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THE NATURAL PRODUCT CHEMISTRY OF TERPENOIDS - A TRIBUTE TO THE REMARKABLE LEGACY OF ACADEMICIAN PAVEL VLAD

Aculina Aricu

Institute of Chemistry, 3, Academiei str., Chisinau MD-2028, Republic of Moldova
e-mail: aculina.aricu@ichem.md; aculina.aricu@gmail.com

Abstract. This paper is devoted to the research priorities and some new lines in terpenic compounds studies, developments of methods of investigation into fine organic synthesis established by academician Pavel Vlad. The name of academician Pavel Vlad is associated with a number of remarkable fundamental and applied ideas. Under his guidance and with his direct contribution new approaches to determining the absolute configuration of a series of labdanic diterpenoids and-converting them into bi-, tri- and tetra- cyclic compounds have been designed. Novel universal methods for synthesizing tetrahydrofurans from 1,4-glycols, olefins from tertiary alcoholic acetates, as well as dienones by means of photodehydrogenation of unsaturated cyclic ketons have been developed by academician Pavel Vlad. It has been established that the 1,4-glycols not only oxidizes the primary and secondary alcohols in the respective carbonyl compounds, but also dehydrates the tertiary alcohols. The scientific school founded by academician Pavel Vlad is leading in the investigations of superacidic cyclisation reaction of terpenoids, and also of the regularities of the mentioned reaction in different classes of terpenic compounds, such as alcohols, their acetates, acids, esters, phenylsulphones. Molecular rearrangement was performed in the diterpene and sesquiterpene series. Efficient ozonolytic methods for norlabdanic compounds preparation, as well as a new theory for evaluating the structure-ambra odour relationship have been developed.

Keywords: labdane diterpenoid, tetrahydrofuran, ozonolytic method, superacidic cyclisation, structure-ambra odour relationship.

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List of abbreviations and notations:

Ac_2O	Acetic anhydride
AcOH	Acetic acid
AO	Atomic orbital
$Cu(OAc)_2 \cdot H_2O$	Cupric acetate monohydrate
DMSO	Dimethylsulphoxide
ECM	Electronic computing machine
EtOH	Ethanol
GC	Gas-chromatography method
H_2tpp	Tetraphenylporphyrin
IR	Infrared spectra
MeOH	Methanol
Me_3SiCl	Trimethylsilyl chloride
MO	Molecular orbital
NMR	Nuclear magnetic resonance
p-TsOH	*p*-Toluenesulphonic acid
p-TsCl	*p*-Toluenesulphonyl chloride
Py	Pyridine
TMCS	Trimethylchlorosilane

Introduction

Academician Pavel Vlad is, undoubtedly, one of the most remarkable personalities who founded new directions in national science of Republic of Moldova, and contributed to its worldwide development and validation. It is significant that he, like no other, perfectly perceived the winds of time, directing research in the subtle realms of the chemistry of natural compounds, making essential contributions and thus taking the fame of the Republic of Moldova beyond its borders due to the scientific school of bioorganic chemistry, and chemistry of natural and biologically active compounds.

The purpose of this paper is to put forward concisely some of the most valuable scientific contributions of academician Pavel Vlad and his disciples to the field of natural product chemistry of terpenoids, including:

- determination of the absolute configuration of (-)-sclareol;
- synthesis and composition of ambroxide, structural and electronic origin of ambergris odour;
- development of ozonolytic methods for obtaining norlabdanic compounds;

- development of general methods of photocatalytic dehydrogenation of Δ^8-drimen- and Δ^8-11-homodrimen-7-ones and regio-selective dehydration of tertiary methylcyclohexanic alcohols;
- superacidic cyclization of terpenoids;
- molecular rearrangement of some terpenoids;
- synthesis of nitrogen-containing drimanic and homodrimanic compounds.

Background

Determination of the absolute configuration of (-)-sclareol

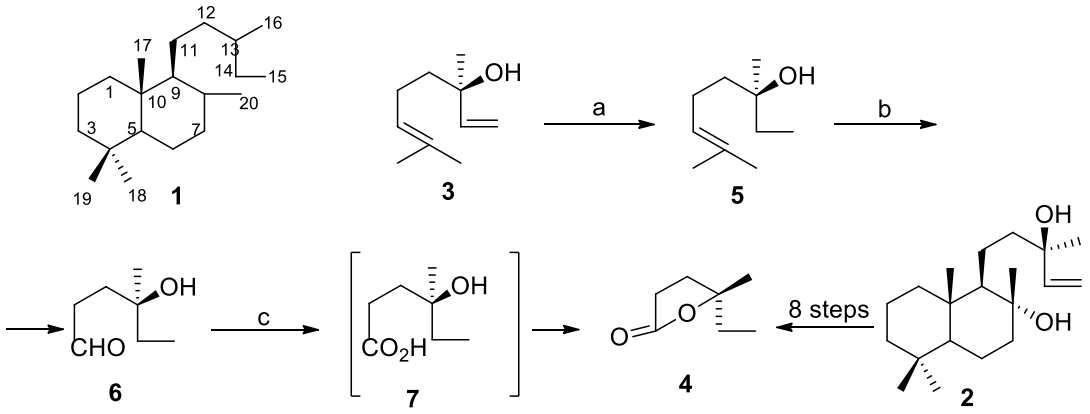
The extensive fundamental research carried out within the scientific school of academician Pavel Vlad was focused on the elaboration of general methods for determining the absolute configuration of a series of labdane diterpenoids.

The group of labdane diterpenoids comprises bicyclic diterpene compounds, derivatives of the hypothetical hydrocarbon (**1**), named labdan. The stereochemistry of the bicyclic structural fragment of labdane diterpenoids was established strictly and unambiguously [1]. Much more complicated has been the determination of the stereochemistry of the aliphatic structural fragment in compounds with asymmetric centres at C-13 or with conjugated double bond system, reflected by the contradictory data obtained with the physico-chemical research methods. Taking this fact into consideration, a general chemical method was developed for correlating the side chain configuration of the most important representatives of the labdanic group with compounds with determined configuration. Subsequently, most labdanic diterpenoids with respective structure were correlated with these selected representatives.

As the spectral and optical methods led to contradictory results, it was decided to achieve a strict chemical correlation of (-)-sclareol (**2**) with linalool (**3**) - reference compound of known configuration, obtaining from both compounds one single substance, a (-)-γ-methyl-γ-caprolactone (**4**), without touching the asymmetric centres concerned.

(-)-Linalool (**3**) was selectively hydrogenated in the presence of Raney nickel (Raney Ni) as a catalyst in dihydrolinalool (**5**). Its ozonation and reduction of ozonide with hydrogen in the presence of palladium on coal as a catalyst leads to oxyaldehyde **6**. Upon oxidation with potassium permanganate in acetic acid medium, oxyacid **7** is formed, which is spontaneously lactonized to give (-)-γ-methyl-γ-caprolactone (**4**) (Scheme 1) [2]. Because the sign and value of the specific rotation of lactone **4** on relactonization do not change, it appears that relactonization (and lactonization) takes place with the retention of the asymmetric centre configuration with the cleavage of acyl-oxygen bonds. Thus, lactone **4** has the *S* configuration, and (-)-linalool (**3**) - the *R* configuration.

It should be noted that the configuration of lactone **4** can be determined independently of linalool, using the Hudson-Klyne lactone rule. This rule refers only to lactones, which were obtained from oxyacids with a secondary hydroxyl group to the asymmetric centre. In the case of oxyacid **7** the hydroxyl group is tertiary. The underlying control established that the lactone rule is also applicable in the case of lactones, obtained from oxyacids with tertiary hydroxyl group at the asymmetric centre. The configuration of lactone **4**, determined according to the Hidson-Klyne rule, coincides with the configuration determined from linalool (**3**). Consequently, the production of lactone **4** from (-)-linalool (**3**) represents an independent confirmation of its configuration.



Reagents and conditions: a) H_2, Raney Ni; b) 1. O_3, 2. H_2/Pd/C; c) $KMnO_4$, AcOH.

Scheme 1. Determination of the absolute configuration of (-)-sclareol (2) at the C-13 asymmetric centre [2-4].

The next step of the work consisted in obtaining (-)-γ-methyl-γ-caprolactone (**4**) from sclareol (**2**), keeping the configuration at the asymmetric center C-13 intact. Through a series of transformations, it was established that the absolute configuration of the sclareol (**2**) at the asymmetric center C-13 is *R* [3]. Establishing the sclareol configuration at C-13 simultaneously determined the absolute configuration of 57 labdanoids, which were correlated with sclareol (**2**).

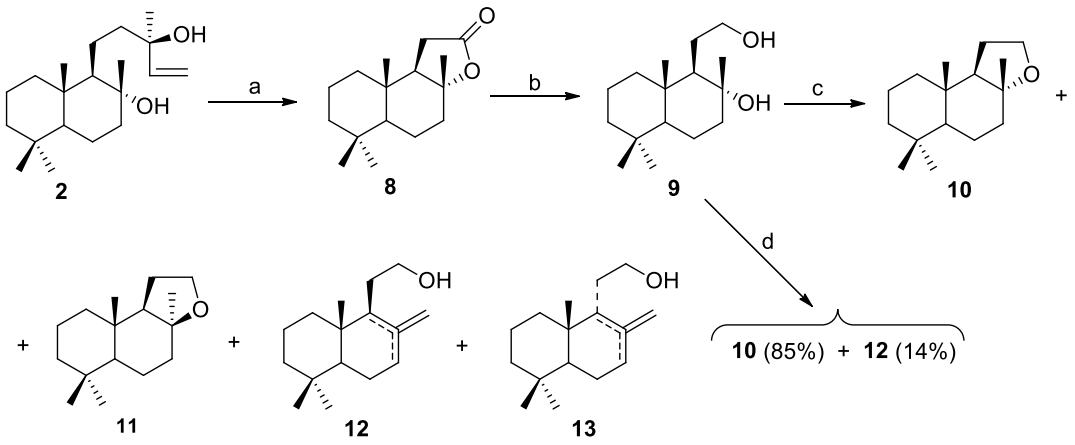
Synthesis and composition of ambroxide

At the beginning of the 60's of the XXth century, the extraction of the labdanic diterpenoid sclareol (**2**) was organized on an industrial scale from vegetable waste, accumulated after the distillation of essential oil from clary sage [4], and the preparation of odorous compounds on its basis, called "ambrial" [5] and "ambroxide" [6,7]. Ambroxide was more precious, but its production on a technological scale was imperfect, with a yield of only 20%.

At the beginning of this research, ambroxide was obtained from sclareol (**2**) in three stages [6,7] according to Scheme 2. In the first step the sclareol (**2**) was oxidized with a chromium mixture, taken in an amount corresponding to 10 g-oxygen atoms per 1 mol of sclareol (**2**). The yield of norambreinolide (**8**) was 50-55%. The unsaponifiable fraction of the neutral part, which constituted ~20%, had a strong amber odour, but its composition, as well as the composition of the acidic part, of the oxidation product, which accounted for 40-45% of this product, did not have been studied. The yield of diol **9**, which was obtained by reducing norambreinolide (**8**) with potassium borohydride in isopropanol, was relatively low (~50%), and the reduction method still had a number of shortcomings; it was necessary to use a relatively large excess of reducing agent (2.5 mol per mol of lactone), isopropanol was lost and a large amount of wastewater was obtained. It was demonstrated that an effective lactone reducer is lithium borohydride, obtained *in situ* from KBH_4 and LiCl in isopropanol [6].

The developed method of reducing norambreinolide (**8**) decreased the reducer consumption by 47%. The yield of diol **9** was increased by up to 65%. Isopropanol consumption decreased by 80% as it became possible to regenerate it. As a result, the cost of production was reduced by 27%. This method was implemented at the experimental plant of the Union Research Institute for Synthetic and Natural Odoriferous Compounds (Moscow). The economic effect of implementation was 311 rubles per kilogram of production. The diol dehydration technology **9** in oxides **10** and **11** under production conditions had a low yield. In the third step, the diol **9** was dehydrated by vacuum distillation in the presence of *p*-toluenesulphonic acid. The product of the reaction was considered to be a mixture of oxides **10** and **11**, the stereochemistry of which has not been strictly established [7].

The study of ambroxide by the GC method showed that the composition of ambroxide was more complex than it was considered. To determine the composition of the ambroxide, it was separated by column chromatography with Al_2O_3. The data obtained showed that the summary content of oxides **10** and **11** (actual ambroxide) did not exceed 45-48%. One of its basic components (~40%) was the mixture of bicyclohomopharnesenols (**12**) and (**13**), epimers at the asymmetric centre C-9, practically odourless.



Reagents and conditions: a) $Na_2Cr_2O_7$, H_2SO_4; b) $LiBH_4$; c) *p*-TsOH, reflux; d) DMSO, Me_3SiCl, 22°C, 17 h.

Scheme 2. Synthesis of ambroxide (10) [6-8].

New methods have been developed for obtaining tetrahydrofurans from 1,4-diols, using as reagents compounds obtained at the DMSO interaction with trimethylchlorosilane (TMCS). These have been shown to be quite effective for the dehydration of 1,4-diols containing secondary oxy- groups and, in particular, tertiary oxy- groups, obtaining high yields of tetrahydrofurans. It should be noted that when dehydrating diol **9**, isoambroxide (**11**) is not formed, which is less valuable. The reaction proceeds stereospecifically with the formation of only oxide **10** (85%), which is highly valued in perfumery, and a small amount (14%) of a mixture of unsaturated alcohols **12** [8].

Structural and electronic origin of ambergris odour

The first systematic research on the dependence of amber odour on the structure of decalinic cyclic compounds was performed by Ohloff, G. and his collaborators [9,10]. They specified the structural element that ensures the existence of the amber odour, formulating the so-called 1,2,4-triaxial rule of trans-decalinic compounds: amber odour is exhibited by transdecalinic derivatives containing the structural fragment **14** with three axial substituents. One of them can be the hydrogen atom, another one - an alkyl group, and the last one - a polar group, usually containing oxygen atoms.

As the number of amber compounds multiplied, it became difficult to detect the structural element **14**. It was necessary to make changes to the triaxial rule and to introduce additional notions. It was concluded that the reason for these deviations from the triaxial rule is that this rule took into account only the chemical and steric structure of the substances, but not their electronic structure. In order to take into account, the electronic structure, a logical-structural analysis was used through a package of STRAC application programs in dialogic mode with the electronic computing machine ECM [11,12]. The detailed analysis of the electronic structure of a large number of decalinic compounds made it possible to highlight the presence in the molecules of amber-smelling compounds of a structural fragment with certain geometric and electronic characteristics, a fragment responsible for the existence of the smell.

In the molecules of all amber-smelling compounds there is a molecular orbital (MO) (binding MO) located in the energy zone between 0.2233 and 0.2556 a.u. with a vast contribution of the atomic orbitals (AO) of the axial, tertiary, allylic hydrogen atoms and those located at the carbon atoms, united with oxygen atoms. The acceptor molecular orbital enters with high AO coefficients of hydrogen atoms from cycles B and C, but not from cycle A. In all active compounds there are groups of atoms, which introduce the largest contributions in the MO-acceptor and which include the oxygen atom, and two hydrogen atoms, mentioned above. These atoms form a triangle at the apex of which they are located. This triangle, named as the “amber triangle”, has certain characteristics in Å, as indicated on the drawing included in Figure 1.

Thus, the norlabdanic compounds have the smell of amber, which contain a structural fragment that ensures the existence of the “amber triangle”. The 1*S* function of the hydrogen atoms, which form the triangle, has the same unique sign in the MO-acceptor.

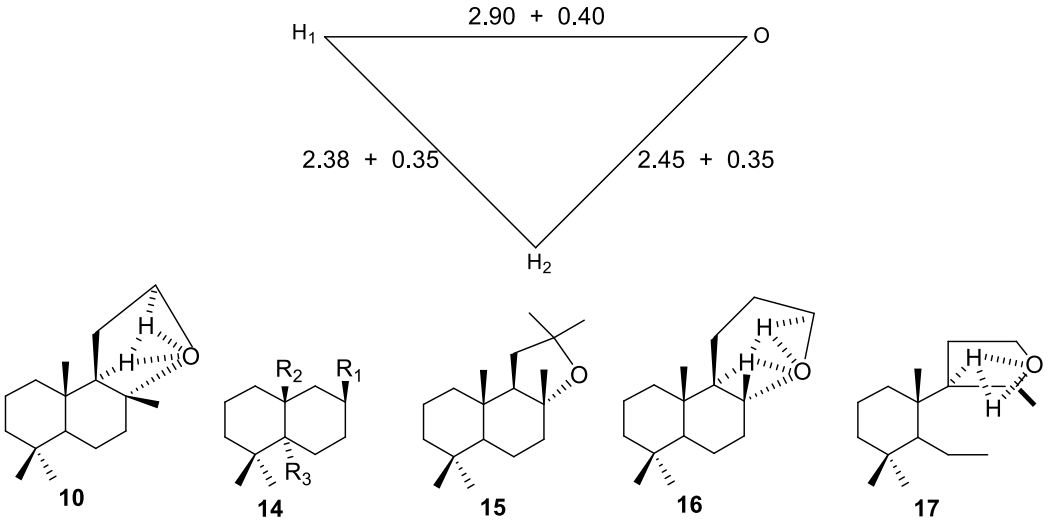


Figure 1. Structural and electronic origin of ambergris odour [14].

The hydrogen atom H-1 being more distant from oxygen, always has a negative charge. The value of the negative charge of the oxygen atom varies between - 0.24 and - 0.31 ē, and the surface of the amber triangle varies between 2.66 and 2.99 Å^2. The charge density in the triangle is approximately constant and equals to σ= -0.1 ē/Å^2. The amber triangle is located in cycles B and C, but not in cycle A [14].

The following are some examples that illustrate the structure of the amber triangle and its influence on the smell (Figure 1).

In ambrox (**10**) the amber triangle consists of C-9 and C-12 -α-oriented hydrogen atoms and the oxygen atom, and in the homofixer (**16**) of C-9 and C-13 α-oriented hydrogen atoms and the oxygen atom. Substitution of hydrogen atoms at C-12 in ambrox (**10**) with methyl groups leads to the disappearance of the amber triangle and compound **15** is odourless. In compound **17** the amber triangle is formed as indicated in the respective formula.

The notion of "amber triangle" allowed to explain the influence of small structural changes on the amber odour, as well as the existence of odour in compounds that do not meet the conditions of Ohloff's triaxial rule [13-15].

Thus, a series of new amber-smelling perhydronaphthofuranic, erhydronaphthopyranic and perhydroindenopyranic derivatives were synthesized, which are of interest to the perfumery industry.

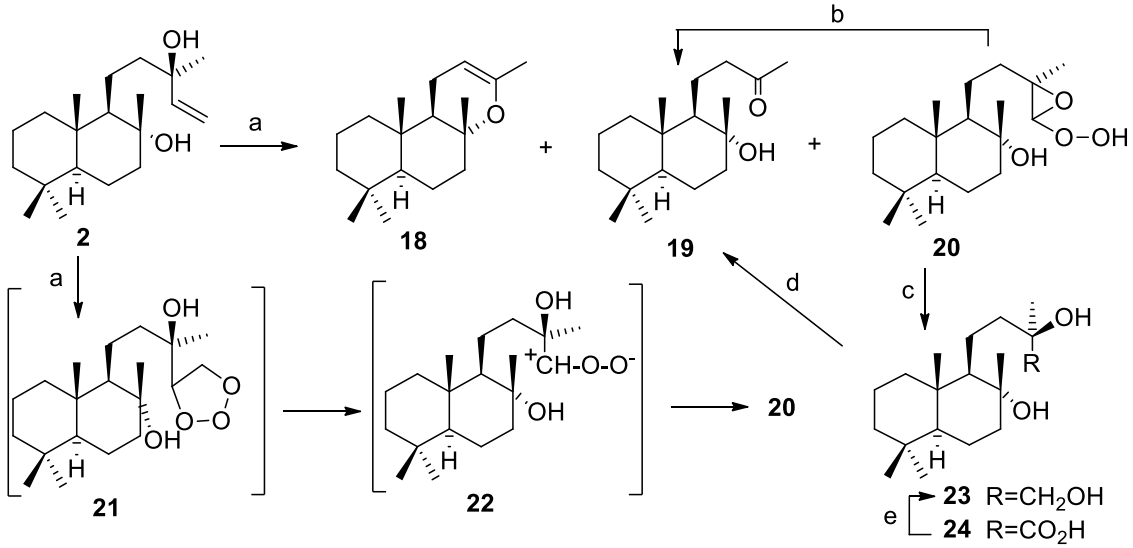
Methods of production and technologies for the production of a series of odorous compounds were developed and implemented in the perfumery and tobacco industries.

Development of ozonolytic methods for obtaining norlabdanic compounds

Norlabdanic compounds represent both theoretical and practical value. They served as starting compounds in the production of drimanic sesquiterpenoids and superior terpenoids and found use in the perfumery, cosmetics and tobacco processing industries [13]. These compounds were obtained by oxidative cleavage of a series of labdanoids. Chromium(VI) compounds or potassium permanganate were used as oxidants. However, as a rule, these oxidants are not selective and lead to the formation of complex mixtures of substances. A strong oxidant is ozone. However, it has been used relatively rarely in the cleavage of labdane diterpenoids, probably due to the fact that some ozonation products are explosive [16]. It was established a number of harmless ozonolytic methods for obtaining norlabdane derivatives from a range of accessible labdane deterpenoids.

Sclareol (**2**) is one of the basic labdanoids used to obtain norlabdanes. For this reason, it was studied in detail its ozonation reaction with the purpose to develop selective methods for the preparation of practically valuable compounds and the study of the influence of ozonation conditions on the direction of reaction and the character of the formed products.

When ozonation of sclareol (**2**) occurs in ethyl acetate in the presence of 5% pyridine (by volume) at -65÷-70°C, a mixture of three substances is obtained: sclareoloxide (**18**) (yield 37%), oxyketone **19** (yield 17%) and the unstable epoxyhydroperoxide **20** [17,18] (Scheme 3), separated chromatographically on silica gel.



Reagents and conditions: a) O_3, AcOH, Py, 78%; b) reflux, 170ºC, 30 min; c) $LiAlH_4$, Et_2O, 70%; d) $NaIO_4$, EtOH, $NaHCO_3$, 83%; e) $LiAlH_4$, Et_2O, 95%.

Scheme 3. Ozonolytic transformations of the (-)-sclareol (2) [17,18].

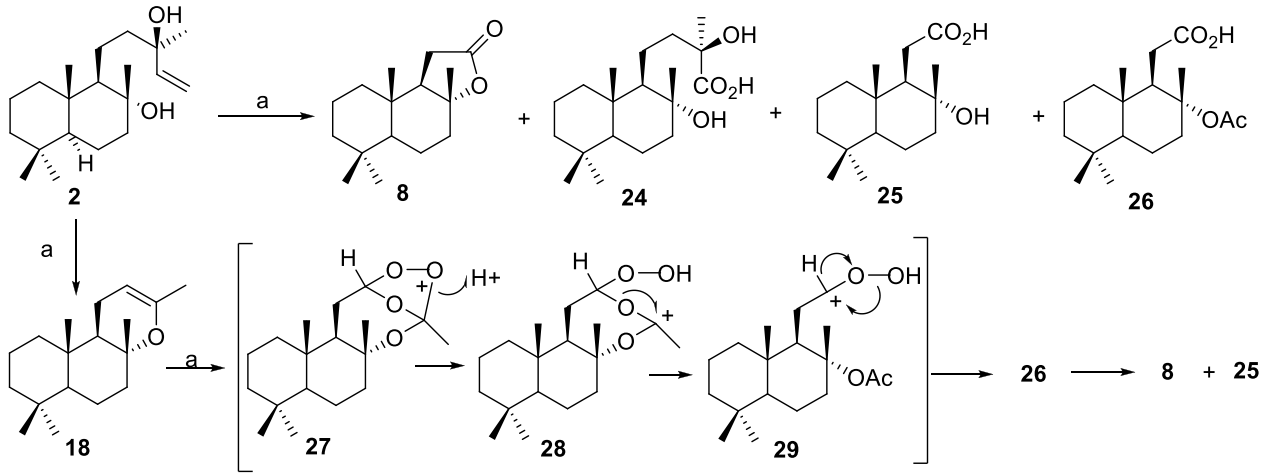
The structure of compound **20** results from spectral data (it contains three functional groups - tertiary hydroxyl, hydroperoxide and epoxy) and its chemical transformations: the hydroperoxide test with KI is positive upon reduction with $LiAlH_4$ triol **23** is formed, which is also obtained when reducing the known sclareolic acid (**24**) with the same reagent. Upon heating, the compound **20** removes carbon monoxide and gives oxyketone **19**. The last result allowed to propose an efficient way to obtain the valuable compound sclareoloxide (**18**): the total ozonation product is heated in hexane solution and the solvent is distilled *in vacuo*, giving a sclareoloxide (**18**) yield of 78%. This method (Scheme 3) has been patented [19].

The formation of epoxyhydroperoxide (**20**) takes place through the intermediates molozonide (**21**) and thiterion **(22)**.

The ozonation reaction of sclareol (**2**) in acetic acid medium at 20°C takes place in a particular way (Scheme 4). The neutral fraction contains norambreinolide (**8**) (26%), and the acidic one - sclareolic acid (**24**) (10%), oxyacid **25** (7%) and acetoxyacid **26** (39%) [20].

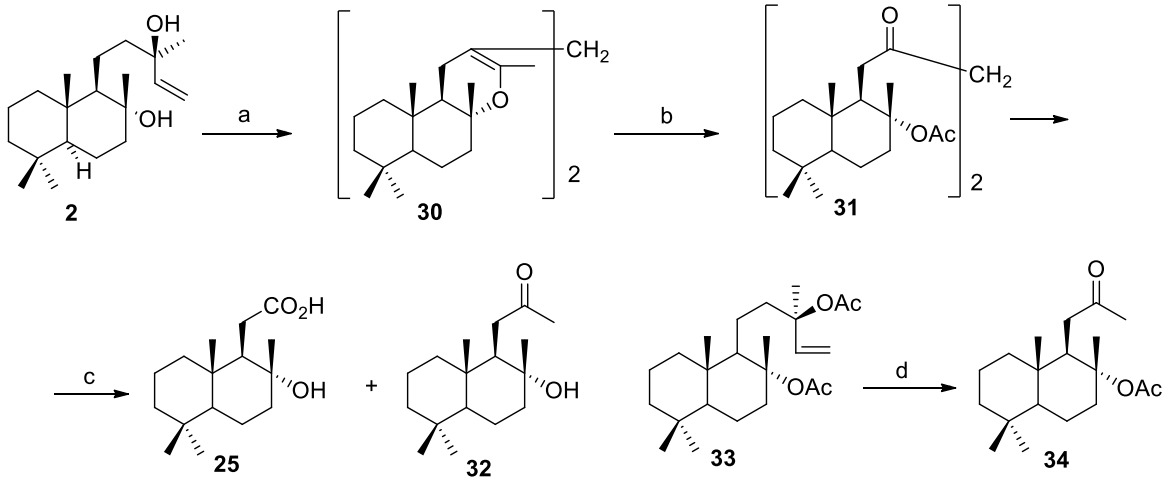
Proceeding from the composition of the reaction product, it was suggested that **2** should be saponified and lactonized by heating to 130-140°C, and then purified by crystallization. The yield of norambreinolide (**8**) was 69%. The possible mechanism of transformation of sclareol (**2**) into norambreinolide (**8**) includes as intermediates sclareoloxide (**18**), ozonide **27** and its transformation products **28** and **29**.

The product of ozonation of sclareol (**2**) in methanol at 15-20°C has turned out to be unusual, as well as the subsequent treatment of the product with anhydrous ammonium chloride - dimer **30** in high yield (80%) (Scheme 5) [14,16].



Reagents and conditions: a) O_3, AcOH, Py.

Scheme 4. Ozonolytic transformations of the (-)-sclareol (2) in acetic acid [20].



Reagents and conditions: a) 1. O_3, MeOH, 2. NH_4Cl, 80%; b) 1. O_3, MeOH, 2. H_2O, reflux; c) KOH, EtOH, reflux; d) O_3, $Cu(OAc)_2H_2O$, reflux.

Scheme 5. Ozonolytic transformations of the (-)-sclareol (2) in methanol [16].

In turn, the dimer **30** being ozonated in hexane at -65÷-70°C and upon heating (70°C) of the ozonide in the presence of water, gives an unstable compound **31** in quantitative yield. By cleaving it with an alcohol-based mixture, the mixture of 11-bishomodriman-8*α*-al-12-one (**32**) (46% yield) and oxyacid **25** (48% yield) were obtained [16] (Scheme 5). Thus, it appears that by changing the ozonation conditions of the sclareol (**2**), compounds with different structure can be selectively obtained.

Thus, by researching the products of the sclareol (**2**) ozonation reaction, the mechanism of this reaction was established, obtaining new relevant data on the ozonolytic transformations of allyl alcohols. This study allowed to establish the optimal conditions for obtaining sclareoloxide (**18**) by the method of ozonation with a low degree of environmental pollution and acceptable under production conditions. The process of obtaining sclareoloxide (**18**) by ozonation of sclareol was patented [21] and implemented at the Tobacco Factory in Chisinau in order to obtain flavouring compositions for tobacco.

Development of general methods of photocatalytic dehydrogenation of Δ^8-drimen- and Δ^8-11-homodrimen-7-ones and regio-selective dehydration of tertiary methylcyclohexanic alcohols

In addition to the interest in the practical properties, norlbdane and drimane compounds are an attractive target for fundamental research, leading to the discovery and development of many reactions of general interest. Among these, it was highlighted the photooxidative dehydrogenation reactions of Δ^8-drimen- and Δ^8-11-homodrimen-7-ones in *α,α′*-dienone and regioselective dehydration of tertiary methylcyclohexane alcohols with Swern reagent.

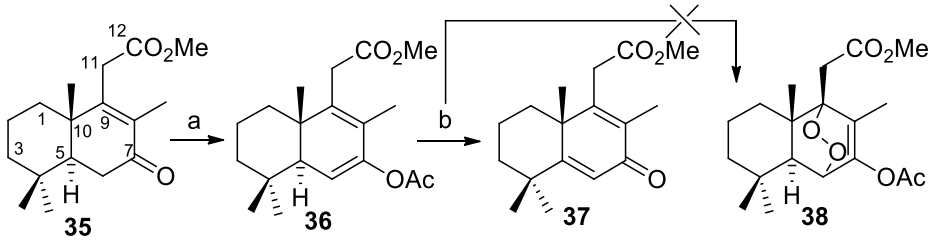
Synthesis of dienesters by photooxidative dehydrogenation reaction

A general method was developed for the transformation of drimanic and homodrimanic compounds containing the 8-en-7-onic structural fragment into *α,α′*-dienone [18,22]. The research began by obtaining 11-homodrim-8(9)-en-7-on-12-oic acid methyl ester (**35**).

Aiming at preparing 11-homodrimane derivatives with oxygen-containing functional groups at the C-6 and C-9 atoms from readily available methyl 7-oxo-11-homodrim-8-en-12-oate (**35**), it was studied the photooxidative oxygenation of the enol acetate derived from **35**, namely, methyl 7-acetoxy-11-homodrima-6,8-dien-12-oate (**36**), in the presence of tetraphenylporphyrin (H_2tpp). It was taken into account that conjugated 1,3-dienes preferably react with singlet oxygen according to the [4+2]-cyclo-addition pattern to give endoperoxides [22]. However, data from elemental and spectral analyses convincingly demonstrated that the reaction product formed in high yield (93%) was not endoperoxide **38**. The molecule contained no peroxide or acetate groups, but the ester function retained and, a dienone group appeared (IR and ^{1}H and ^{13}C NMR data). Hence, it follows that product was identified as methyl 7-oxo-11-homodrima-5,8-dien-12-oate (**37**) (Scheme 6).

Thus, it was interesting to check whether the oxidative transformation of ketoester **35** has a general character for trans-decalinic enones. This method of photooxidative dehydrogenation has also been used for compounds of the drimanic sesquiterpenoid series. Under the conditions indicated above, the enolacetate **39** of 7-ketoisodrimenine (**40**) was converted in 69% yield to natural compound 11,12-epoxyhydrim-5,8-diene-7,11-dione (**41**) (Scheme 7).

Under similar conditions, the diacetate **42**, which was obtained directly from hydroxyketone **43** (59%) or *via* monoacetate **44** (73%), was also subjected to the photooxidative dehydrogenation reaction in the presence of mesotetrafenylporphyrin; this resulted in the formation of compound **45** in a yield of only 36%. The reaction performed in the presence of the Rose Bengal photosensitizer, which worked with a yield of 63%, proved to be more effective. Thus, the photooxidative dehydrogenation reaction of 7,11,12-triacetoxyhydrim-6,8(9)-diene (**46**), obtained from 11,12-diacetoxyhydrim-8(9)-en-7-one (**47**), was carried out with a yield of 99%.



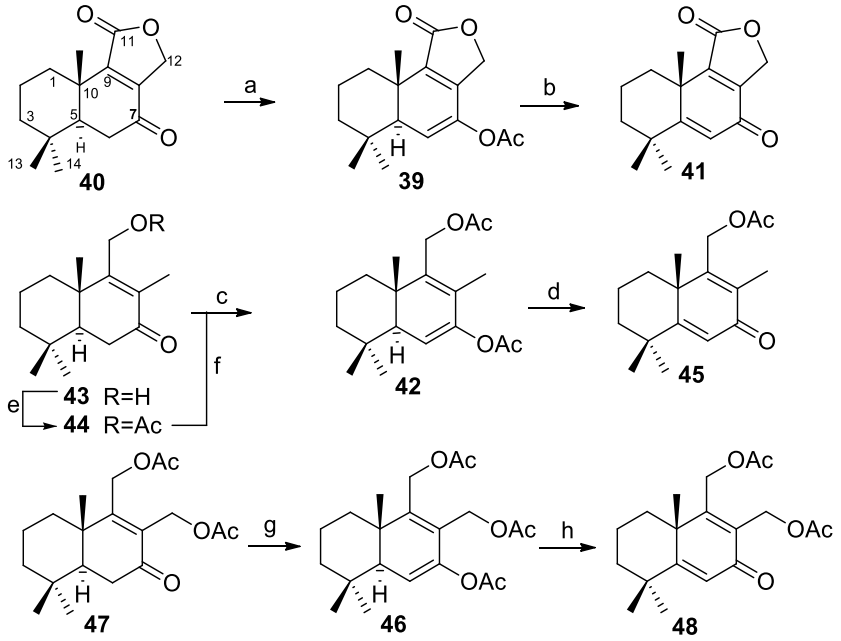
Reagents and conditions: a) CH_2=C(Me)OAc, *p*-TsOH, Ar, reflux, 3 h, 98%; b) O_2, *hν*, H_2tpp, CCl_4, 20°C, 5 h, 90%.

Scheme 6. Synthesis of dienesters by photooxidative dehydrogenation reaction [22].

The enoldiacetate **46** reaction takes place in the presence of mesotetrafenylporphyrin to give 11,12-diacetoxyhydrim-5,8(9)-dien-7-one (**48**) in a yield of 53% (Scheme 7). The spectral data of compound **48** confirm the presence in its molecule of the structural fragment α,α'-dienonic characteristic also for compounds **37**, **41** and **45**. Thus, the possibility of photosensitized oxidative dehydrogenation of drimanic compounds and 11-homodrimanic derivatives containing the 7-keto-8-one structural fragment has been demonstrated.

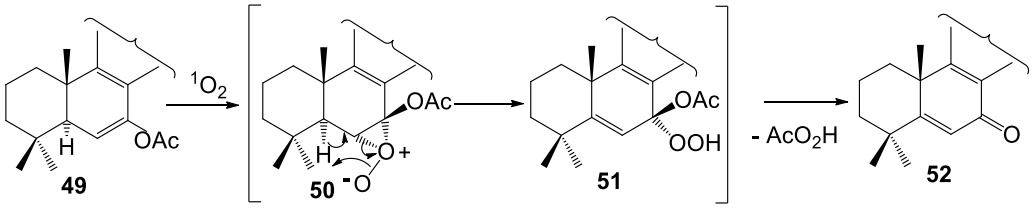
The above-described pathway of reaction of diene enol acetates **36**, **39**, **42**, and **46** with singlet oxygen can be interpreted as follows (Scheme 8) [18,22]. Diene systems in these compounds contain an electron rich 6,7-double bond. Because singlet oxygen is electrophilic, it reacts with compounds of the type **43** according to the ene reaction pattern involving the 6,7-double bond to give peroxyepoxide **50** rather than according to the [4+2]-cycloaddition route. Singlet oxygen is known to be sensitive to steric factors and, hence, the addition at the 6,7-double bond should occur from the sterically more accessible α-side of type **49** molecules to give peroxyepoxide **50**. This is also favoured by the stereoelectronic requirements of the stereospecific end photosensitized oxygenation: the newly formed C–O bond and the cleaved allylic C–H bond should be *cis*-arranged, and the allylic C–H bond should be perpendicular to the Δ^6-bond plane, as only in this case, can the electron pair of the cleaved C–H bond interact with π-bond electrons to give a new double bond.

Thus, in the case of compounds with structure **49**, the steric and stereoelectronic factors act in the same direction, thus promoting the stereospecific formation of peroxyepoxide **50**, which is then converted regioselectively into unstable allylic hydroperoxide **51**, which eliminates peracetic acid being converted into the final product **52**.



Reagents and conditions: a) CH_2=C(Me)OAc, *p*-TsOH, reflux, 2 h, 75%; b) O_2, hν, H_2tpp, CCl_4, 12°C, 14 h, 69%; c) CH_2=C(Me)OAc, C_6H_6, *p*-TsOH, reflux, 6 h, 59%; d) O_2, hν, Rose Bengal, CCl_4, 20°C, 20 h, 63%; e) Ac_2O, Py, 20°C, 24 h, 97%; f) CH_2=C(Me)OAc, *p*-TsOH, reflux, 6 h, 72.6%; g) CH_2=C(Me)OAc, *p*-TsOH, Ar, reflux, 6 h, 99%; h) O_2, hν, H_2tpp, CCl_4, 20°C, 4 h, 53%.

Scheme 7. Synthesis of dienesters by photooxidative dehydrogenation reaction [22].



Scheme 8. Mechanism of interaction of diene enolacetates containing the 8-en-7-one structural fragment with singlet oxygen [22].

Regioselective dehydration of tertiary alcohols by Swern reagent

It was shown that the ability of Swern reagent to dehydrate tertiary methylcyclohexane alcohols is general, and in the case of primary-tertiary and secondary-tertiary diols two reactions can be performed simultaneously - dehydration of tertiary alcohol and oxidation of primary or secondary alcohol to carbonyl compound [23].

During previous investigations of labdanic compounds, some interesting effects of Swern reagent have been established: along with the oxidation of primary or secondary alcohol, Swern reagent has simultaneously promoted the process of dehydration of tertiary alcohol. The lack of data on the dehydrating properties of Swern reagent in the literature has stimulated the interest in determining whether the dehydration reaction of tertiary methylcyclohexane alcohols is general, how dehydration of epimeric alcohols occurs and whether this reaction can serve as a chemical test to determine the configuration of nominated alcohols.

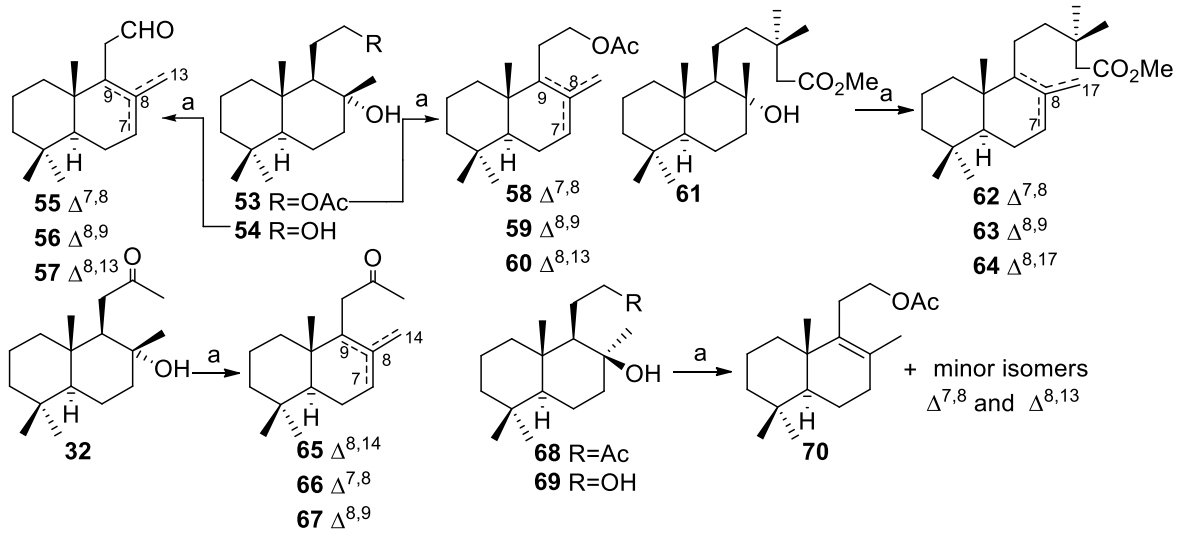
The performed study comprised compounds **32**, **53**, **54**, **61** and **69**, which possess the initially necessary structural fragment (Scheme 9) [23]. Also, the products of dehydration of compounds **32**, **53**, **54**, **61** and **69** with phosphoryl chloride in pyridine were studied for comparison purposes. The identification of the dehydration products of the nominated compounds was performed by comparing the chromatographic and spectral data with the authentic, previously obtained controls. The isomeric composition of the dehydration products was determined from NMR spectroscopy data. Based on the obtained experimental results, it was established that the dehydration of compounds **32**, **53**, **54**, **61** and **69** with both Swern reagent and $POCl_3$ in pyridine results in very similar reaction products by composition: the initial alcohols with equatorial hydroxyl group produce isomeric mixtures wherein the exocyclic double bond isomer predominates, and upon dehydration of the axial hydroxyl group compound **69**, the reaction product is in both cases almost exclusively the tetrasubstituted endocyclic ethylene bonded isomer [18].

Thus, the obtained results demonstrate clearly that the property of the Swern reagent to dehydrate tertiary alcohols is of general nature. Compared to the classic dehydrating reagent - $POC1_3$ in pyridine, the Swern reagent was found to be more effective, the dehydration conditions being much milder. In addition, in the case of primary-tertiary or secondary-tertiary glycols, two transformations can be performed simultaneously - dehydration of the tertiary hydroxyl group and oxidation of the primary or secondary hydroxyl group to carbonyl. Like phosphoryl chloride ($POC1_3$) in pyridine, the Swern reagent can be successfully used to determine the hydroxyl group configuration of tertiary methylcyclohexane alcohols.

Thus, it was shown that the Swern reagent can be suitably used to determine the hydroxyl group configuration of tertiary methylcyclohexane alcohols [18].

Superacidic cyclization of terpenoids

The scientific school founded by academician Pavel Vlad is leading in the investigations of superacidic cyclisation reaction of terpenoids, and also of the regularities of the mentioned reaction in different classes of terpenic compounds, such as alcohols, their acetates, acids, esters, phenylsulphones.

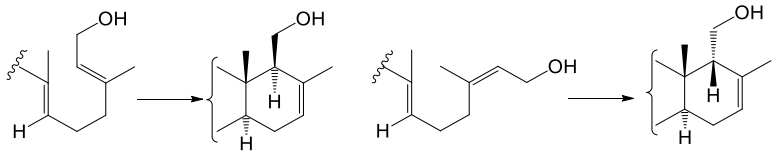


Reagents and conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, -60ºC, 45 min.

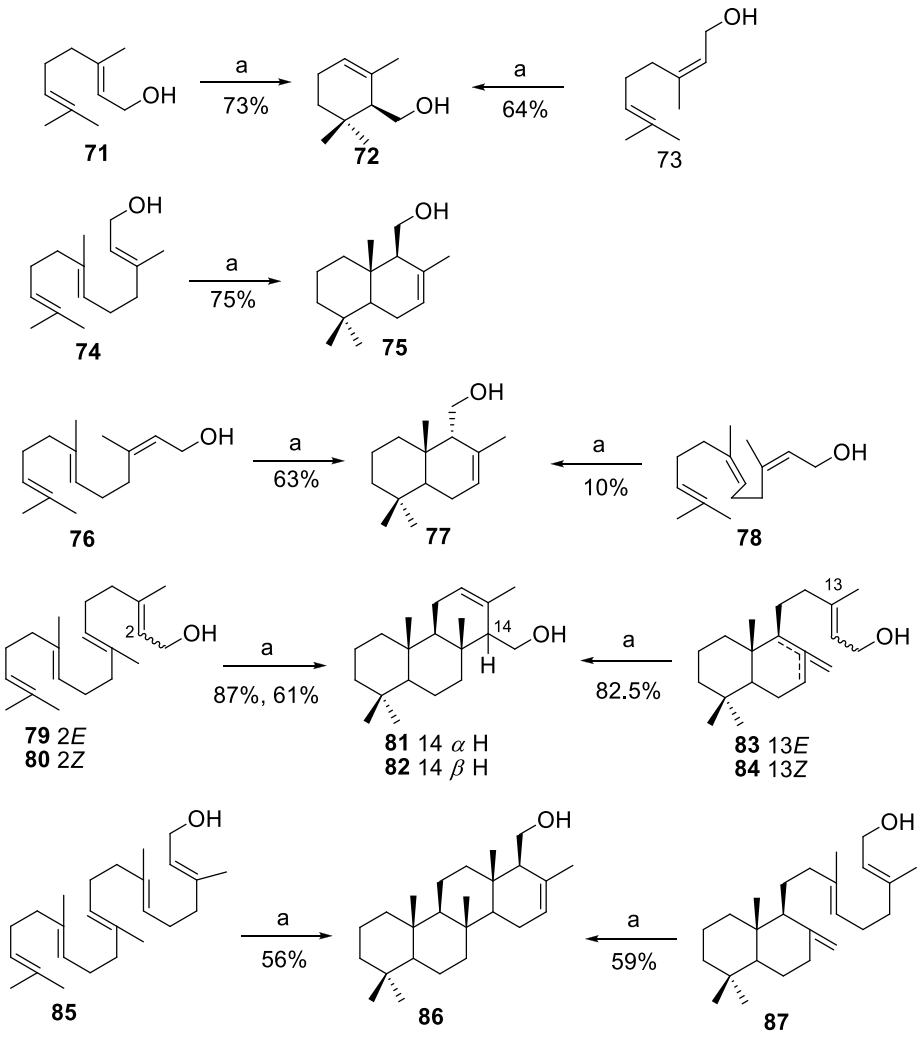
Scheme 9. Regioselective dehydration of tertiary alcohols by Swern reagent [23].

One of the basic features of the class of terpene compounds is the diversity of their cyclic structures. According to the biogenetic rule of isoprene, formulated by Ruzicka, L., the biogenesis of these structures takes place by electrophilic cyclization of aliphatic isoprenoids containing 1,5-polyene systems [24]. In order to confirm this postulate rule and to develop accessible and efficient methods for the synthesis of cyclic terpenoids, systematic research into the cyclization reaction of isoprenoids *in vitro* has been undertaken.

However, notwithstanding the successes achieved, all known processes for carrying out the cyclization reaction of terpenoids, using conventional protic acids and Lewis, do not allow to obtain in good yield cyclic terpenoids with regular structure, which contain in their molecules more than two carbocycles [25]. In order to increase the yield of the oxygenated fraction in the cyclization product, fluorosulphonic acid, which is superacid and, which according to the literary data, ensures much higher structural selectivity of cyclization reaction [26,27]. The superacidic cyclization of acyclic and partially cyclized terpenols takes place according to the general Scheme 10, giving completely cyclized homoallylic alcohols; the configuration of the hydroxymethylene group of these product is governed by the configuration of the starting allylic alcohol. Examples of the cyclization of polyprenols C-10 – C-25 are given in Scheme 11.



Scheme 10. Superacidic cyclization of terpenols, general scheme [25].



Reagents and conditions: a) FSO_3H, *i*-$PrNO_2$, -80°C, 10 min-1 h.
Scheme 11. Superacidic cyclization of terpenols [25,28-30].

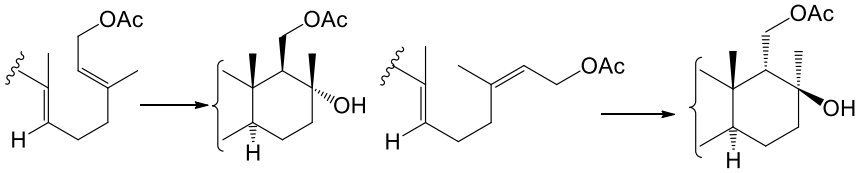
Hence, the superacidic cyclization of polyprenols is structure- and chemo- selective, stereospecific, and it is also biomimetic for the aliphatic alcohols. The only by-products of the reaction are hydrocarbons and polymeric compounds. The cyclization can be carried out directly without protection of the hydroxyl group. Unlike the reaction of polyprenols with conventional acids, the primary and tertiary allylic alcohols give different products on their interaction with superacids.

The cyclization of polyprenol acetates, occurs in a structure-, chemo- selective and stereospecific way but leads to bifunctional derivatives according to the general Scheme 12. In this case, as well, the by-products are small amounts of hydrocarbons and polymeric compounds; some examples of such reactions are given in Scheme 13.

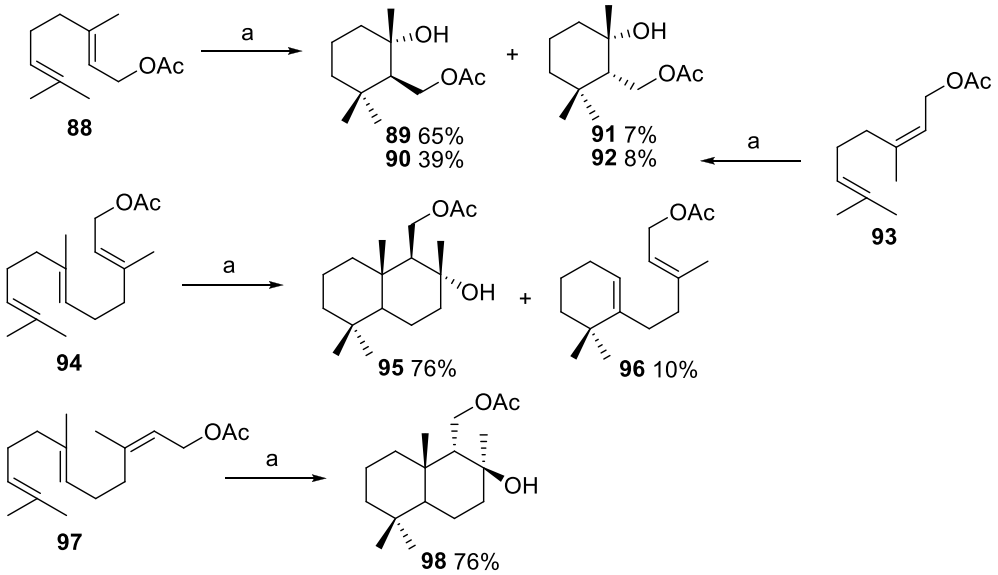
The formation of the mixture of compounds **89**-**92** on cyclization of geranylacetate (**88**) and nerylacetates (**93**) is due perhaps to the conformational mobility of the monocyclic system. The cyclization of *E,E*-farnesyl acetate (**94**) gives in low yield *β*-monocyclofarnesyl acetate (**96**), which becomes the main compound (yield 70%) if the reaction is interrupted after one minute; both this fact and the formation of epidrimenol (**77**) on cyclization of *Z,Z*-farnesol (**78**) indicate that the cyclization process is a stepwise and not a concerted one.

It should be particularly mentioned that the superacidic cyclization of the aliphatic sesterterpenoids **85** and **107** affords stereospecifically in one step and high yield the tetracyclic scalarane sesterterpenes **86** and **106**, containing respectively seven and even eight chiral carbon atoms (Scheme 14) [28,30].

The afore-mentioned data demonstrate that the synthetic possibilities of the reaction of electrophilic cyclization of isoprenoids are considerably extended by passing from the usual acids to superacids. Varying such parameters as acid-substrate ratio, temperature, medium acidity, acid concentration and reaction duration, it is largely possible to direct the structural and stereochemical reaction course [29]. It is very important to note that in the superacidic medium it is possible to follow the behaviour of the carbocations by NMR spectroscopy and consequently to select conditions to carry out the reaction to the desired product.



Scheme 12. Superacidic cyclization of terpenoacetates, general scheme [25].

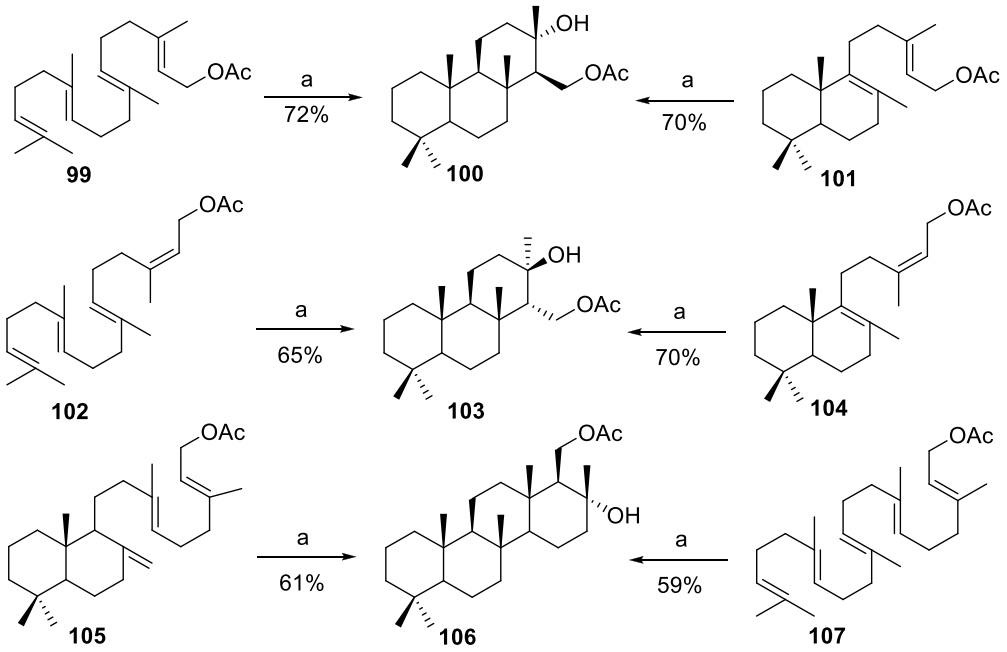


Reagents and conditions: a) FSO_3H, *i*-$PrNO_2$, -80°C, 10 min-1 h.
Scheme 13. Superacidic cyclization of polyprenol acetates [25,28].

Finally, in a superacidic medium it is possible to obtain compounds which are not formed with usual acids. In Scheme 15 this affirmation was illustrated by the transformations of geranylacetone (**113**). This remarkable achievement of academician Pavel Vlad brings a considerable contribution to the development of the biogenetic rule of isoprene in the series of terpenoids, and opened perspectives in the search of new compounds with specific properties, valuable for science and practice.

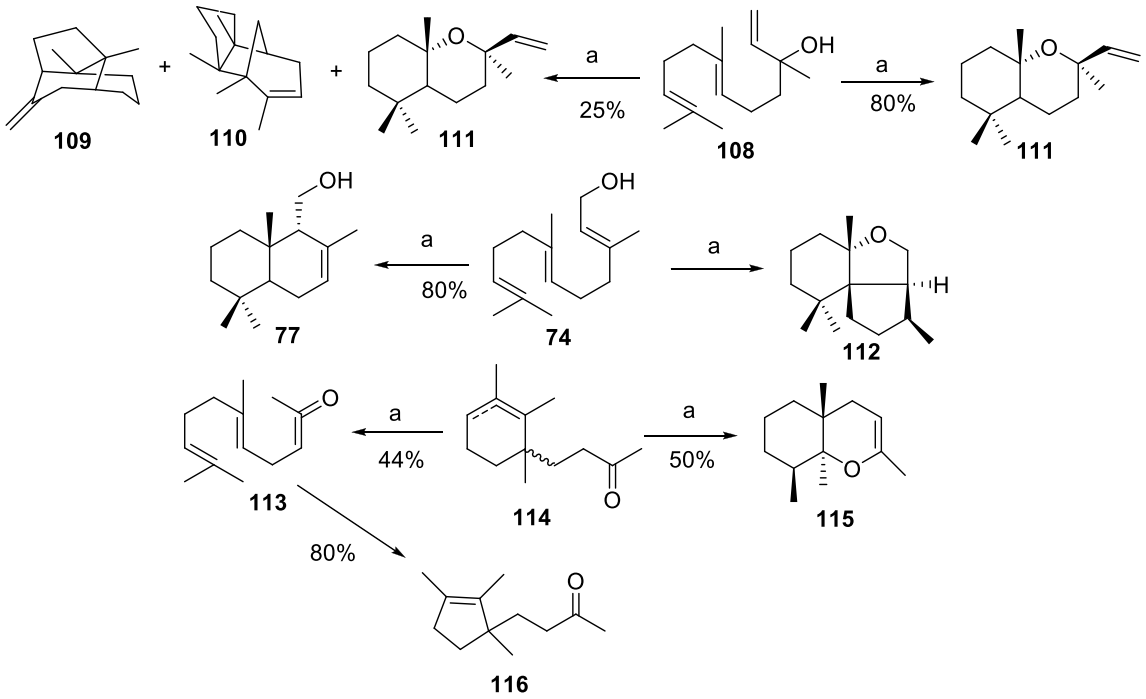
Molecular rearrangement of some terpenoids

A specific feature of terpenoids is the molecular rearrangement, which contributes to the production of terpenoids with unusual structure, with new carbon skeletons and have special properties [31]. Molecular rearrangement of terpenoids is initiated by carbocations. More frequently, molecular rearrangement is performed in the monoterpenic, sesquiterpene and diterpene series.



Reagents and conditions: a) FSO_3H, *i*-$PrNO_2$, -80°C, 10 min-1 h.

Scheme 14. Superacidic cyclization of polyprenol acetates [28-30].



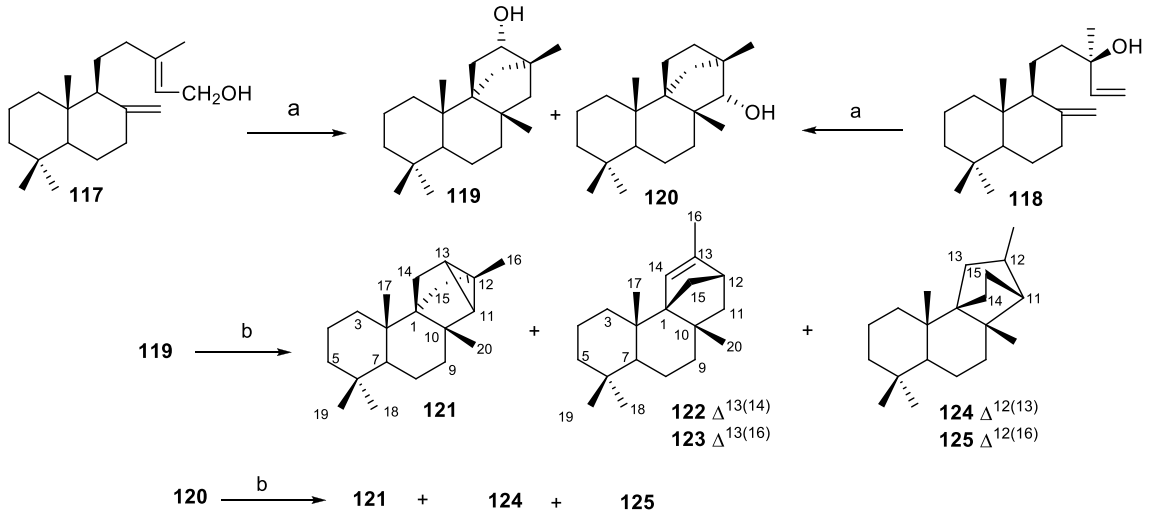
Reagents and conditions: a) FSO_3H, *i*-$PrNO_2$, -80°C.

Scheme 15. Cyclization and rearrangements of farnesol (74), nerolidol (108), and geranylacetone (113) [25,29].

In the electrophilic cyclization of labdanic diterpenoids - *ent*-copalol (**117**), manool (**118**), *etc*. - tetracyclic alcohols **119** and **120** were obtained with a new tetracyclo [10.2.1.01.10.02.7] -pentadecanic carbon backbone (Scheme 16) [32]. The alcohol **119** was reacted with phosphorus oxychloride in pyridine to give the mixture of hydrocarbons **121**-**125** [33]. Dehydration of the alcohol **120** with phosphorus oxychloride in pyridine gave the mixture of hydrocarbons **121**, **124** and **125** [34]. It should be noted that hydrocarbons **121**, **122** and **124** have new carbon skeletons.

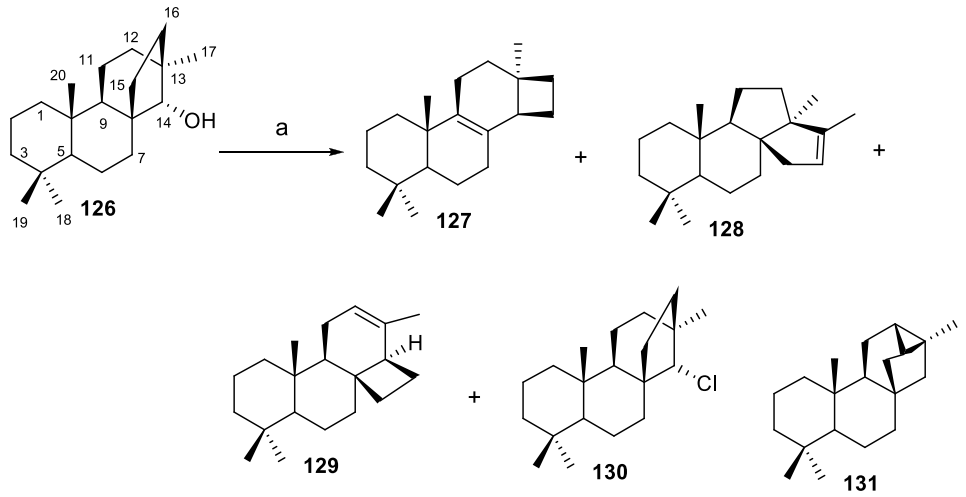
At the interaction of many labdanic compounds with conventional acids, along with other products, the 14*α*-hibanol (**126**) was formed [32]. In order to obtain compounds with new carbon skeletons, the reaction of this alcohol with phosphorus oxychloride was studied [35]. Three tetracyclic hydrocarbons **127**-**129** and tetracyclic chloride **130** were obtained from the reaction (Scheme 17). The hydrocarbons **127**-**129** have new carbon skeletons, they come as a result of the solvolysis of the hydroxyl group of the compound **126** and the migration 1,2 of the C-C bonds, adjacent to the carbocationic center. The structure of tetracyclic hydrocarbons **127**-**129** was determined by the X-ray diffraction.

The tetracyclic hydrocarbon **121**, obtained by dehydrating tetracyclic alcohols **119** and **120**, is an analogue of tetracyclic trachylobane **131**. Given the properties of the latter, it was of interest to study the interaction of hydrocarbon **121** with acid, in order to obtain tetracyclic compounds with grouped carbon backbones.



Reagents and conditions: a) HCO_2H / H_2SO_4; b) $POCl_3$, Py.

Scheme 16. Molecular rearrangement of *ent*-copalol (117) and manool (118) [32].



Reagents and conditions: a) HCO_2H / H_2SO_4; b) $POCl_3$, Py.

Scheme 17. Molecular rearrangement of 14*α*-hibanol (126) [35].

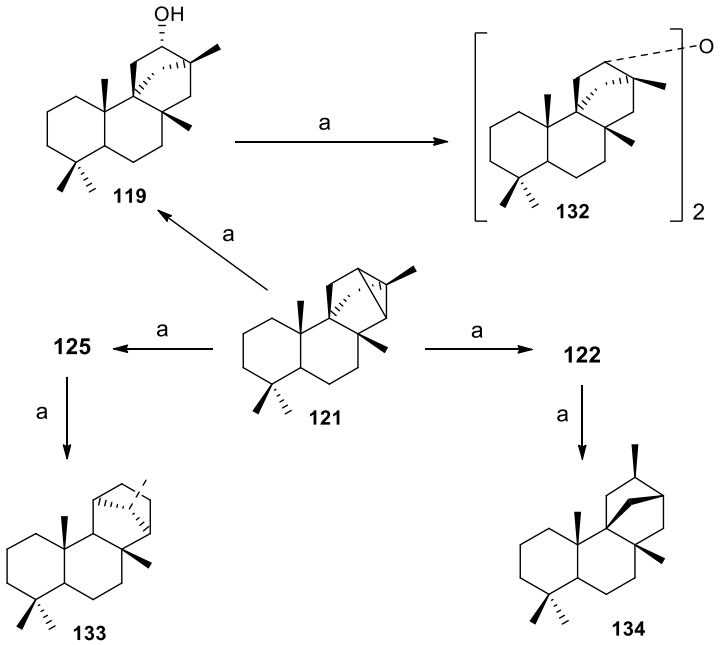
The reaction of compound **121** with fluorsulphonic acid has been studied [36]. At a temperature of -100°C a single product is obtained - alcohol **119** (91% yield); whilst at -75°C, in addition to the alcohol **119**, a small amount (13%) of ether **13** is obtained; and, at -50°C, along with alcohol **119** (60%) and ether **132** (11%), a small amount of hydrocarbons **122** (2%) and **125** (6%) are formed. Therefore, in the last conditions, the cleavage of the propane cycle takes place in all three possible directions. When performing the reaction at 22°C, the reaction products are the known hydrocarbons **133** (54%) and **134** (18%) (Scheme 18) [37].

Thus, the isomerization of hydrocarbon **121** with superacid at low temperatures takes place with the cleavage of the C-12 – C-13 bond and the formation of the pentadecanic [10.2.1.01,10.02,7] carbon skeleton compound, and at the usual temperature the primary carbocations, generated at the cleavage of the propane cycle of compound **121**, is further isomerized to give pentadecanic **133** and **134** tetracyclo[10.2.1.01.10.02.7] - and tetracyclo[10.2.1.02.11.03.8] carbon backbone compounds.

Kauranic diterpenoids, derivatives of the carbon skeleton **135**, are widespread in nature, these being the biogenetic predecessors of plant hormones, gibberellins. A large number of kauranic compounds are known to possess diverse biological activity, including anticancer activity. A rich source of tetra- and pentacyclic diterpene compounds is the waste formed during sunflower processing, in which, the basic product is the *ent*-kaur-16-en-19-oic acid (**136**) [38]. Thus, it was developed a simple and effective method for isolating this acid from the etheric extract of waste [39]. Along with the acid **136** by silica gel column chromatography, 15α-angeloyl-*ent*-kaur-16-en-19-oic acid (**137**) was isolated, which on saponification with KOH in EtOH passes into 15α-oxi-*ent*-kaur-19-oic (**138**). The last compound was obtained by oxidizing the acid **136** with SeO_2 (68%). Treatment of the oxyacid **138** with the Collins reagent gives 15-oxo-*ent*-kaur-16-en-19-oic acid (**139**) (84%) (Scheme 19) [40].

In most cases, kauranic compounds are found in natural sources together with the derivatives of pentacyclic *ent*-atisan (**140**), *ent*-beieran (**141**) and *ent*-trahiloban (**142**). According to data provided by Wenkert, E. in the process of biosynthesis of mixtures of derivatives of *ent*-kauran (**135**), *ent*-atisan (**140**), *ent*-beieran (**141**) by means of non-classical carbocation **143** the pentacyclic *ent*-trahiloban **142** was obtained, which, then turn into derivatives of *ent*-kauran, *ent*-beieran and *ent*-atisan [41].

From the point of view of biological activity, the greatest interest is in the *ent*-atisan derivatives **140**, but these are found in natural sources in the form of very complex mixtures. So, it was resorted to the use of super acid as an isomerizing reagent of *ent*-kaur-16-en-19-oic acid (**136**).



Reagents and conditions: a) FSO_3H.

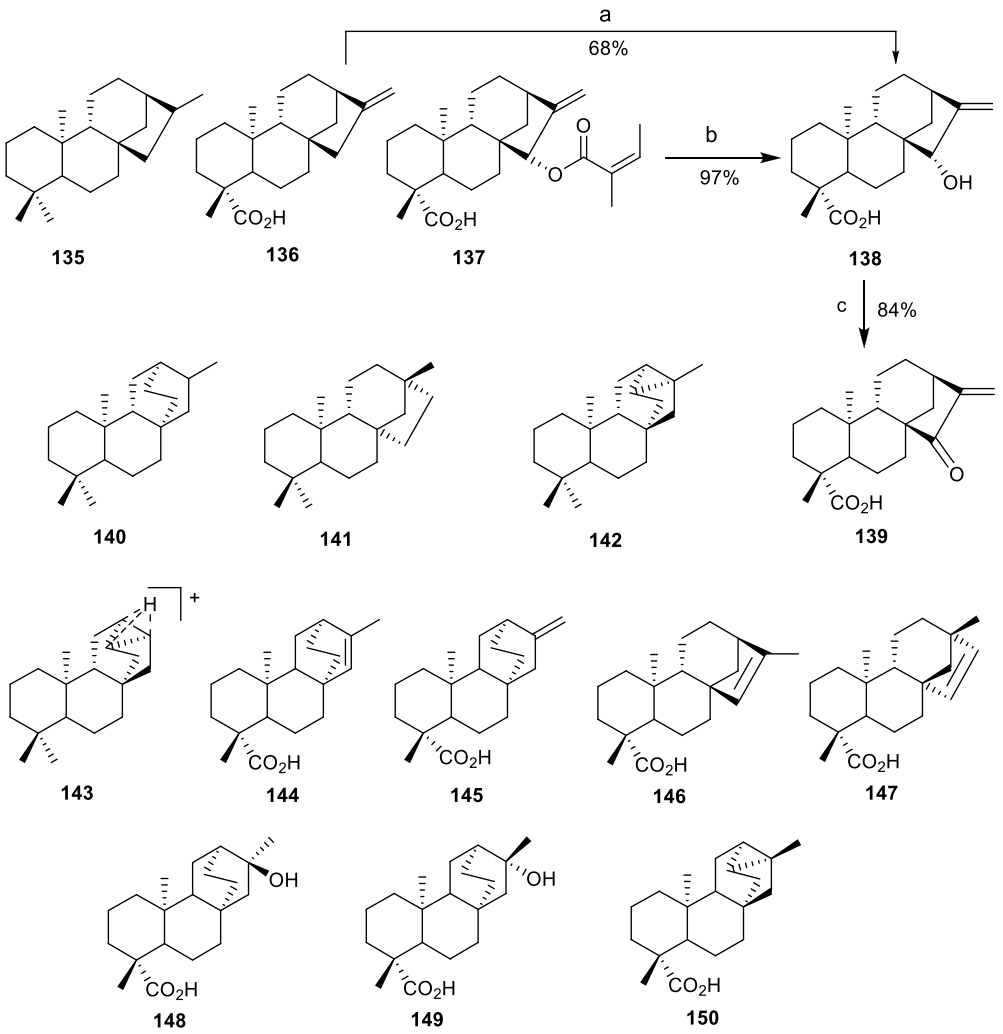
Scheme 18. Molecular rearrangement of hydrocarbon (121) with fluorsulphonic acid [36,37].

Using the chromatographic methods, the following acids were isolated and identified: *ent*-atis-15-en-19-oic (**144**) (8%), *ent*-atis-16-en-19-oic (**145**) (22%), *ent*-kaur-15-en-19-oic (**146**) (17%), *ent*-beier-15-en-19-oic (**147**) (7%), *ent*-atis-16β-ol-19-oic (**148**) (5%) and *ent*-atis-16α-ol-19-oic (**149**) (4%).

Under the same conditions (Scheme 19), the isomerization of *ent*-trachyloban-19-oic acid (**150**) takes place with the formation of the mixture of the same substances, which have been listed above. Thus, when treating *ent*-kaurenoic acid (**136**) with superacid, preferably *ent*-atheic tetracyclic diterpenoids **144**, **145** and **148**, **149** are formed in a 39% total yield, and taking into account the unreacted starting compound - 62%. By isomerization of *ent*-trachyloban-19-oic acid (**150**) the main compounds are also artisans. The total yield of atheic compounds **144**, **145** and **148**, **149** is 73% [42,43]. Thus, molecular rearrangement allowed obtaining compounds with unique structures, difficult to obtain by other ways.

Synthesis of nitrogen-containing drimanic and homodrimanic compounds

The synthesis of nitrogen containing drimanic and homodrimanic compounds and the study of their biological activity is a less studied field of terpenoid chemistry [44]. According to literature data, the presence of the nitrogen atom in terpenic compounds amplifies their bioactivity [44]. At the same time, these compounds can be easily transformed into water-soluble salts, which facilitated the study of their biological activity. It was developed methods for the synthesis of nitrogen containing drimanic and homodrimanic compounds, in order to use terpenoids as chiral syntones to obtain compounds with practical value [18].



Reagents and conditions: a) SeO_2, EtOH, 68%; b) NaOH, EtOH, reflux, 97%; c) $CrO_3 \cdot 2Py/CH_2Cl_2$, 84%.

Scheme 19. Molecular rearrangement of kauranic diterpenoids [40].

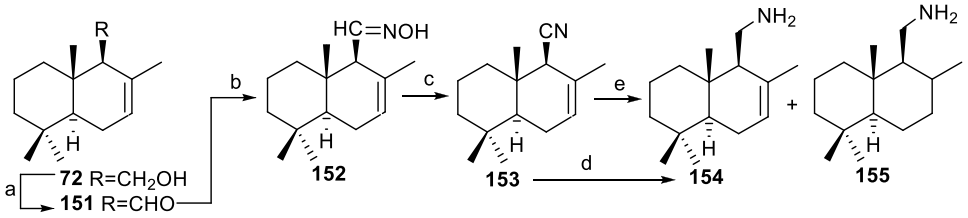
*Synthesis of 11-aminodrim-7-ene (**154**) from drimenol (**72**)*

Many drimanic sesquiterpenoids, including their prototype - drim-7-en-11-ol (**72**), possess various types of biological activity. In order to obtain nitrogen-containing drimanic compounds, an efficient method has been developed for the synthesis of the amino-analogue of drimenol (**72**) - 11-amino-drim-7-ene (**154**), starting from drimenol (**72**) (Scheme 20) [45].

So, drimenol (**72**) was oxidized to drimenal (**151**) under the conditions of the Swern reaction. Drimenal oxime (**152**) was synthesized by reacting drimenal (**151**) with hydroxylamine hydrochloride in a mixture of ethanol and pyridine. According to the chromatographic data, a mixture of *Z* and *E* isomers was obtained in a yield of 80%, the ratio of isomers *Z* and *E* in the mixture being about 1:4. At the next step, the oxime **152** was subjected to reduction under various conditions, obtaining the amine **154** in rather modest yields, between 20 and 30%. To improve the yield of amine **154**, an alternative pathway was also tested: conversion of oxime **152** to the corresponding nitrile **153**, with subsequent reduction to amine **154**. The optimal methods for the synthesis of nitrile **153** proved to be the reaction of the oxime **152** with *p*-TsCl or with Ac_2O in Py. The expected product, 11-aminodrim-7-ene (**154**), was obtained in a 50% yield when refluxing nitrile **153** with $LiAlH_4$ in Et_2O in the presence of anhydrous $AlCl_3$. Whereas in the reduction of nitrile **153** with $NaBH_4$ and $CoCl_2.6H_2O$ in methanol, the mixture of drimenylamine (**154**) and 7,8-dihydro-11-aminodriman (**155**) was obtained in a yield of 91%. Drimenilamine (**154**) and its mixture with 7,8-dihydro-11-aminodriman (**155**) are of interest for testing for potential biological activity.

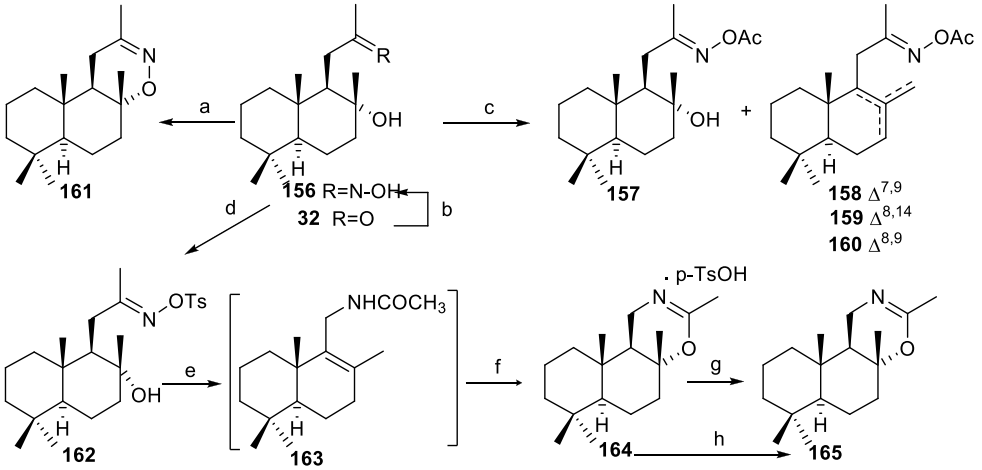
*Synthesis of nitrogen-containing drimanic sesquiterpenoids from 11-dihomodriman-8α-ol-12-one (**32**)*

The research described here refers to the synthesis of nitrogen-containing compounds by Beckmann rearrangement of oxime **156** of the 11-bishomodriman-8α-ol-12-one (**32**) in the presence of various reagents [46]. Oxime **156** was obtained from hydroxyketone **32** at its interaction with hydroxylamine hydrochloride in the solvent mixture ethanol and pyridine (Scheme 21).



Reagents and conditions: a) P_2O_5, DMSO, 20°C, 95%; b) $NH_2OH{\cdot}HCl$, EtOH, Py, 80%; c) 1. Ac_2O, Py, 64%, 2. *p*-TsCl, Py, 90%; d) $LiAlH_4$, $AlCl_3$, Et_2O, 50%; e) $NaBH_4$, $CoCl_2{\cdot}6\ H_2O$, MeOH, 20°C, 91%.

Scheme 20. Synthesis of 11-aminodrim-7-ene (154) from drimenol (72) [45].



Reagents and conditions: a) 86% H_3PO_4, 60-70°C, 82%; b) $NH_2OH{\cdot}HCl$, EtOH, Py 94%; c) Ac_2O/Py, reflux; d) *p*-TsCl/Py, 20°C, 90%; e) CH_3CN, reflux; f) *p*-TsOH, 95%; g) 10% KOH, MeOH, 95%; h) Al_2O_3, 58%.

Scheme 21. Synthesis of nitrogen-containing drimanic sesquiterpenoids from 11-dihomodriman-8α-ol-12-one (32) [46].

According to chromatographic and spectral data, the reaction product is a mixture of the *Z* and *E* isomers. As a result, the *E* isomer is more thermodynamically stable and the *Z* isomer easily converts to the *E* isomer, oxime **156** was used in subsequent reactions as a mixture [46]. It is known that Beckmann rearrangement stereospecifically occurs as a result of anti-migration of the larger radical. Thus, the basic product of the Beckmann rearrangement of the oxime **156** will be an amide. It has been established, however, that when oxime **156** was treated with Ac_2O in pyridine at 105-110°C it does not regroup, but converts to acetate **157** (90%) and a small amount (5%) of the mixture of acetates of isomeric oxymes **158**-**160** in a ratio of approx. 5: 4: 1. When the solution of oxime **156** in 86% H_3PO_4 is heated by 86%, Beckmann rearrangement also does not take place, as a result of dehydration and cyclization it forms (1*S*,2*S*,4a*S*,8a*S*)-2,5,5,8a-tetramethyldecahydro-1*N*-naphtho[1,2][5,6]-3-methyl-4,5-dihydro[1,2,6]-oxazine (**161**). Following the interaction of oxime **156** with *p*-toluenesulphonic acid hydrochloride at room temperature, oxytozilate **162** was obtained, which upon reflux in CH_3CN removes water and *p*-TsOH acid, regrouping according to Beckmann rearrangement, to form an almost quantitative mixture of unsaturated amide **163** and *p*-TsOH acid. Under the influence of *p*-TsOH, the compound **163** was cyclized to give a salt, which according to IR and NMR data has been identified as the *p*-toluenesulphonic acid salt of (1*S*,2*S*,4a*S*,8a*S*)-2,5,5,8α-tetramethidecahydro-1*N*-naphtho[1,2][5,6]-3-methyl-4,5-dihydro[1,2,6]-oxazine (**164**). *p*-TsOH acid was removed by treatment with a 10% KOH solution in MeOH, obtaining 1,3,6-oxazine **165**. The product **165** was also obtained by passing the salt solution of compound **164** through a column with Al_2O_3 (grade II Brockman activity), the structure of oxazine **165** being confirmed in indirectly and by obtaining its picrate and hydrochloride.

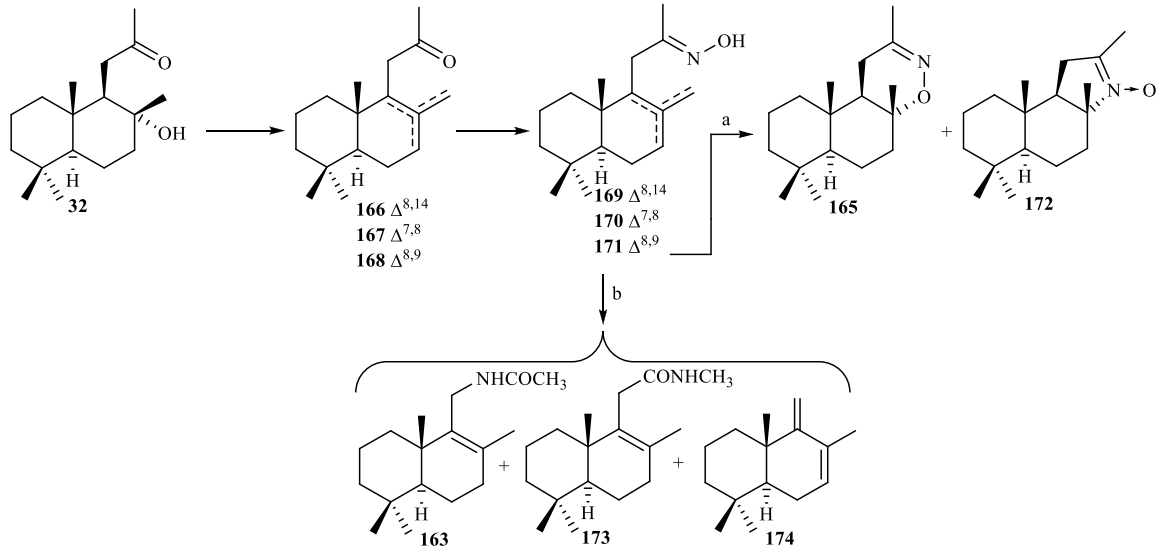
Thus, new nitrogen-containing drimanic sesquiterpenoids have been synthesized as a result of this research, some of which contain the 1,2,6- and 1,3,6-oxazine rings.

*Synthesis of nitrogen-containing drimanic sesquiterpenoids from 11-dihomodriman-8 (9)-en-12-one (**168**)*

In order to develop an efficient method of regioselective dehydration of hydroxyketone **32**, its reaction with a series of reagents was studied in detail (Scheme 22) [47]. In most reactions, mixtures of unsaturated ketones **167** and **168** were obtained, the majority being 11-dihomodrim-8 (9)-en-12-one (**168**). The ratio of unsaturated ketones in mixtures was determined by ^{1}H NMR spectroscopy. Two ways were used to obtain the oxime **171** individually.

The first way includes the reaction of the mixture of ketones **167** and **168** with the hydroxylamine hydrochloride in a mixture of ethanol and pyridine, obtaining the mixture of oxymes **170** and **171**, from which oxime **171** was isolated by recrystallization.

The second way consisted in isolating the mixture of ketones **167** and **168** by column chromatography on silica gel impregnated with $AgNO_3$.



Reagents and conditions: a) 1. 86% H_3PO_4, 2. CF_3CO_2H; b) 1. *p*-TsCl/Py, 2. PCl_5.

Scheme 22. Synthesis of nitrogen containing drimanic sesquiterpenoids of 11-dihomodrim-8(9)-en-12-one (168) [47].

From thus isolated ketone **168**, oxime **171** was subsequently obtained. As it results from the spectral data, oxime **171** represents the mixture of *Z* and *E* isomers in the ratio of ~1:1. Both isomers were isolated individually by chromatography of this mixture on a silica gel column. The determination of stereochemistry of these isomers was preceded by the observation previously established through the example of oxime **156** of 11-bishomodriman-8α-ol-12-one (**32**), namely, that the oxime with lower retention factor (*Rf*) in thin-layer chromatography (TLC) has the configuration *Z*, and a higher *Rf* - configuration *E*. From the fact that the *E* isomer is energetically more favourable, and the *Z* isomer can easily be transformed into the *E* isomer, the isomeric mixture was used in the reaction. Research of the reaction products of oxime **171** has shown that by heating it to 70-80°C in 86% H_3PO_4 as a result of intramolecular cyclization were obtained (-2*S*,2*S*,4a*S*,8a*S*)-2,5,5,8a-tetramethyldecahydro-1*H*-naphtho[1,2-e]-3-methyl-4,5-dihydro-[1,2,6]-oxazine (**165**), previously synthesized from 11-dihomodriman-8α-ol-12-one (**32**) [46], along with (1*S*,2*S*,4a*S*,8a*S*)-2,5,5,8a-tetramethyldecahydro-1*H*-naphtho[1,2-d]-2-methylpyrroline-*N*-oxide (**172**) (Scheme 22). Its structure was elucidated based on spectral data, and the absolute stereochemistry of *N*-oxide **172** was also confirmed based on the X-ray study.

Upon refluxing of the solution of oxime **171** in CF_3CO_2H, compounds **165** and **172** were also obtained. As a result of the reaction of oxime **171** with *p*-TsCl in pyridine at 20°C, 11-acetylaminodrim-8(9)-ene (**163**) and its isomer -methylaminooxodrim-8(9)-ene (**173**), with a total yield of 40%, and drim-7(8),9(11)-diene (**174**) (13%) was also isolated from the reaction mixture. At the interaction of oxime **171** with PCl_5 in ethyl ether at 0°C within 30 min, amides **163** and **173** were obtained in a total yield of 30%, and diene hydrocarbon **174** by 13%, respectively. Increasing the reaction time to 0°C or increasing the process temperature to 20°C considerably increases the yield of diene hydrocarbon **174** and the formation of other by-products takes place.

Thus, as a result of the research performed, the new drimanic nitrogen containing compound **172** was synthesized, with an unusual structure, containing the pyroline *N*-oxide ring. Also using as the starting compound 11-dihomodriman-8α-ol-12-one (**32**), 11-acetylaminodrim-8(9)-ene (**163**) and 11-methylaminooxodrim-8(9)-ene (**173**) drimane amides were synthesized, with potential biological activity.

Biography of Academician Pavel Vlad

Academician Pavel Vlad was born on June 6, 1936, in the village Lipnic (Soroca County), where he graduated high school in 1953. The same year, he took the exams and was enrolled at the Faculty of Chemistry of the State University of Moldova. After graduating the university (1958) he was assigned to the Institute of Chemistry of the Academy of Sciences of Moldova in the Laboratory of Chemistry of Natural Compounds. Under the guidance of academician Gheorghe Lazurievski he continued his doctoral studies (1958-1961) and in 1964 he defended his doctoral thesis in chemistry with the topic “Stereochemistry of some diterpenoids of the labdan group”. During his postgraduate studies, Pavel Vlad was assigned to a six-month training at the Institute of Organic Chemistry and Biochemistry in Prague [48]. There, jointly with Milan Soucek, under the guidance of a prominent scientist Vlastimil Herout, Pavel Vlad carried out investigations on the research topic *the establishment of absolute configuration of linalool and nerolidol*, which were published in the Collection of Czechoslovak Chemical Communications [2,3].

After two decades of intense research work, he crowns the results in an impressive doctor habilitate dissertation, entitled “Research on Labdanic diterpenoids”, presented at the Specialized Scientific Council of the prestigious Institute of Organic Chemistry of the U.S.S.R. Academy of Sciences.

In 1974, Pavel Vlad was appointed deputy director for scientific activity, and in 1975, director of the Institute of Chemistry of the A.S.M. In March 1995, the A.S.M. General Assembly appointed academician Pavel Vlad as Vice President of the Main Scientific Forum of the Republic of Moldova, the Academy of Sciences of Moldova. He held this position for 9 years.

In 2004, academician Pavel Vlad returned at the Institute of Chemistry of the A.S.M, where continued his scientific activity as head of the Laboratory of Terpenoid Chemistry, which he led from 1977 until 2010 [48].

The scientific results obtained by academician Pavel Vlad and his disciples have been published in many scientific journals in the country and abroad. The results of research conducted over the years have been aggregated in

over 400 scientific publications, including three monographs, four textbooks, 16 review papers and 52 patents, with participation in 45 international conferences and symposia.

Academician Pavel Vlad
(06.06.1936-24.03.2017)

Academician Pavel Vlad paid great attention to practical applications in his scientific work. Under his guidance, original and efficient methods of preparation of known compounds were developed and implemented in the perfume industry - norambreinolyd, sclareol, drimenone, ambroxide; as well as new compounds - ketoxide, ambrol, ionoxide, 14 odorous compositions for tobacco were obtained from local raw material, 9 of which were implemented at the Chisinau Tobacco Plant for the production of "Zimbru" and "MT" cigarettes, producing an economic effect of about 3 million lei.

Academician Pavel Vlad inventions were appreciated with diplomas and medals of the EREN of the MSSR (1978, 1984), with two bronze (1981) and silver (1984) medals of the EREN of the USSR, with mention diplomas of the AGEPI (1996-2001). The cycle of inventions "Odoriferous compounds for perfumery, cosmetics and tobacco industry based on local renewable raw materials - production waste" won four gold medals and one silver medal at the International Invention Salons in Geneva, Switzerland (1999, 2001), Brussels, Belgium ("Eureka", 1995, 1996, 2001). In 2001, academician Pavel Vlad was awarded the WIPO Gold Medal "Outstanding Inventor".

Under the guidance of a demanding mentor, academician Pavel Vlad, 3 doctor habilitate theses and 16 doctoral theses in chemical sciences were prepared and defended.

Highly appreciated for his professional qualities and scientific results, he earned the title of university professor (1990), and soon became a full member of the Academy of Sciences of Moldova (1992). He was a two-time State Prize winner, a World Intellectual Property Organization Award winner. He was decorated with the *Order of the Republic*, with the *Badge of Honor* Order, with the Medal for *Courage at Work* and the ASM *Dimitrie Cantemir* Medal. In 2011 he was awarded the honorary title "Emeritus of the Republic of Moldova"

Conclusions

This paper summarizes the most valuable achievements in the field of natural product chemistry attained by academician Pavel Vlad and his disciples. Of these, there must be mentioned the establishing of absolute configuration of (-)-sclareol, development of new methods of synthesis of ambroxide.

Additionally, it was established that the norlabdanic compounds have smell of amber, which contain a structural fragment that ensures the existence of the "amber triangle" which allowed explaining the influence of small structural changes on the amber odour, as well as the existence of odour in compounds that do not meet the conditions of Ohloff's triaxial rule. Methods of production and technologies for the production of a series of odorous compounds were developed and implemented in the perfumery and tobacco industries.

Some other worth-mentioning achievements include the development of ozonolytic methods for obtaining norlabdanic compounds, with a low degree of environmental pollution and acceptable under production conditions, and the development of general methods of photocatalytic dehydrogenation of Δ^8-drimen- and Δ^8-11-homodrimen-7-ones and regio-selective dehydration of tertiary methylcyclohexanic alcohols; synthesis of nitrogen-containing drimanic and homodrimanic compounds with amplified biological activity; investigations of molecular rearrangement of some terpenoids allowed obtaining compounds with unique structures, difficult to obtain in other ways.

Furthermore, the investigations were performed on the superacidic cyclisation reaction of terpenoids, and also on the regularities of the mentioned reaction in different classes of terpenic

compounds, such as alcohols, their acetates, acids, esters, phenylsulphones. This remarkable achievement of academician P. Vlad brings a considerable contribution to the development of the biogenetic rule of isoprene in the series of terpenoids, and opens perspectives in the search of new compounds with specific properties, valuable for science and practice.

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Short biography of the author

Professor Aculina Aricu is the Director of the Institute of Chemistry in Chisinau (Republic of Moldova). Graduated in 1981 from the Faculty of Chemistry of the Moldova State University and began working at the Institute of Chemistry of the Academy of Sciences of Moldova, under the guidance of academician Pavel Vlad (Laboratory of Chemistry of Natural and Biologically Active Compounds). Under the guidance of academician Pavel Vlad, prepared and defended her doctoral thesis in bioorganic chemistry (1990) and, defended her doctor habilitate thesis entitled "Structural and stereoselective synthesis of drimanic and norlabdanic compounds" (2012).

Professor Aculina Aricu is the author and co-author of over 150 scientific publications, including 3 monographs, 4 review papers, more than 50 articles in international journals, and 22 patents for inventions of which 4 are implemented in practice.

Fields of scientific interest: organic and bioorganic chemistry; chemistry of natural and physiologically active compounds; development of chemo-, regio- and stereoselective methods of the synthesis of optically active norlabdanic and drimanic compounds, including nitrogen and halogen-containing derivatives, as well as terpeno-heterocyclic hybrid compounds based on accessible natural labdane diterpenoid sclareol.

Professor Aculina ARICU
Institute of Chemistry, 3, Academiei str.
Chisinau MD 2028, Republic of Moldova
E-mail: aculina.aricu@ichem.md
aculina.aricu@gmail.com