SYNTHESIS AND APPLICATION OF THE 11-BISHOMODRIMANE -8α-OL -12-ONE

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Abstract: This review deals the methods of preparation of the 11-bishomodrimane-8α-ol-12-one, a convenient synton for the synthesis of drimanic and bishomodrimanic compounds, including the biologically active ones. The triterpenic tetracyclic derivatives of the onoceranic range and the fragrance compounds with ambergris odour can be also obtained from this compound.

Keywords: 11-Bishomodrimane-8α-ol-12-one, 11-monoacetate of drimane-8α,11-diol, 12-hydroperoxy-8α,12-epoxy-homodrimane, onocerane diol, *nor*-ambraketal, synthesis.

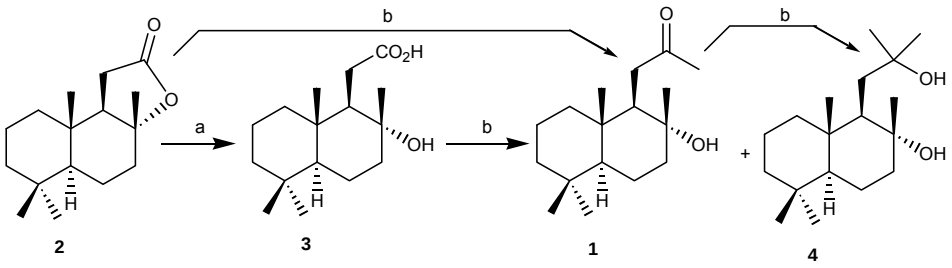
Introduction

11-Bishomodrimane-8α-ol-12-one (14,15,16-trinorlabdane-8α-ol-12-one) is a relatively accessible compound, which has been and may be further used as a starting material to prepare both sesqui – and higher terpenoids. The present review deals with the methods of obtaining of this compound as well as its usage.

Synthesis of 11-bishomodrimane-8α-ol-12-one

The first synthesis of the hydroxy ketone (1) was effectuated by the authors [1] from norambreinolide (2) with the aim to confirm firmly the absolute configuration of drimane sesquiterpenoids through their correlation with labdane diterpenoids, whose stereochemistry was known [2]. Norambreinolide (2) was saponified with alcoholic base to give the hydroxy acid (3), which was treated with methyllithium giving the mixture of the hydroxy ketone (1) and the bitertiary diol (4) (scheme 1), separated by column chromatogrphy on alumina. The yield of the hydroxy ketone (1), taking into account the recovered starting compound (12%), was up to ~80%. The yield of a bitertiary diol (4), obtained on further reaction of the hydroxy ketone (1) with methyllithium was ~18%. The structures of the hydroxy ketone (1) and diol (4) were proved by the data of elemental analysis and IR-spectroscopy. In such a way, the reaction of the hydroxy acid (3) with methyllithium gives not only the target compound (1), but also the by-product (4). Besides, a part of the starting hydroxy acid (3) remains unchanged. However, if the reaction is carried out up to the complete use of the hydroxy acid (3), then the yield of diol (4) increased in the detriment of the yield of the target hydroxy ketone (1).

Latter it was found out that the method of obtaining of the hydroxy ketone (1) can be simplified as it can be obtained in a good yield (65%) directly from the reaction of norambreinolide (2) with methyllithium [3], avoiding the saponification step of lactone (2). In order to obtain a high yield of the hydroxy ketone (1) the optimal molar ratio of norambreinolide and methyllithium should be 1:2. Under such conditions the yield of diol (4) constituted 18%, and the amount of the recovered starting lactone (2) was up to ~2%. If the molar ratio of lactone (2) and CH_3Li is lower (1:1.5), the amount of the unchanged starting lactone raised. However if the ratio is bigger (1:4), the yield of the hydroxy ketone (1) is smaller, due to the increase of the yield of diol (4) (scheme 1).



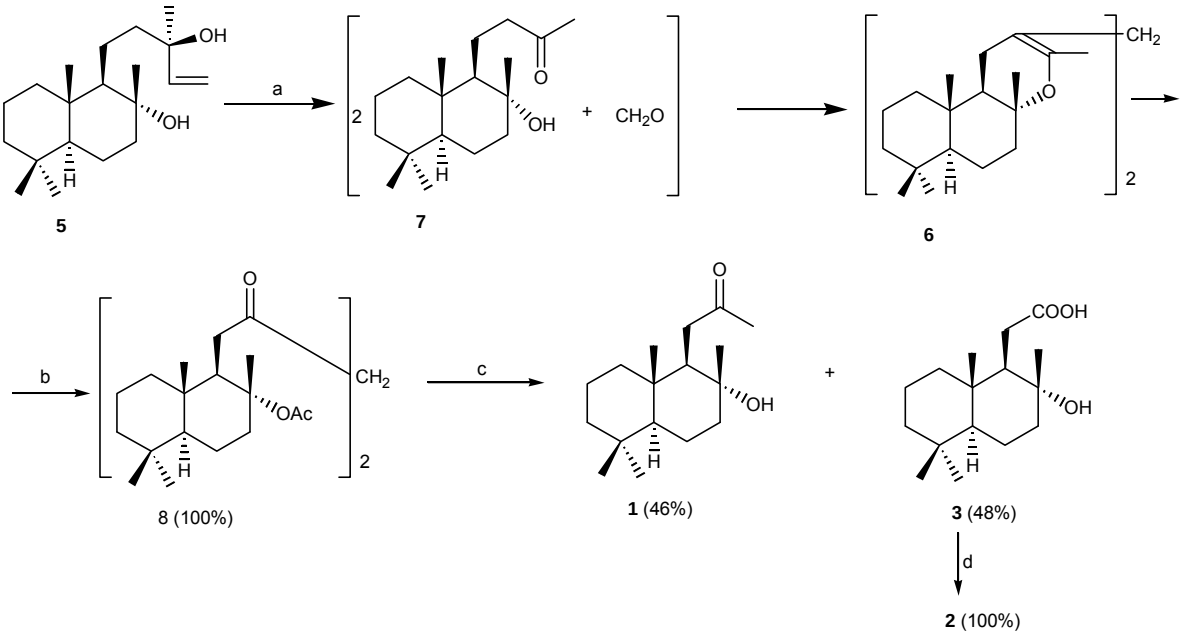
Reagents: a) KOH, MeOH; b) CH_3Li, Et_2O;

Scheme 1

It is necessary to note that latter an alternative, shorter route for the preparation of the hydroxy keton (1) from sclareol (5) was elaborated [4] (scheme 2). On the ozonolysis of sclareol (5) and subsequent treatment of the ozonolysis products with ammonium chloride the dimeric product (6) was formed [4], whose structure was proved by spectral data and confirmed by the X-ray analysis. Compound (6) resulted on condensation of methanal, the cleavage product of

the vinyl group of sclareol (5), with two molecules of the intermediately formed hydroxy ketone (7) or its zwitterions precursors.

This route to compound (6) was confirmed by the fact that on the simultaneous ozonolysis of (5) and hexadeuterobutadiene the reaction product (6) contained two deiterium atoms. It should be noted that the best results were obtained on treatment of the ozonolysis products with ammonium chloride. If ammonium nitrate was used instead of NH_4Cl, the yield of the dimeric product (6) dropped to 67%. In order to carry out this transformation a lot of acids, either acid and neutral salts, the cationite Ku-2, P_2O_5, and other reagents were tested. But in the all causes the compound (6) was obtained in low yield, or it is not formed at all.



Reagents: a) 1. O_3, CH_3OH, 2.NH_4Cl; b) 1. O_3, C_6H_{14}, 2. H_2O, Δ; c) KOH, EtOH, Δ, 1h; d) Δ.

Scheme 2

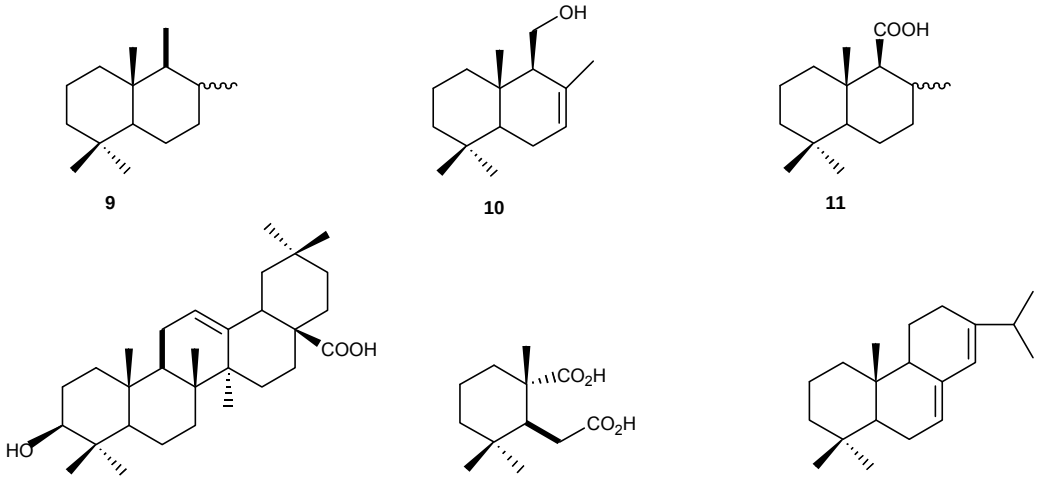
On ozonolysis of bis-(8α,13-epoxy-14,15-bisnorlabd-12-en-12-yl) methane (6) in hexane at -65÷-70^{0}C and subsequent heating of the ozonolysis products in water at 70^{0}C, the unstable bis(13,14,15,16-tetranorlabdane-8α,acetoxy-12-on-12-yl) methane (8) was obtained. The reaction product is not stable, readily decomposed in solution of organic solvents and during chromatography. That is why it was characterized only on the basis of spectral data and was used further without purification [5] (scheme 2).

The alkaline cleavage of the compound (8) afforded a mixture (1:1) of the hydroxy acid (3) (48%) and the hydroxy ketone (1) (46%). The hydroxy acid (3) is easily transformed into lactone (2) in a good yield , which, as was pointed out above, can be converted into the hydroxy ketone (1) in the yield of 65%. Taking into consideration this fact, the overall yield of the hydroxy ketone (1) from compond (6) constituted ~77%. Hence, hydroxy ketone (1) can be synthesized from sclareol (5) or norambreinolide (2), in a high yield. This lactone (2) can also be obtained from sclareol (5) as well as from other labdane diterpenoids [6].

Application of hydroxy ketone (1)

Correlation of drimane sesquiterpenoids with labdane diterpenoids

The group of drimane sesquiterpenoids includes compounds with the drimane (9) carbon skeleton. These compounds are of practical interest because many of them are biologically active [7,8]. The stereochemistry of drimane sesquiterpenoids was determined by the authors [9], who transformed drimenol (10) into the known acids (11) and (12). The saturated acid (11) was obtained on degradation of oleanolic acid (12), and drimic acid (13), was prepared on oxidation of abietic acid (14).

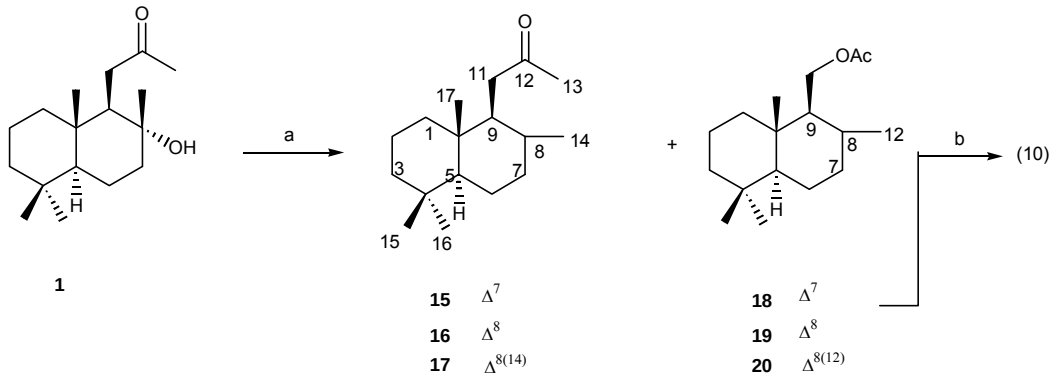


9 **10** **11**

12 **13** **14**

Latter on Wenkert E. and Strike D.P. [10] synthesized drimenol (10) and some related compounds, starting with drimic acid (13), correlating thus drimane sesquiterpenoids with tricyclic diterpenoids of known stereochemistry. However, on transformation of abietic acid (14) to the drimic one (13), the asymmetric center C-9 is distroit, and it was necessary to reconstruct it, but there were no guaranty that the reestablished configuration would be the same as it was in abietic acid (14).

More firmely correlation of drimane sesquiterpenoids with labdane diterpenoids was accomplished via the hydroxy ketone (1), in which all asymmetric atoms of the bicyclic part of sclareol (5) were kept unchanged [1]. On oxidation of the hydroxy ketone (1) by the complex of boron trifluoride etherate and the concentrated hydrogen peroxide (94%), a complex mixture of compounds which containes ketones (15)-(17), acetates (18)-(20) and a γ-lactone, of unknown structure was formed. The overall yield of acetates (18)-(20) constituted 31%, and that of drimenyl acetate (18) - 8%. On saponification of compound (18) with an alcoholic solution of potassium hydroxide drimenol (10) was obtained, confirming in such a way that the stereochemistry of the bicyclic systems of drimane sesquiterpenoids and labdane diterpenoids is identical. It should be mentioned that the hydroxy ketone (1) is not oxidized by either perbenzoic or monoperphtalic acids, and that ester (20) is biologically active [7,8]. Latter this compound was found in natural sourses and was called albicanyl acetate [10]. It should be note that, according to [11], the unsaturated ketone (17) has amber odour (scheme 3).



1

15 Δ^7
16 Δ^8
17 $\Delta^{8(14)}$

18 Δ^7
19 Δ^8
20 $\Delta^{8(12)}$

Reagents: a) $BF_3 \cdot H_2O_2$, Et_2O, 25°C, 1,5 h; b) KOH, EtOH, Δ;

Scheme 3

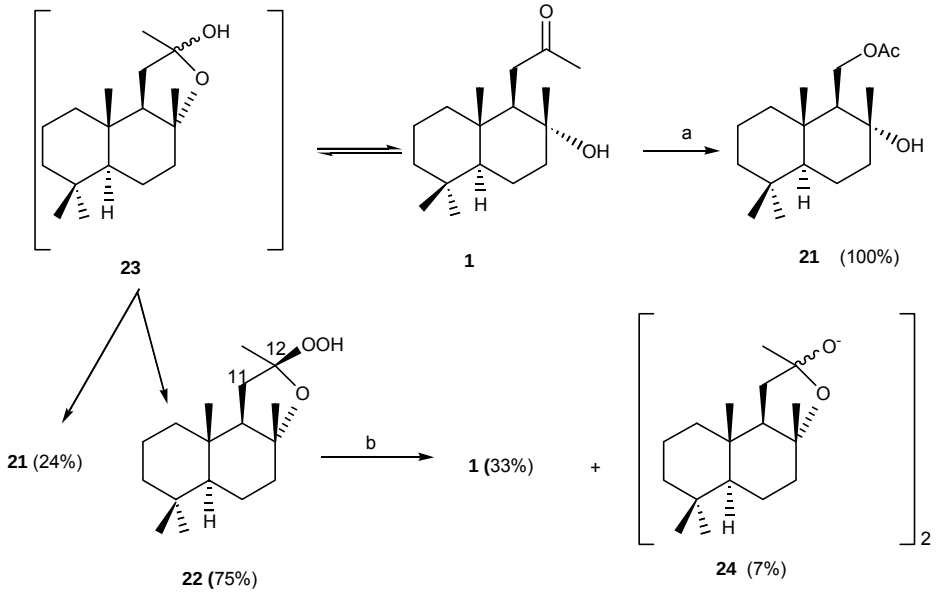
Synthesis and use of 11-monoacetate of drimane-8α,11-diol (21) and 12-hydroperoxy-8α,12-epoxy-homodrimane (22)

The oxidation of the hydroxy ketone (1) with an excess of trifluoroperacetic acid, prepared in situ from trifluoroacetic anhydride and 50% hydrogen peroxide, in dichloromethane solution in the presence of sodium hydrogen carbonate, with the molar ratio $NaHCO_3$:$(CF_3CO)_2O$, ca. 1:1, afforded the 11-monoacetate of driman-8α,11-diol (21) in quantitative yield [3] (scheme 4). The yield of the hydroxy acetate (21) constituted only 30-40% if the reaction was carried out without sodium hydrogen carbonate. In this case, the dehydration products of the hydroxy acetate (21) were formed.

To assure a high yield of hydroxy ester (21), the ratio of sodium hydrogen carbonate and trifluoroacetic anhydride is of particular importance. If this ratio is more than one, the yield of hydroxy acetate (21) is lowered because of the simultaneous formation of hydroperoxide (22). The yield of compound (22) reached the maximum value (75%) if the molar ratio $NaHCO_3$:$(CF_3CO)_2O$ was 6.4:1. In this case, the yield of hydroxy acetate (21) drops to 24% (scheme 4).

Hydroperoxide (22) is formed from the cyclic semi-acetale form (23) of the hydroxy ketone (1) which are in equilibrium in solution. Structural elucidation of hydroperoxide (22) was accomplished on the basis of spectral data and its further chemical transformations. Thus, the reaction of (22) with triethyl phosphite affords a mixture of products, from which hydroxy ketone (1) and the dimeric homodrimane (24) were isolated. The structure of hydroperoxide (22) and the dimeric peroxide (24) were confirmed by X-ray analysis.

The hydroxy acetate (21) proved to be a convenient starting material for the synthesis of a range of drimane sesquiterpenoids, in particular, of their first representative drimenol (10) and its acetate (18), as well as their double bonds isomers. Barrero A.F. et al. [12, 13] synthesized drimenol acetate (18) in a low yield on dehydration of the hydroxy acetate (21) with $SnCl_4$. Authors [14] accomplished the synthesis of the albicanyl acetate (20) starting with the hydroxy acetate (21). The hydroxy acetate (21) was dehydrated with thionyl chloride into the mixture of acetates (18)-(20), which was subjected to oxidation with m-CPBA. The peracid oxidized only the the isomers (18) and (19), isomer (20) remains unchanged. Recently, the dehydration of hydroxy acetate (21) on the interaction with a wide range of dehydration reagents was investigated in detail [15, 16]. The best regioselectivity was obtained on the reaction of the hydroxy acetate (21) with Me_3SiSO_3Me, in acetonitrile. As a result, drimenyl acetate (18) was obtained in 65-70% yield besidesdiene (25) was formed in ~17% yield. Their mixture was separated by column chromatography [17]. In this case, the isomers of drimenyl acetate (18) were not formed. Drimenyl acetate is also the predominant component of the reaction products of the hydroxy acetate (21) with $Me_3SiSO_3CF_3$. Unfortunately, the products, in which the isomers (19) and (20) considerably predominated, were not obtained.



Reagents: a) 50% H_2O_2, $(CF_3CO)_2O/NaHCO_3$ (1:1), CH_2Cl_2,; b) $P(OEt)_3$;

Scheme 4

It is necessary to note, that the authors [18] describes a simple convenient and efficient one-step method for the transformation of the hydroxy acetate (21) into drimenol (10). It was found that on treatment of hydroxy acetate (21) with an ethanolic solution of H_2SO_4 under mild conditions the dehydration and the simultaneous deacetylation took place, giving a crystalline mixture of drimenol (10) and albicanol (25) in 10:1 ratio in an 60% overall yield. Recrystallization of this mixture from hexane gave pure drimenol (10) (yield 53%). This method of thetransformation of the hydroxy acetate (21) into drimenol (10) was patented [19]. It should be menthioned that drimenol (10) and its acetate (18) have been used as starting compounds for the synthesis of a large number of natural drimanic sesquiterpenoids and their analogous, a part of which possess biological activities [7,8, 20-22].

The spectral data demonstrated that hydroperoxide (22) in $CDCl_3$ solution is in equilibrium with its C-12 epimer (27) (ratio 1:4). Obviously, in other solvents the hydroperoxide (22) (scheme 5) is also in equilibrium with its epimer at C-12, while on crystallization from petroleum ether only the less soluble epimer (22) was precipitated, gradually shifting the equilibrium towards the compound (22). The mixture of hydroperoxides (22) and (27) proved to

be readily obtained in a good yield on treatment of the alcoholic solution of the hydroxy ketone (1) at room temperature with 30% hydrogen peroxide in the presence of acetic acid as a catalyst [23] (scheme 5). The mixture of hydroperoxides (22) and (27) possess a high antifungal activity, in particular against *Candida albicans* [24].

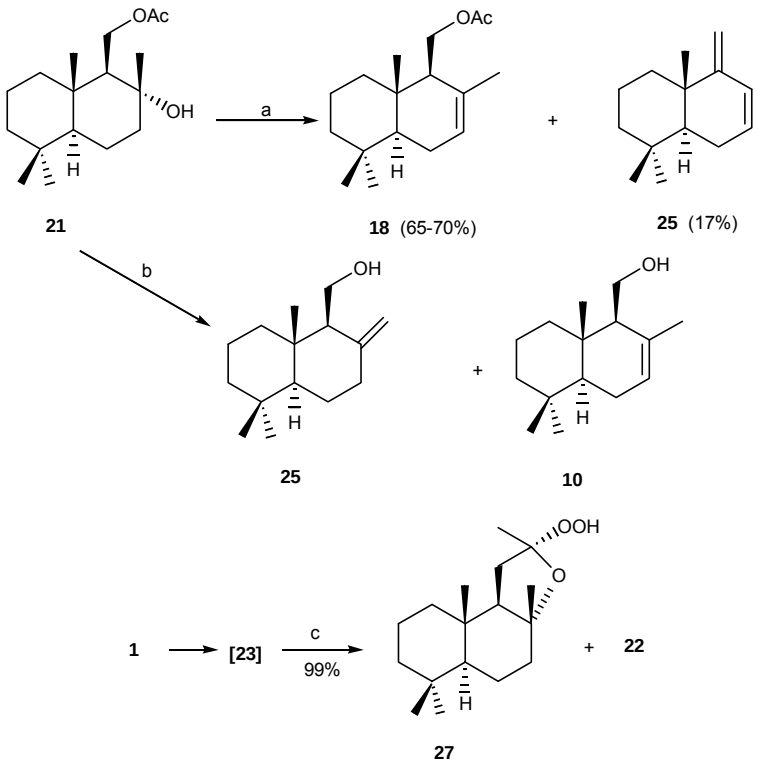
Efficient synthesis of triterpenoid onoceranediol (32) from the mixture of 12-hydroperoxy-8α,12-epoxy-11-bihomodrimanes (22) and (27).

The mixture of hydroperoxides (22) and (27) was used as a starting compound for the synthesis of some derivatives of tetracyclic onocerane triterpenoid series.

It is known that the tertiary alkoxy radicals undergo β-cleavage of C-C bonds to give carbon radicals and carbonyl compounds [25,26]. The carbon radicals, in turn, are stabilized either through dimerization or by transformation into olefins with proton elimination. Hence, the alkoxy radical (28), obtained from hydroperoxides (22) and (27), can be converted via the intermediate acetoxy-substituted radical (29) into onoceranediol diacetate (30) [27] and/or drim-9(11)-en-8α-ol acetate (31) [28,29].

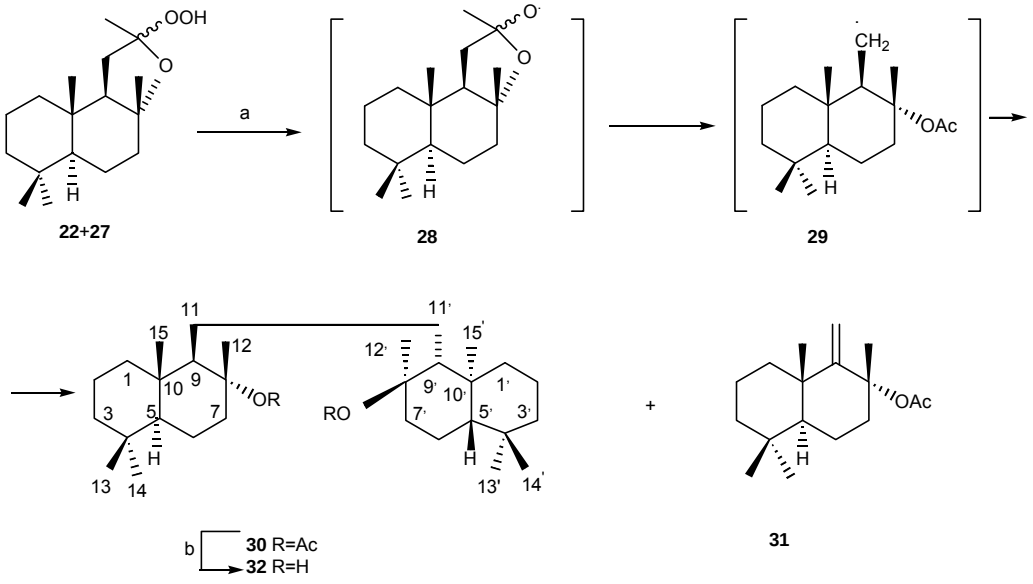
In order to carry out the reductive cleavage of hydroperoxides (22) and (27), their reaction with $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2 \cdot H_2O$ under various conditions was studied. When the reaction was carried out in the mixture of AcOH and H_2O (ratio 9:1), the compounds (22) and (27) are almost totally converted into the hydroxy ketone (1). However in methanol solution, onoceranediol diacetate (30) was the major reaction product (yield 68%), accompanied with the unstable drim-9(11)-en-8α-ol acetate (31) (yield 28%) [30]. On reduction of onoceranediol diacetate (30) by $LiAlH_4$ onoceranediol (32) was formed in 88% yield (scheme 6).

Thus, it was demonstrated that the mixture of hydroperoxides (22) and (27) is a suitable starting material for an efficient short synthesis of the derivatives of tetracyclic triterpenoid with onocerane structure.



Reagents: a) $CH_3SO_3SiMe_3$,CH_3CN, 20°C; b) H_2SO_4, EtOH, 20°C; c) 30% H_2O_2, EtOH, AcOH;

Scheme 5



Reagents: a) $FeSO_4 \cdot 7H_2O$, $Cu(OAc)_2 \cdot H_2O$, CH_3OH, 0°C, 68%; b) $LiAlH_4$, Et_2O, Δ, 88%;

Scheme 6

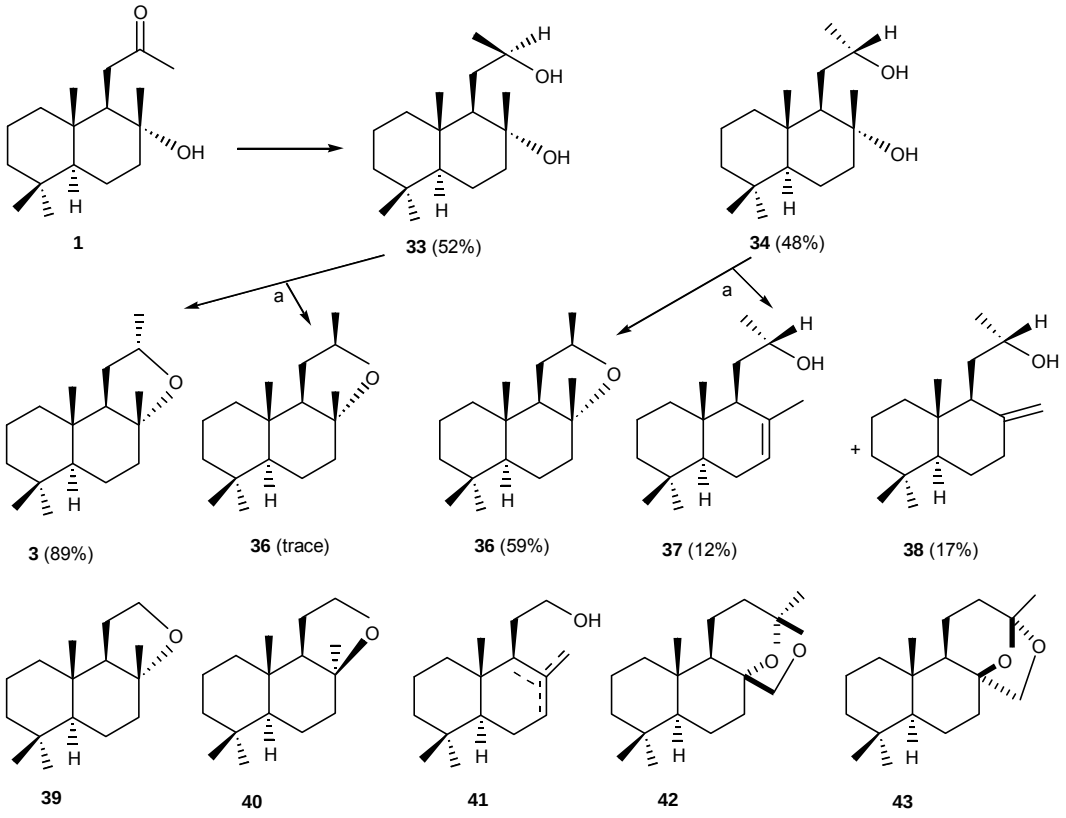
Synthesis of the ambrox analogous

The hydroxy ketone (1) proved to be a convenient starting material for the synthesis of an ambrox analogue with a strong ambergris odour.

On reduction of hydroxy ketone (1) by lithium boron hydride, obtained in situ from potassium boron hydride and lithium chloride in isopropanol according to the method [31], the mixture of epimeric glycols (33) and (34) was formed, in the yields of 52% and 47,8%, respectively. The glycols were separated chromatographically. When glycol (33) was distilled *in vacuo*, in the presence of p-toluenesulfonic acid, according to the procedure [32], mostly one product was obtained – the oxide (35) with a strong ambergris odour in 89% yield, with traces of the epimeric oxide (36) (scheme 6). When glycol (34) was dehydrated under similar conditions the odorous oxide (36) was formed in 59% yield, alongside with the unsaturated alcohols (37) in 17% yield. It should be mentioned that the structure and stereochemistry of compounds (33)-(36) were determined earlier by the authors [33].

The selectivity of glycol (34) dehydration is lower that those of its epimer (33) and the yield of oxide (36) is also lower than of oxide (35). Obviously, this fact can be explained by the mutual repulsion of methyl groups at C-8 and C-12, which are in 1,3-*cis* position on the β-side of the molecule in the pre-reaction conformation of glycol (34), giving the oxide (36) (scheme 6).

Taking into consideration the results of the dehydration of glycols (33) and (34), the following scheme of obtaining of the ambrox analogue from diketone (8) was proposed: compound (8) was treated with base, the product was heated at 135-140^{0}C to convert the hydroxy acid (3) into lactone (2) and the resulting mixture of hydroxy ketone (1) and lactone (2) was reduced by lithium boron hydride, obtained *in situ* from potassium boron hydride and lithium chloride in isopropanol. The reduction product was distilled *in* vacuo in the presence of p-toluenesulfonic acid, giving the analogue of ambrox with a strong ambergris odour. According to the GLC data, the latter contained ambrox (39) (31%), isoambrox (40) (3%), oxides (35) (18%) and (36) (16%), as well as the mixture of bicyclohomofarnesols (41) and bicyclobishomofarnesols (37) and (38) (32%). A strong ambergris odour of this analogue of ambrox (39) is due to the presence in the final product whose yield constituted 48% calculated from sclareol (5), of oxides (35), (36), (39) and (40), the content of which constituted 68% of the weight of the final product. On the ambrox analogue preparation the intermediate products were not purified but used as such.



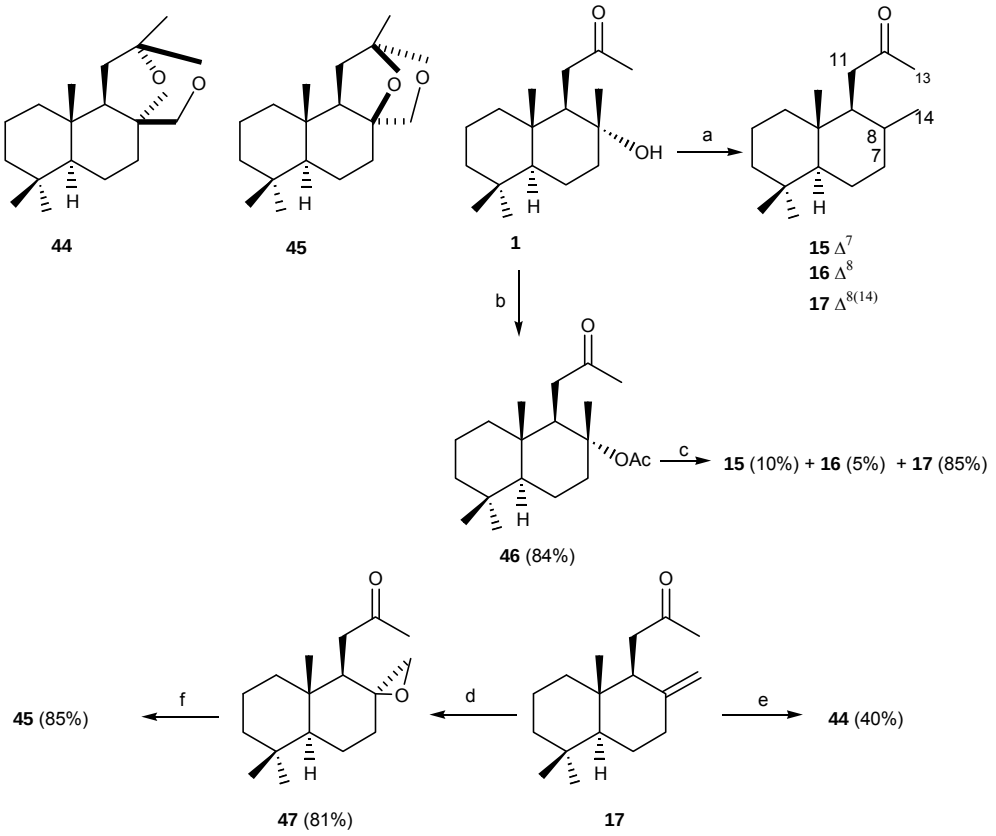
Reagents: a) pTsOH, distilled at 135°C;

Scheme 7

Synthesis of diastereomeric nor-ambraketal (44) and (45).

Ambraketal (42) is known to be among the compounds with a very strong ambergris odour, while its diastereomer (43) is odourless [6, 34]. The authors [35] carried out the synthesis of *nor*-ambraketal (44) and found out that it has a strong ambergris odour as well as ambraketale (42). For the studying of the dependence of odour on structure it was of interest to synthesize also the diastereomer (45) of *nor*-ambraketal (44). A starting compound for this synthesis was the hydroxy ketone (1) [36] . On its dehydration by $POCl_3$ in pyridine or by Swern reagent the mixtures of unsaturated isomeric ketones (15)-(17) were obtained, the prevailing component of which was the target ketone (17), whose content constituted 52% and 58%, respectively [37]. That is why an indirect approach of obtaining ketone (17) from the hydroxy ketone (1) was also efectuated. The hydroxy ketone (1) was acetylated by acetyl chloride in dimethyl aniline to give the ketone (46) in 84% yield. On the pyrolysis of acetoxy ketone (46) on short-time heating at 200^{0}C, without solvent, the mixture of ketones (15):(16):(17) in the ratio 30:18:52 was obtained in 91% yield (scheme 7). If the elimination of acetic acid from acetoxy ketone (46) was carried out on heating in DMSO, in the presence of sodium bicarbonate [38-40] , the mixture of ketones (15):(16):(17) in the ratio 10:5:85 in 100% yield was obtained. The oxidation of the ketones mixture (15)-(17) by monoperphthalic acid afforded the ketone (17), the isomers (15) and (16) being selectively epoxydised. Ketone (17) can also be obtained by column chromatography of the ketones mixture on SiO_2, but this procedure is less convenient.

The oxidation of ketone (17) by a catalytic amount of OsO_4, in the presence of potassium ferrocyanide as a co-oxidant, led to nor-ambraketale (44) in 40% yield. The yield of ketale (44) turned out to be twice lower than on oxidation of ketone (17) by OsO_4 and of tri-methylamine N-oxide [35] (scheme 8).



Reagents: a) $POCl_3$/Py or Swern reagent; b) AcCl, $C_6H_5NMe_2$; c) Δ or DMSO, $NaHCO_3$; d) m-CPBA; e) OsO_4, $K_3[Fe(CN)_6]$; f) $ZnCl_2$

Scheme 8

Since, on the ketone (17) oxidation by OsO_4 and co-oxidants, nor-ambraketale (45) was not formed, an indirect approach was used to obtain the epoxide (47). The latter was obtained in 81% yield on ketone (17) oxidation by m-clorperbenzoic acid. Below are given the reagents which were successfully used for the isomerization of oxide (47), and in brackets are indicated the yields of nor- ambraketale (45): $ZnCl_2$ (85%), SiO_2 (81%), SiO_2, impregnated by H_3BO_3 (80%), Al_2O_3 (78%), Nafion H^+ (75%) (scheme 7).

Thus, when the epoxy ketone (47) is isomerized on treatment with various reagents, the only reaction product was nor-ambraketale (45), its diastereomer (44) is not formed. As expected, the nor-ambraketale (45) is odourless.

Conclusion

The data mentioned above provide an additional confirmation that the hydroxy ketone (1) turned out to be an available and convenient synton to prepared a number of organic compounds, a part of which may be not only of theoretical, but also of practical interest. Obviously, this compound will be of use also on solving other synthetic problems as well.

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