been described, but none is suitable for industrial application.

Scheme 14

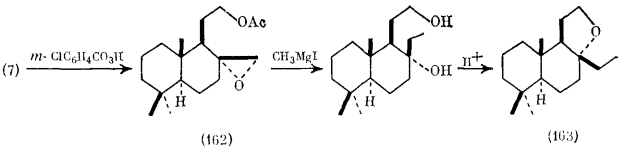


(158) R = CH_3;
(159) R = CO_2CH_3.

The enol lactone (158), obtained from the ketoacid (23), is used as an odorant for tobacco. The ketoacid (23) is formed together with other substances when the pyrolysis products of ambreinolide or the dehydration products of sclareol are ozonised[48]. The lactone (159) has been synthesised for the same purpose[164].

The interaction of the glycol (160), which is a product of the transformation of sclareol[8], with dimethoxymethane gives a low yield of the acetal (161) with a strong odour of ambergris[125]. The scented C_{17} oxide (163) has been obtained from the ketone (7), as shown in Scheme 15.[165].

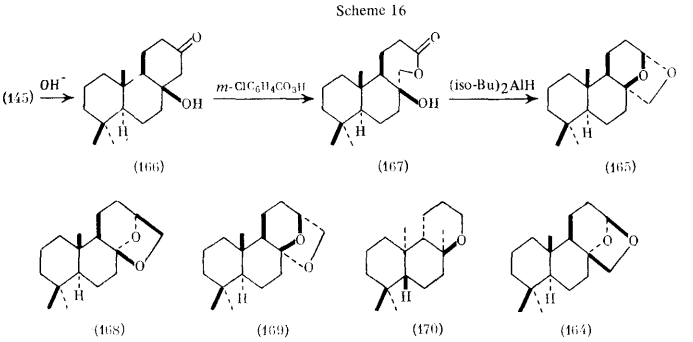
Scheme 15



(162) (163)

When 20-hydroxyambreinolide is reduced with di-isobutylaluminium hydride, the scented ketal (164) is formed. Its diastereoisomer (165) has been obtained analogously from the hydroxylactone (167)—the product of the oxidation of 8-β-hydroxy-13-podocarpanone (166) (see Scheme 16)[151]. The isomers (168) and (169) of these ketals, which have been synthesised from podocarpenone (24),[166] are not scented.

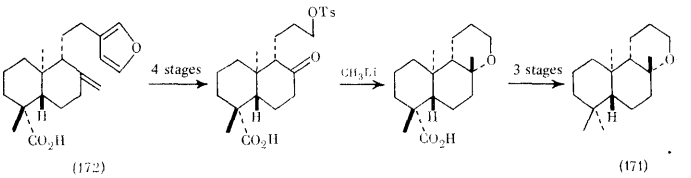
Scheme 16



(166) (167) (165)
(168) (169) (170) (164)

As in the case of compounds of the labdanum series, the oxide (170) of the *enantio*-labdane series has been recently obtained from the ketone (46).[50] Its epimer (171) has been synthesised stereoselectively from daniellic acid (172) in accordance with Scheme 17:

Scheme 17



(172) (171)

The oxides (179) and (171) have the odour of ambergris.

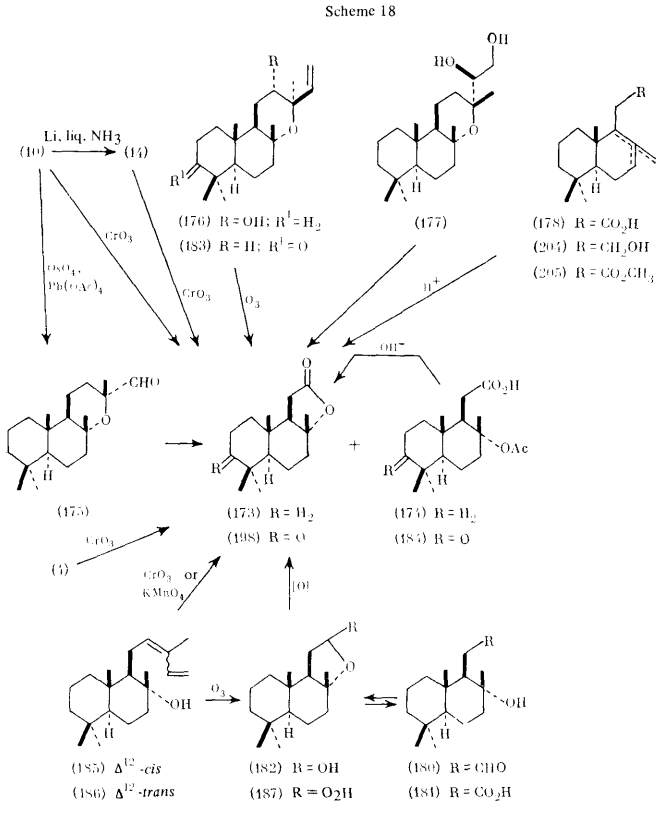
3. C_{16} Perfumes

This group includes a whole series of substances which can serve as full substitutes of ambergris and can be obtained fairly simply from many readily available labdanoids.

One of the main starting materials for these syntheses has been the γ-lactone norambreinolide (173), obtained in a small amount among the ambrein oxidation products[167] and found in tobacco[39]. Together with the acetoxyacid (174), it

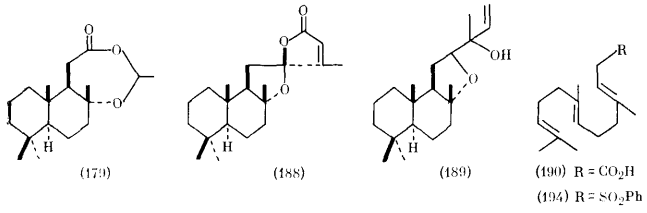
was obtained for the first time by the oxidation of sclareol[23, 55,168,169]. The acetoxyacid (174) gives rise to the lactone (173) on hydrolysis[125] (Scheme 18). According to a patent[170], when the oxidation product is hydrolysed and converted into a lactone, the yield of the lactone reaches 65%, but this method is fairly cumbersome. The method involving the oxidation of sclareol with chromic acid mixture is simpler and more convenient[79,171]. A method analogous[170] to the direct oxidation of manoyl oxide to norambreinolide (173) [172] and a two-stage method via the aldehyde (175) (see Scheme 18)[64] have also been developed. The pathway involving the hydrogenolysis of manoyl oxide [or its epimer (15)] to dihydroabienol[64], which is oxidised to a mixture of compounds (173) and (174), is much more effective[62]. Although many sources of compounds (10) [3,75,95,96,173–178] and (15) [74,179–182] or their mixture[3,183–186] are known, so far only a few of them[187] are of preparative value.

Scheme 18



The mixture of compounds (173) and (174) is formed on ozonisation of 12α-hydroxy-13-epimanoyl oxide (176) [37] and in the multistage transformation of borjatriol (177),[188,189] which is a fairly readily available diterpenoid[190,191]. In principle, the familiar derivatives of the oxy-compounds (10) and (15) with oxygen-containing groups in the 2- and 3-positions[95], in the 3-position[192,193], in the 6-position[117], in the 11-position[176,177], in the 1- and 18-positions[194], and in the 3- and 18-positions[192] can serve as the starting materials for the synthesis of compounds (173) and (174).

In the synthesis of norambreinolide from the above diterpenoids the oxide (8) was found to be an intermediate. It is oxidised to the acetoxyacid (174), which gives rise to norambreinolide on intramolecular transesterification or after the elimination of acetic acid and cyclisation of the mixture of isomeric unsaturated acids (178) formed[162]. The acid (174) has been obtained from sclareol in two stages[195]. It is also formed in the ozonolysis of the oxide (8),[56] but the main product in this instance is the acetoxyaldehyde (125) [7,12] (see above), as in the study of Corey et al.[144]; the lactone (179) and the hydroxyacetate (124) are side products. The latter becomes the main product when the ozonide is reduced[7]. The hydrolysis of the acetoxyaldehyde (125) gives a mixture of sclaral (180) and the hydroxyacid (181). Oxidation can be avoided by carrying out the hydrolysis in an inert atmosphere or by protecting the aldehyde group[7]. The hydroxyaldehyde (180) exists in the form of the hemiacetal (182), which gives rise to a norambreinolide on oxidation[12]. The hemiacetal (182) has been discovered in tobacco[39] and has been suggested as an odorant for the latter[47]. The conversion of the oxide (8) into the acetoxyacid (174) on oxidation with a peracid is of interest[125].



The keto-oxide (183) is apparently converted analogously into the 3-oxoacetoxyacid (184) on treatment with Jones' reagent[65].

Norambreinolide can be conveniently synthesised from *cis*- and *trans*-abienols (185) and (186),[3] since it is the only product of their oxidation by different reagents[156,196,197]. In contrast to *trans*-abienol, the ozonisation of *cis*-abienol led to the peroxide (187) [198] (see Scheme 18). Abienols have been discovered in larches[3,183], for which they are taxonomic characteristics, in other conifers[75,174,180,186,199,200], and in tobacco[41,201]. In some of these plants the content of abienols is fairly high. Nevertheless, owing to their lability[156,202] and the lack of convenient methods for their isolation, abienols have not found practical applications. In particular, on heating *cis*-abienol isomerises to the neoabienols (27) and (28) [73] and it cannot therefore be isolated by distillation.

Norambreinolide is also formed on oxidation of α-levantenolide (188) [36] and the stereoisomeric oxides (189),[203] which are present in small amounts in tobacco.

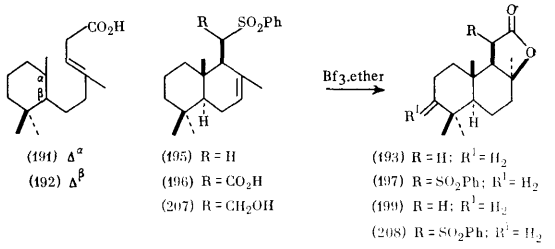
Racemic norambreinolide has been obtained by the cyclisation of homofarnesylic acid (190) [204] or α- and β-monocyclohomofarnesylic acids (191) and (192),[205–207] but the reaction products are complex mixtures of substances and the yield of the lactone (173) is low.

On treatment with acids, norambreinolide isomerises to 8-epinorambreinolide (193).[13,79,204,208] A stereospecific synthesis of this lactone has been achieved[209] as a result of the cyclisation of the sulphone (194) to drimenyl phenyl sulphone (195) [210,211] and the conversion of the latter into the acid (196), its transformation into the lactone (197), and desulphurisation. Compound (196) can be desulphurised and the resulting Δ^7-isomer of the acid (178) can then be converted into a lactone.

The ketoacid (184), whose hydrolysis gives rise to a mixture of the ketolactones (198) and (199), has been obtained from 3α-hydroxymanoyl oxide[65].

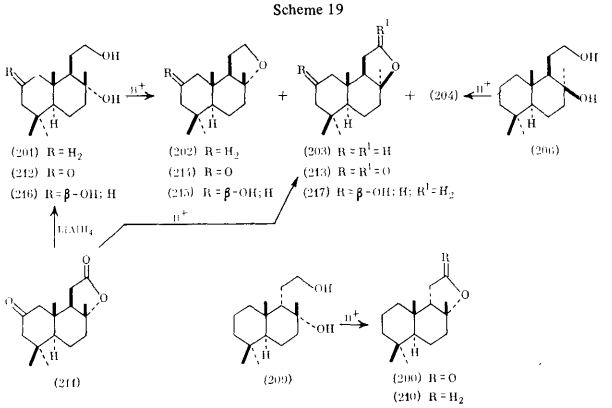
Hydrobromic acid[56] or a mixture of sulphuric and formic acids[207] isomerise the lactones (173) and (193) to the *cis*-lactone (200). Compounds (193) and (200) are also of interest for the synthesis of perfumes.

The diol (201) is formed on reduction of compounds (124), (125), (173), (174), and (179)–(181) with lithium tetrahydroaluminate[8,12,15,125] or on hydrolysis of the hydroxyacetate (124).[7] The possibility of the preparative reduction of norambreinolide with sodium in alcohol[15] has not been confirmed[32].



The diol (201) was obtained also in the reduction of the products of the ozonisation of the oxide (8) [6] and α-levantenolide[36]. In the former case a small amount of the oxide (202) was also isolated. The synthesis of the glycol (201) from the ketone (7), whereby manool can be converted into C_{16} compounds, has been described[83]: the ketone (7) is oxidised with a peracid to the epoxyacetate (162) and the latter is reduced.

Scheme 19



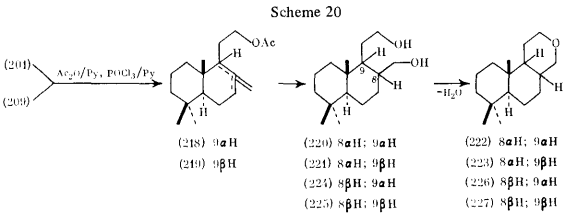
The dehydration of the diol (201) yields the oxides (202) and (203), a mixture of the isomeric alcohols (204), and a mixture of hydrocarbons whose structure has not been elucidated. The hydrocarbons have no odour, the alcohols (204) have a weak odour, while the oxide (203) and particularly the oxide (202) have a strong odour of ambergris and are of great value for the perfume industry. The dehydration of the glycol (201) has therefore been investigated in fair detail and it has been established that the ratio of the products depends on the catalyst and the reaction conditions. The oxide (202) predominates when the dehydration is carried out with naphthalene-β-sulphonic acids[7,14,15], toluene-*p*-sulphonic acid[208], sulphuric acid[32,62], alumina[8,14,15], and toluenesulphonyl chloride[62]. Alumina causes the simultaneous formation of a large amount of hydrocarbons, while toluene-*p*-sulphonic[171] and sulphuric acids give rise to a large amount of the alcohols (204). The latter predominate only on dehydration with dimethyl sulphoxide[212]. They can be obtained by reducing the mixture of the isomeric acids[178] produced by the pyrolysis[7,15] or treatment with sodium carbonate[48] of the acetoxyacid (174) of a mixture of its esters (205), which is a product of the interaction of norambreinolide with alcoholic solutions of acids[15,137,213]. The preparation of individual acid esters (205) [196] and the corresponding alcohols[94,212] has also been described. We may note that the oxide (202) is formed in the reduction of norambreinolide (173) with diborane, but its yield is low (~30%)[62].

If the diol (201) is dehydrated with hydrogen chloride, then the oxide (203) and a mixture of alcohols (204) predominate in the reaction products (see Scheme 19)[14,15,214]. This is also the case when the diol (206), formed by the reduction of the isolactone (193),[13] is dehydrated. Under the influence of acids, the oxide (202) isomerises to the epimer (203).[13] The stereospecific synthesis of the racemic oxide (203), in which the key stage is the cyclisation of the alcohol (207) to the tetrahydrofuran (208), has been achieved[209].

When the diol (209), produced by the reduction of the lactone (200), was dehydrated, the scented oxide (210) was obtained[215].

Like manoyl oxide, 2-oxomanoyl oxide or its ethylene ketal have been converted into compounds (211)–(214). On reduction, the last compound gives rise to the alcohol oxide (215).[63] When the ketolactone (211) is first reduced to the triol (216) and the latter is dehydrated, the yield of the oxide (215) is much lower. The reduction of the lactone (213) with diborane results in the formation of the alcohol oxide (217) (see Scheme 19). Compounds (210), (214), (215), and (217) have the odour of ambergris.

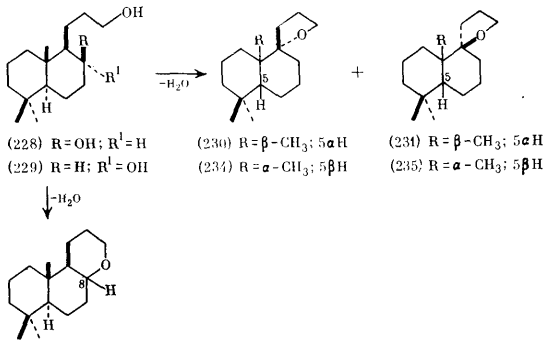
Scheme 20



The diols (201) and (209) have served as the starting materials for the synthesis of perhydronaphthopyran derivatives. They have been converted into mixtures of the acetates (218) and (219), in which the isomers with a semicyclic double bond predominate[216] (see Scheme 20). Their hydroboration led to the glycols (220) and (221), which can be dehydrated to the scented oxides (222) and (223).[217] On the other hand, if the mixture of the acetates (218) and (219) is epoxidised and the products isomerised by treatment with boron trifluoride etherate and reduced, the diols (224) and (225) are obtained[218]; on dehydration, these give rise to the oxides (226) and (227) with the odour of ambergris[219].

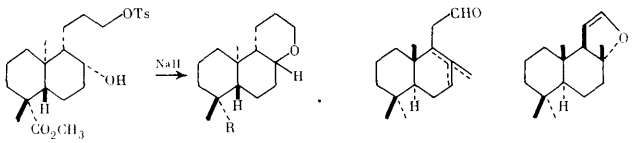
A series of oxy-derivatives of the labdane and *enantio*-labdane series have been described[50]. The reduction of the product of the ozonisation of podocarpenone leads to the epimeric glycols (228) and (229). The interaction of the former with toluene-*p*-sulphonic acid gives rise to a mixture of the spiro-oxides (230) and (231) while the corresponding reaction with the latter gives rise to the oxide (232). Compound (233) is the product of the dehydration of the glycol (228) with toluene-*p*-sulphonyl chloride. The syntheses of the enantiomeric compounds (234)–(236) have been achieved via the same scheme. The oxide (237) has been synthesised from the product of the cleavage of daniellic acid (238). The key stage in this synthesis is the formation of compound (239) on treatment of the hydroxytosylate (238) with sodium hydride (see Scheme 21).

Scheme 21



(228) R = OH; R¹ = H
(229) R = H; R¹ = OH
(230) R = β-CH₃; 5αH
(234) R = α-CH₃; 5βH
(231) R = β-CH₃; 5αH
(235) R = α-CH₃; 5βH
(232) 8βH
(233) 8αH

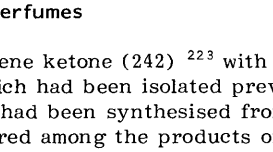
The vacuum distillation of the acetoxyaldehyde (125) leads to a mixture of unstable bicyclohomofarnesanes (240), which have been discovered in tobacco[43] and possess the odour of ambergris[7,12,220,221]. Their mixture as well as the individual γ-isomer are formed on oxidation of the corresponding alcohols[94,212]. The aldehydes (240) could not be obtained by the dehydration of the hydroxyaldehyde (180), since the latter dimerises on treatment with acids[12], but on vacuum distillation it is converted into a mixture of the aldehyde (240) and the oxide (241).[15] However, the attempts to obtain the hydroxyaldehyde (180) by oxidising the diol (201) [12,83,222] or by reducing norambreinolide[142] were unsuccessful, although 8-epinorambreinolide was reduced to the corresponding hydroxyaldehyde[142]. The reports that the γ-isomer of the aldehyde (240) is formed on oxidation of sclareol[16,19,32] were not confirmed[60].



(238)
(236) 8αH; R = CH₃
(237) 8βH; R = CH₃
(239) 8βH; R = CO₂CH₃
(240)
(241)

4. C_{15} and C_{14} Perfumes

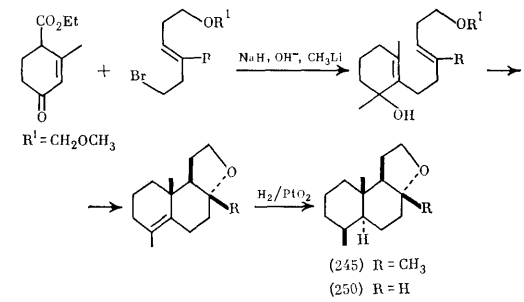
The sesquiterpene ketone (242) [223] with the odour of ambergris[224], which had been isolated previously from tobacco[43,225] and had been synthesised from drimenol (243),[225] has been discovered among the products of the oxidation of sclareol. However, it is much simpler to obtain it from a mixture of the esters (205). It is oxidised to the ketoester (244), whose hydrolysis yields the ketone (242).[226] If the mixture of the acids (178) is oxidised, the yield of the ketone (242) is lower[223]:



(243)
(242) R = CH₃
(244) R = CH₂CO₂CH₃

The scented noranalogue (245) of the oxide (202) without one methyl group at C(4) has been achieved recently[227] via Scheme 22.

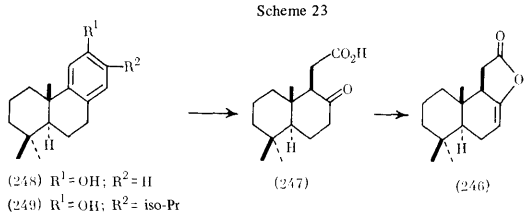
Scheme 22



(245) R = CH₃
(250) R = H

The enol lactone (246), synthesised together with its homologue (158) from certain labdanoids, has been recently used as an odorant for tobacco[48]. The corresponding keto-acid (247) was obtained from 12-hydroxypodocarpane (248) [228] and ferruginol (249) [229] (see Scheme 23), i.e. from readily available products of the conversion of resin acids.

Scheme 23

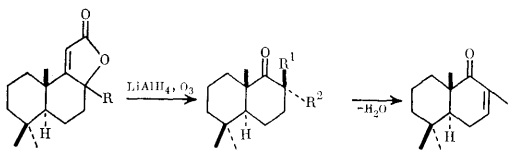


(248) R¹ = OH; R² = H
(249) R¹ = OH; R² = iso-Pr
(247)
(246)

The scented C_{14} analogue (250) of the oxide (202), lacking the methyl groups at C(4) and C(8), was also synthesised in accordance with Scheme 22.[227]

The scented ketone (251) has been found in the products of the oxidation of sclareol[123]. It had been synthesised earlier[46] from $\Delta^{9,11}$-dehydronorambreinolide (252) (Scheme 24), which had been obtained in its turn from norambreinolide[46,129] and has been recommended as a tobacco odorant. The synthesis of its C(8)-epimer (253) has also been described[129].

Scheme 24



(252) R = β-CH₃
(253) R = α-CH₃
(254) R¹ = CH₃; R² = OH
(255) R¹ = OH; R² = CH₃
(251)

On reduction with lithium tetrahydroaluminate and ozonisation, the lactones (252) and (253) give rise to the hydroxyketones (254) and (255). The lactone (252) can be converted into the hydroxyketone (254) by ozonisation and hydrolysis (223), but this procedure is less effective. The dehydration of the hydroxyketones (254) and (255) leads to the ketone (251).[129,223] The synthesis of the latter from drimenol is more complex[230].

IV. DEPENDENCE OF THE ODOUR OF PERFUMES OBTAINED FROM LABDANOIDS ON THEIR STRUCTURE

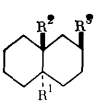
The question of the dependence of odour on the structure of substances is fairly complex and has not so far been solved. There does not exist a single theory of odour which would explain all the known facts and would have predictive

power. There is no objective criterion even for a qualitative estimation of odour. The human nose, capable of distinguishing several thousands of smells, is sufficiently sensitive, but the information obtained with its aid is to some extent subjective[231,232].

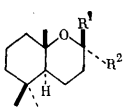
Two aspects of olfaction are distinguished: (1) the interaction of the molecules of the scented substance with the receptors of the olfactory nerve cells of the nasopharynx and (2) the transformation of the resulting primary excitation into a signal and its transmission to the olfactory brain hemisphere. The chemist is interested primarily in the way that the molecules of perfumes interact with the receptors of the olfactory nerve cells giving rise to the perception of a specific odour, i.e. how the structure of the given substance determines its odour[232].

Among the existing theories (more precisely hypotheses) of odour, the stereochemical theory of Amoore[233–235] has been most widely accepted; according to this theory, on the surface of the receptor there are alveoles of definite shape and size, each of which corresponds to a particular primary odour. Within the alveoles, there are strictly localised sections having an enhanced chamical affinity, which interact with the functional groups of scented substances. Consequently the odour is determined by the form of the molecule (or part of it) and by the nature and position of the functional groups. If the molecules of a given substance can be accommodated within an alveole of only one type, it possesses a primary odour and if it can be accommodated in alveoles of several types it has a complex odour.

Taking into account the structure of the perfumes (116), (117), (119)–(121), (202)–(204), and (240), Stoll[14,15] concluded that the odour of ambergris is characteristic of decalin derivatives of the type indicated with an oxygen-containing ring or a double bond at C(2) and an alcoholic or aldehyde group in the side chain. Compounds (52), (53), (71), and (72) as well as other substances with the same odour were discovered later. Ohloff[35] surveyed the data which had accumulated in the light of the sterochemical theory of odour and formulated the 1,2,4-triaxial rule. According to this rule, the odour of ambergris or any of its six constituent primary odours[53,236] is characteristic of compounds with a *trans*-decalin skeleton and three axial substituents (one of which can be an oxygen-containing group) located in the 1-, 2-, and 4-positions, as shown in formula (256), or molecules with a similar steric structure (or structural fragment), for example, tetrahydrochroman derivatives[129]: (52), (100), (109), (257), and (258). In the last case it is not essential that one of the substituents should contain oxygen. Incidentally, the nature of the substituent is not very important and affects only the shade or intensity of the odour. The data of Ohloff et al.[50] have shown that the oxygen-containing group need not necessarily be axial, provided that it is attached to a carbon atom with one more substituent. The environment of the centres responsible for the odour also does not play a special role. Indeed, despite structural changes, the oxides (163), (202), (214), (215), (245), and (250) and the ketals (52), (71), (72), (78), (81), (101), (102), (105)–(108), (164), and (165) have the odour of ambergris.

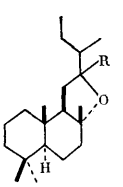


(256)



(257) $R^1 = CH_3$; $R^2 = H$

(258) $R^1 = CH_2{=}CH_2$; $R^2 = CH_3$



(259) R = α-H

(260) R = β-H

The π-electrons of the double bond or the keto-group can play the role of one of the axial substituents[35]. This explains the odour of compounds (119)–(121), (204), (240), (242), and (251), as well as a series of decalin derivatives with the keto-group at C(2).[237] Although compounds (53), (56), (92)–(96), (99), and (118) contain ketal and oxy-groups, they do not satisfy the triaxial rule and have no odour. Compounds (10), (15), and their derivatives, (259) and (260),[238] apparently have no odour owing to their high molecular weight.

The ambergris odour of *enantio*-labdane derivatives is as a rule weaker and has a different shade than that of their labdane enantiomers[50], which indicates yet again the chirality of the olfactory receptors and supports the stereochemical theory of odour.

However, a whole series of facts conflicting with the triaxial rule are known. Thus compounds (97), (98), (139), (171), (222), (223), (226), (227), and (233) do not satisfy its requirements but nevertheless have the odour of ambergris and conversely compounds (206), (168), (169), and many others, which do satisfy the requirements of the rule, nevertheless lack odour. If the environment of the centres responsible for the ambergris odour is not important, it is difficult to account for its disappearance on passing from the ketal (52) to its keto- and hydroxy-derivatives (57)–(59), on passing from the oxide (117) to its derivatives (113), (130), and (134)–(136), and also on conversion of compound (116) into compound (8), of compound (232) into compound (118), and of compound (52) into compound (65).

Thus small changes in the structure of the substance, which are insignificant from the standpoint of the triaxial rule, sometimes lead to unpredictable and inexplicable changes in odour or even to its disappearance. In view of the numerous exceptions, the rule so far lacks reliable predictive power and its value is reduced. Nevertheless it is already evident that odour is a property of the molecule as a whole and in this sense it should depend on its structure and stereochemistry. Further accumulation of factual data will probably help to elucidate the essential features of this dependence.

V. THE MANUFACTURE AND PRACTICAL APPLICATIONS OF PERFUMES BASED ON LABDANE DITERPENOIDS

As already mentioned, sclareol, manool, manoyl oxide, larixol, and others are quite readily available. This as well as the great value for perfumery of the compounds obtained from them having the odour of ambergris has made the synthesis of the latter not only of academic but also of practical interest. The method of synthesis of the oxide (202), known as "ambrox" and "ambroxide" from sclareol was the first to be patented[14,15]. Subsequently individual stages of its synthesis were frequently modified in order to adapt them to industrial conditions[20,32,171,208,239,240]. The industrially manufactured ambroxide and other products are mixtures of substances.

Simpler methods of synthesis of perfumes from sclareol and manool have also been developed. They consist in their oxidation by chromium(VI) compounds and the pyrolytic distillation of the oxidation products[16–18]. The method of preparation of this type of mixture of substances (ambrial) from sclareol was improved[19,32,33]. It was also shown that the distillation of the oxidation product can be replaced by its treatment with ascarite[34,241], although the nature of the perfumes is then altered[242]. However, their structure cannot be regarded as finally established, since it has been found[78] that the composition of the sclareol oxidation product

is in reality much more complex than had been previously believed[60].

The method of synthesis of the mixture of ketals (52) and (53) from manool has been reproduced under semi-industrial conditions[104].

Ambrial and ambroxide are used in the perfumery industry. Certain cleavage products of labdanoids are used to improve the quality of tobacco products. The following compounds have been patented for such purposes: (201), (202),[45] (173), (181), (252),[46] (180),[47] (158), and (246).[48]

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Very substantial advances have been made in the chemistry of perfumes bases on labdanoids. Several tens of substances with the odour of ambergris have been obtained from readily available diterpenoids (sclareol, manool, and others). The manufacture of some of these has been started. Interest in these compounds has been growing, because they have not only highly effective properties as perfumes but also possess a complex odour which embraces a fairly wide range of different shades.

During the last 10–15 years sources of new labdanoids, which can also be used in the syntheses of perfumes, have been discovered. The recently discovered method of introducing a double bond into the side chain of saturated labdanoids via organoselenium compounds leads to estensive possibilities. The search for perfumes based on *enantio*-labdane diterpenoids, already discovered in more than 30 plants, is promising. It is desirable to continue the study of the dependence of odour on structure since extensive factual data have been accumulated on these compounds; they also have a rigid carbon skeleton, which is very important in the solution of this problem. Finally, so far there are few methods of preparation of perfumes from labdane diterpenoids which are suitable for industrial applications.

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