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Terpenes in Superacids: Synthetic Aspect

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Abstract

Possibilities to use superacids for the synthesis of optically active natural compounds are analyzed in the review. The revealed regularities of cationoid rearrangements of terpenoids under the conditions of super-nucleophilic media and low temperatures are taken into account. Mono- and sesquiditerpenoids and their analogs are chosen as the subject of investigation. Results of works published since 1984 till 2004, including those supervised by Prof. V. A. Koptyug, are reviewed.

Key words: super-acids, terpenoids, cationoid rearrangements, selectivity

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INTRODUCTION

One of the goals of studies of terpenoid behaviour in superacids is to broaden the possibilities for obtaining new substances on the basis of available natural compounds and their analogues. The structural features of terpenoids, their polyfunctional character and conformational mobility, the use of special reaction conditions (ultra low temperatures, super-nucleophilic environment) provide a variety of molecular rearrangements. Unlike for acid-catalysed processes, the reactions of terpenes conducted in superacids provide: a) multistage transformations of primarily formed cations as a consequence of super-nucleophilic properties of the medium; b) the formation of dications; c) rapid transformation into carbocations due to the high acidity of initial substrates, which prevents cation polymerisation; d) high structural selectivity and stereochemical selectivity due to ultra low temperature.

While studying the behaviour of terpenoids in superacids, especially under the conditions of direct observation of carbocations, we revealed definite "control levers" for cationoid transformations [1, 2]: the nature of acid medium, the type of reaction generating the cation centre (solvolysis or electrophilic addition to the double bond), generation temperature, temperature of defrosting the acid solution. Relying on the revealed regularities, we may perform directed synthesis of optically active natural compounds in superacids; reaction yields may be comparable with those for conventional multistage synthesis, as well as the synthesis on solid catalysts [3]. In addition, in superacids one can carry out chemical transformations that could not be conducted under other conditions, and new compounds with original properties can be obtained.

MONOTERPENOIDS

Terpenoids of the pinane series – α- and β-pinenes and their oxygenated derivatives – are organic compounds that attract special attention of chemists. This is likely to be connected with the availability of these compounds as they are extracted from natural sources (in particular, from turpentine of conifers) and are more widespread in nature than monoterpenes of other series. Organic synthesis involving oxygen-containing derivatives of 2- and 3-carene, pinane terpenoids for the purpose of obtaining new compounds with potential biological activity is the area of permanent attention of researchers in organic and medical chemistry [4, 5].

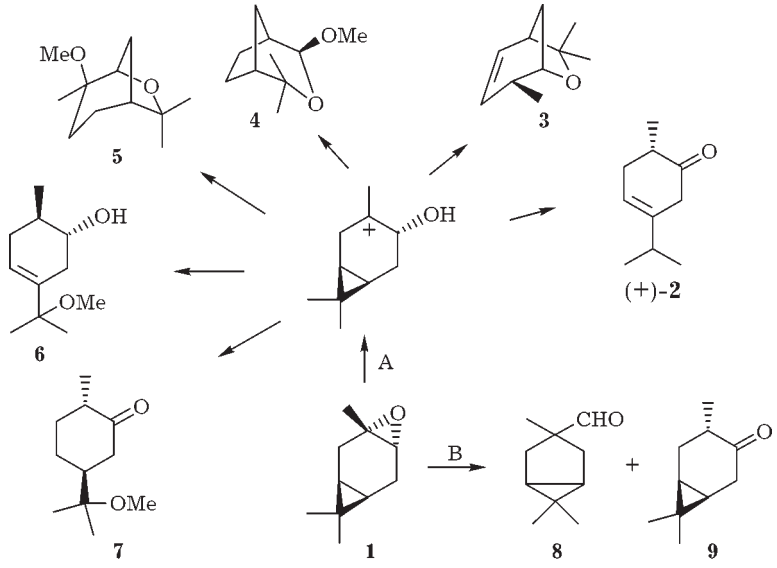
The use of superacid media allows one to obtain greater diversity of products than that for reaction in usual acid media [6, 7]. For instance, under the action of protonic acids on epoxide **1**, mainly the products with the conservation of the carane framework are obtained, the compounds with bicyclo[3.1.0]hexane framework are formed only to a small extent [8]. At he same time, compounds **2**–**7** (Scheme 1) are formed in the system HSO_3F–SO_2FCl at −110 °C [6].

Compounds **2**–**7** were not isolated previously after acid splitting of epoxide **1**. Their formation can be explained by primary opening of the epoxide cycle, followed by rearrangements with split of cyclopropane ring and stabilization of the resulting ions due to the interaction with internal or external nucleophiles, or proton detachment. It was shown in [6] that the use of solid superacid TiO_2/SO_4^2 as the acid catalyst of isomerization of epoxide **1** allows one to obtain a different mixture of products than that formed with liquid superacids; aldehyde **8** and ketone **9** dominate. So, in liquid superacid, from *trans*-epoxycarane **1** bicyclic ethers **3**–**5** with bicyclo[3.2.1]octane framework were obtained for the first time.

The authors of [7] studied the behaviour of α-pinene epoxide 10 in the system HSO_3F–SO_2FCl (−110 °C); ethers **11**–**13** (Scheme 2) were obtained as three major products.

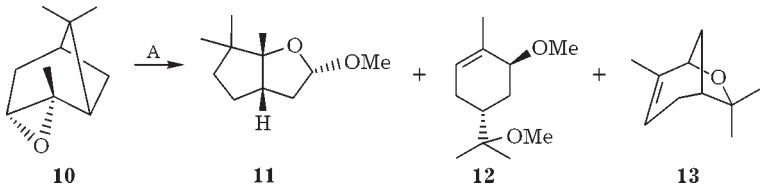
These compounds also were not isolated before from the acid splitting of epoxide **10**; compound **11** with the framework of oxabicyclo[3.3.0]octane was obtained for the first time.

Interesting results were obtained by us when studying the transformations of alkyl methanols with 2- and 3-carene framework in the system HSO_3F–SO_2FCl (−100 °C) [9]. It was demonstrated that 2-carene-4α- and 3-carene-2α-alkyl methanols, as well as oxy-*n*-menthadienes undergo heterocyclization under the indicated conditions, with the formation of products that depend on the structural features of initial compounds: bicyclic ethers with oxabicyclo[3.2.1]octane, oxabicyclo[2.2.2]octane and oxabicyclo[4.3.0]nonane skeleton. Thus, the mix-



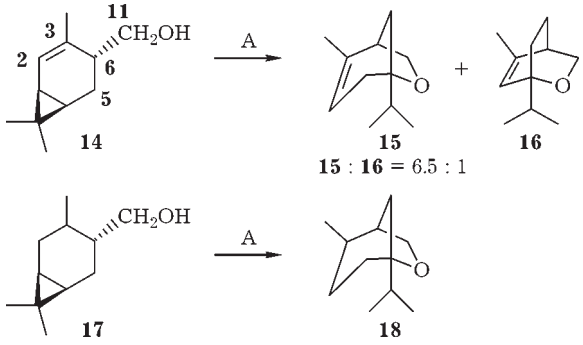
A: 1) HSO_3F–SO_2FCl, −100° C; 2) MeOH; B: TiO_2/SO_4^{2-}

Scheme 1.



Scheme 2.

ture obtained through the interaction of valterol **14** (*trans*-4-hydroxymethyl-2-carene) with the system HSO_3F – SO_2FCl (−100 °C) was composed of 4-methyl-1-isopropyl-7-oxabicyclo[3.2.1]oct-3-ene **15** and 5-methyl-1-isopropyl-2-oxabicyclo[2.2.2]oct-5-ene **16** (~6.5 : 1).

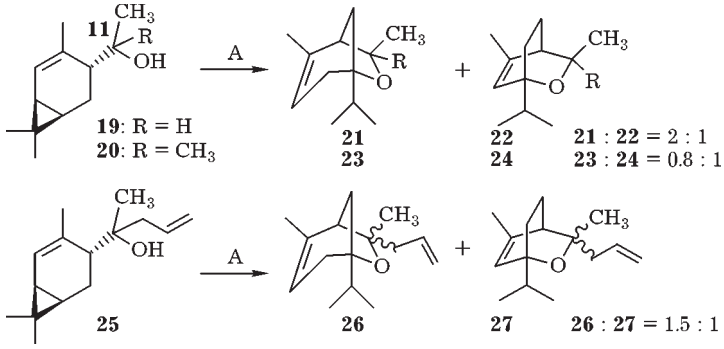


Compound **17**, analogue of valterol but containing no double bond, gives compound **18** as the major product under the experimental conditions.

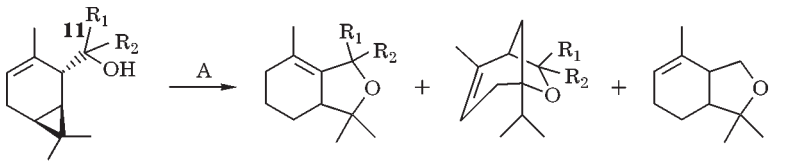
The ratio of products with oxabicyclo[3.2.1]- and oxabicyclo[2.2.2]octane skeletons is affected by the degree of substitution of carbinol carbon atom C^{11} and the nature of the radicals at this atom in the initial substrate (Scheme 3). Thus, the interaction of *trans*-4-(1-hydroxy-1-methylethyl)-2-carene **19** and *trans*-4-(1-hydroxy-1-methylethyl)-2-carene **20** with the system HSO_3F–SO_2FCl (−110 °C) results in the formation of the mixtures of compounds **21** and **22**, **23** and **24**, respectively: an increase in the degree of substitution at the carbinol carbon C^{11} leads to a decrease in the fraction of products with oxabicyclo[3.2.1]- and oxabicyclo[2.2.2]-octane frameworks. The results of these transformations are comparable with those for compound **25** with the formation of products **26** and **27** (see Scheme 3).

The position of the double bond in initial alcohols also affects the composition and structure of the resulting bicyclic ethers (Scheme 4). In alcohols that are the derivatives of 3-carene, opening of cyclopropane ring under reaction conditions occurs with the formation of carbocations with *p*- and *m*-menthane framework; as a rule, their cyclization leads to ethers with bicyclo[4.3.0]nonane framework (**31–34**) and bridge skeletons (**15**, **21** and **23**).

Alcohols with the carane skeleton containing no double bonds also form polycyclic ethers in superacid media. For example, diol **35** forms bicyclic ether **36** as the only product. Under the same conditions, alcohol **37** forms products **38** and **39**, with the yield of 50 and 38 %, respectively (Scheme 5). Neutralization of the acid solution of a mixture of epimeric 8-hydroxymethyl-1,4,4-trimethyltricyclo[5.1.0.$0^{3,5}$]octanes **40** leads to the formation of polycyclic ether **41**



Scheme 3.



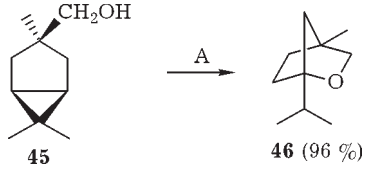
28: $R_1 = R_2 = H$ **31** (77 %) **15** **32**
29: $R_1 = CH_3$; $R_2 = H$ **33** **21** **33** : **21** = 3 : 7
30: $R_1 = R_2 = CH_3$ **34** **23** **34** : **23** = 5 : 3

Scheme 4.

as the major product. For transformations of compound **43** as example, it was shown that in the case if the carane derivative already possesses an ether bond, then only opening of the three-membered cycle occurs in superacids (see Scheme 5, compounds **43** and **44**).

So, carane derivatives undergo cyclization in superacid (see Schemes 3–5), as a rule, with the formation of bicyclic ethers. In this situation, the structure of reaction products depends on the mutual position of cyclopropane ring and carbinol group. The listed transformations can be considered as the directed synthesis of bicyclic ethers because the reactions of these substrates in weakly acidic media proceed non-selectively as a rule, with the formation of a complicated mixture of products [10, 11].

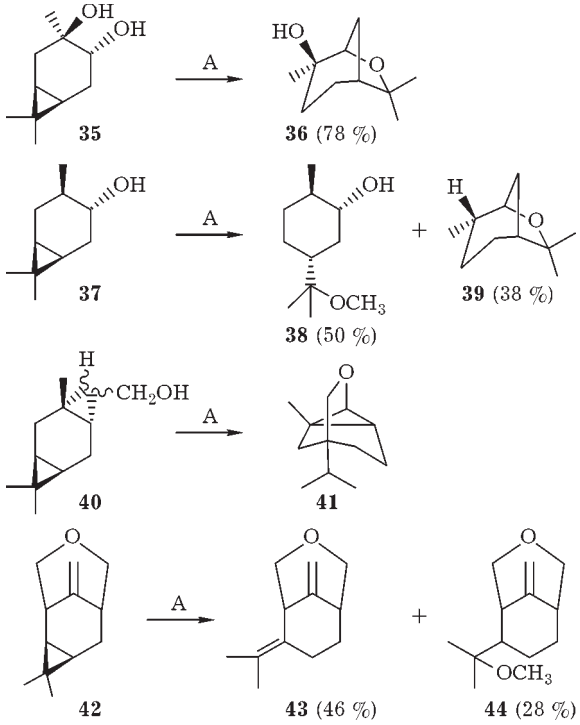
Monoterpene alcohols incorporating the cyclopropane ring but having the skeleton different from carane also form cyclic ethers in superacids.



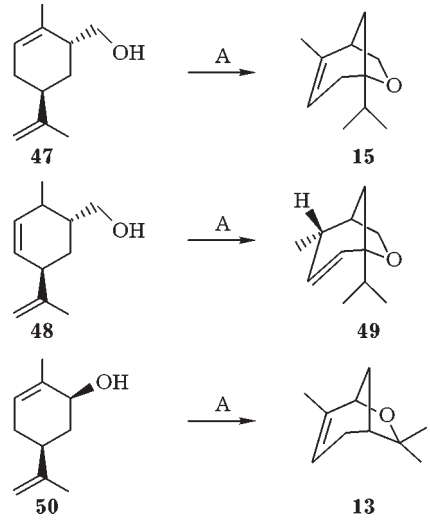
45 **46** (96 %)

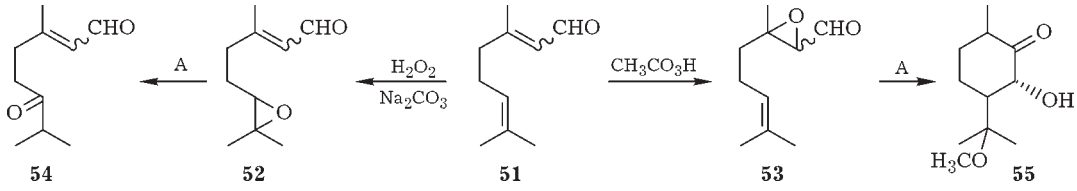
Oxy-derivatives with *p*-menthadiene skeleton of different structures **47**, **48** and **50** in superacids form bicyclic ethers **15**, **49** and **13**, respectively; each reaction is characterised by a single transformation product.

The described transformations open a short way to the synthesis of difficultly available substituted bicyclic oxygen-containing heterocycles from available renewable raw material – primary, secondary and tertiary terpene alcohols.



Scheme 5.





Scheme 6.

In [12], we studied the transformations of isomeric monoepoxides of citral **51** (6,7- **52** and 2,3- **53**) within a broad range of acid media, however, it is necessary to stress that it is the HSO_3F–SO_2FCl condition under which acyclic ketoaldehyde **54** is synthesized from compound **52** and cyclic ketoalcohol **55** from compound **53** (Scheme 6). So, prescribing the position of epoxide cycle in the initial citral molecule **51**, it is possible to obtain directly either acyclic compounds **54** or the products with cyclic structure **55**.

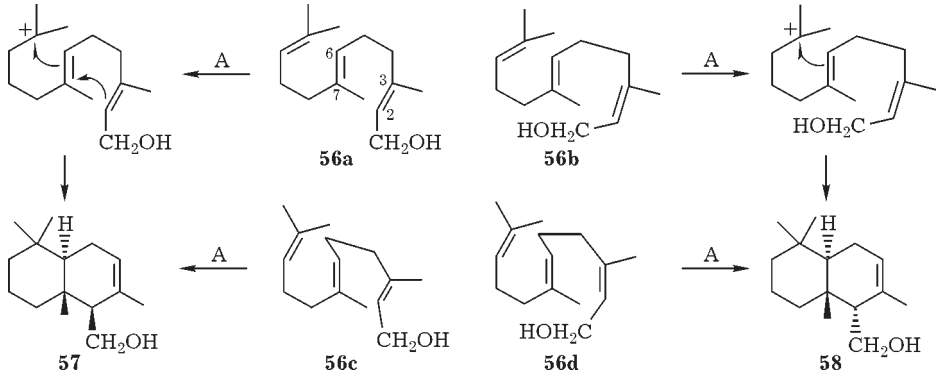
SESQUITERPENOIDS

According to biogenetic schemes, pyrophosphates of isomeric farnesols form allyl carbocations after the detachment of the pyrophosphate group. Further cyclization of these carbocations can explain the origin of almost all the sesquiterpenoids [13]. However, the major part of these transformations has not been implemented *in vitro*. We showed fort he first time that the cyclization of 2,3-*trans*- **56a,c** and 2,3-*cis*- **56b,d** farnesols in superacids proceeds structurally selectively and stereospecifically with the formation of drimenol **57** and epidrimenol **58**, respectively [14] (Scheme 7).

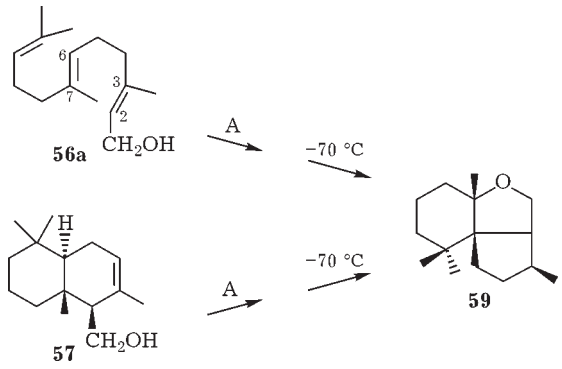
Heating of the acid solution of compounds **56a** and **57** in the solution of HSO_3F–SO_2FCl (−110 °C) to −70 °C and subsequent slaking lead to the new compound **59** as the sole product [14]. So, using liquid superacid as the acid medium we succeeded to realize *in vitro* the biogenetically similar transformation of farnesol into drimenol **57**, and also to obtain the new compound **59** varying the temperature of unfreezing the acid solution.

For transformations of nerolidol **60** (tertiary acyclic alcohol, isomer of compound **56**) in HSO_3F–SO_2FCl (−100 °C) as example, it was demonstrated [14] that even in the presence of readily detachable group – allyl hydroxyl – and predictable site of the formation of cation centre, variation of the ratio of superacid to the initial substrate can cause substantial changes in reaction route. For example, in the process of cyclization of alcohol **60** in the case of the high excess of superacid (20 : 1), mainly carbocyclization is observed, for lower ratio (5 : 1) heterocyclization occurs (Scheme 8).

Tricyclic compounds **61**–**63**, the products of deep rearrangement of the cation primarily formed during carbocyclization, are new compounds; compound **64** is natural biologically active substance (−)-8-epicaparrapy oxide for which only multistage syntheses were described [15] and which is also obtained through biosynthesis from compounds **56** and **60** [16]. It was

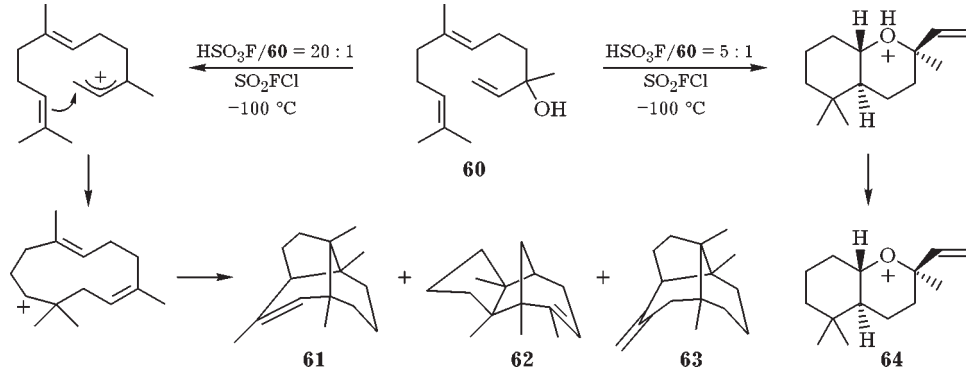


Scheme 7.

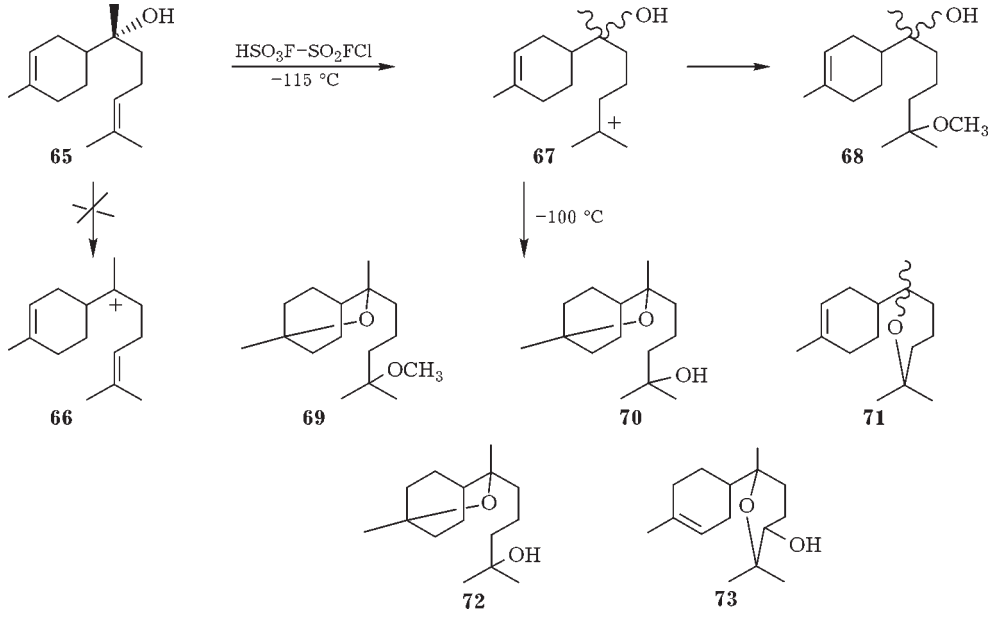


shown previously [17] that cyclization of compounds **56** and **60** in acid media results in the formation of a complicated mixture of products; the major component is represented by α-bisabolol **65** (Scheme 9). Under superacid conditions, varying the temperature of unfreezing the acid solution or the ratio of substrate to HSO_3F (see Scheme 8), one can carry out directed and single-stage synthesis of either natural compounds **57**, **58** and **64** or new compounds **59**, **61–63**.

In [18], we studied rearrangements of tertiary alcohol **65** – α-bisabolol, potential precursor of bisabolyl cation **66**; its cyclization in biogenetic schemes results in the formation of



Scheme 8.



Scheme 9.

various bicyclic sesquiterpenes. In the investigations, we failed to generate cation 66: in the system $HSO_3F–SO_2FCl$ the reaction started with protonation of the isopropylidene group with the formation of the observed ion **67**; its slaking gave the sole product **68**. Further rearrangements of ion **67** during slaking of the acid solution resulted in the formation of cyclic oxides **69–71** which are similar in structure to natural oxides **72** and **73** that were extracted from *Matricaria chamomilla* [19].

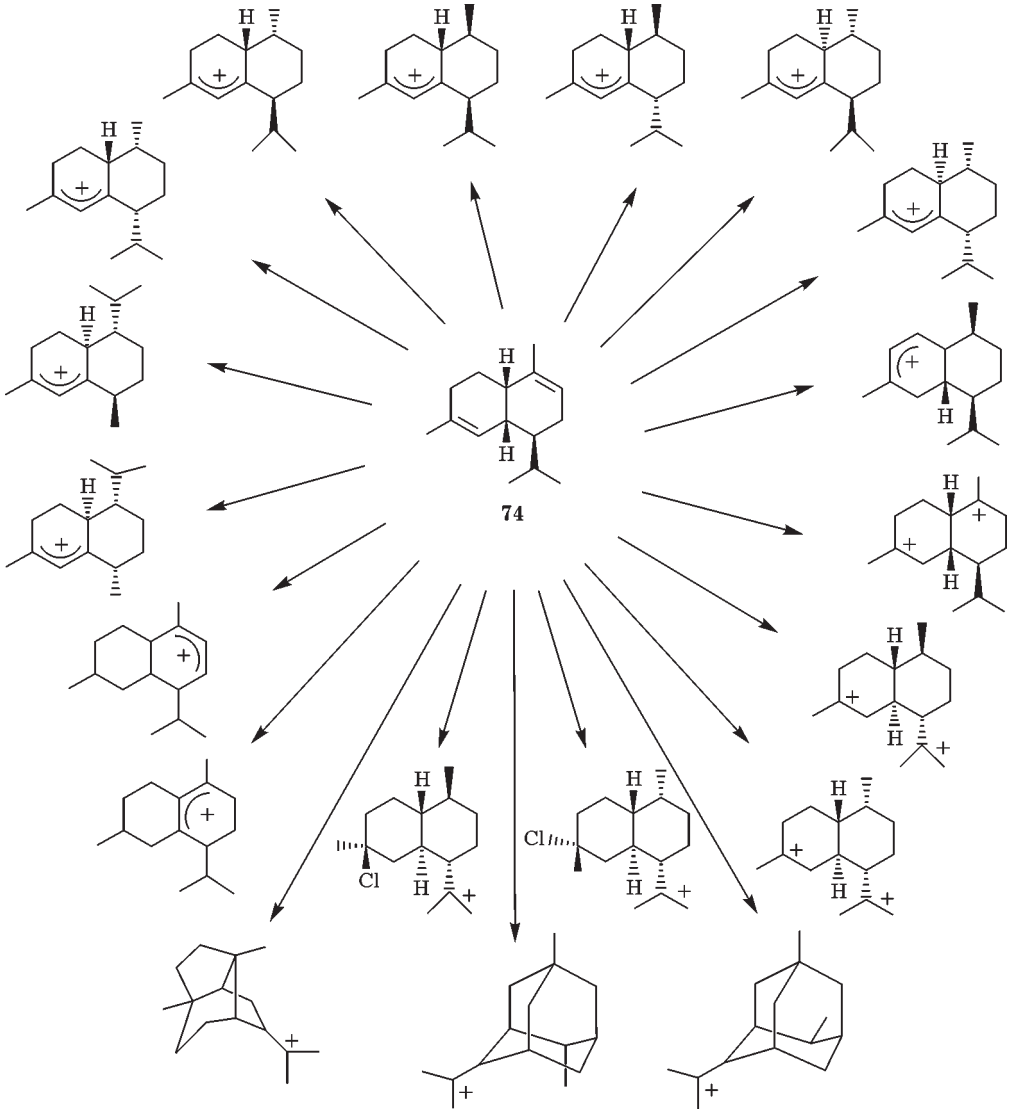
A good illustration of the possibility to obtain different compounds from terpenes in superacids is provided by the data reported in [20]. The authors showed that starting from only one optically active diene **74** and varying the following parameters:

1) type of the reaction of ion generation (protonation of diene or solvolysis of the corresponding dihydrochloride);

2) acidity of the system;

3) temperature of generation and unfreezing of the solutions of ion salts, it is possible to obtain 19 different stable carbocations – optical isomers (Scheme 10). The interaction of these ions with nucleophiles leads to the formation of alkenes and dienes – either natural terpenes or previously unknown compounds.

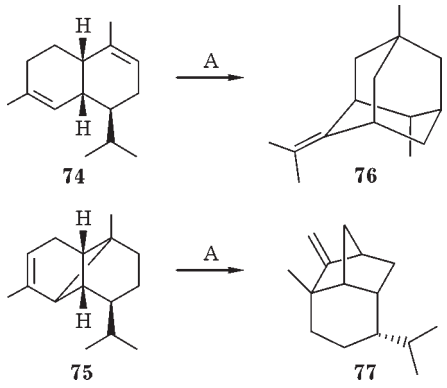
Without going into the details of the mechanisms of rearrangements in carbocations the



Scheme 10.

structure of het majority of which was studied through direct observation, we shall focus on the synthetic advantages of the studied transformations. In the biogenetic schemes for sesquiterpenes, one of the key positions belongs to diene **74** – α-murolene which is considered as a precursor of tricyclic compounds with cubebane, copabornane and copaane skeletons.

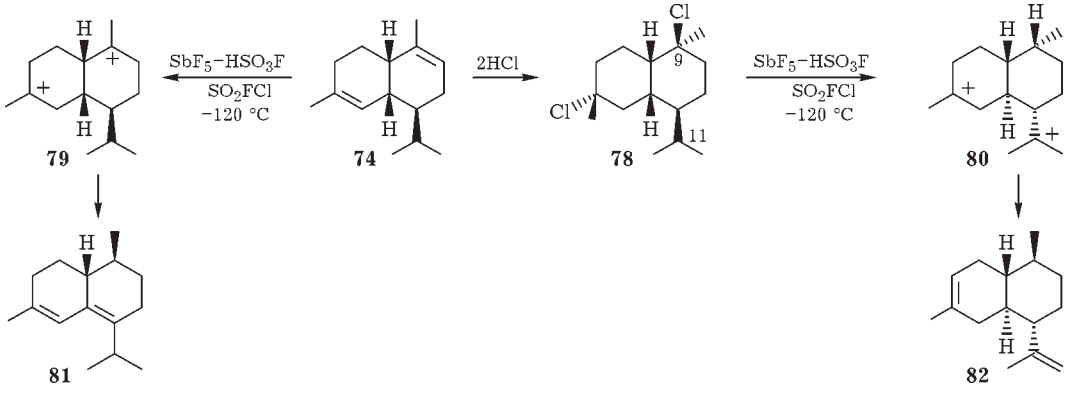
However, under the conditions of acid catalysis, the attempts to obtain tricyclic products from diene **74** and olefin 75 – α-copaene were unsuccessful. At the same time, in the system HSO_3F–SO_2FCl new previously unknown compounds were obtained from diene **74** and olefin **75**: tricyclic compounds **76** and **77**, respectively [21].



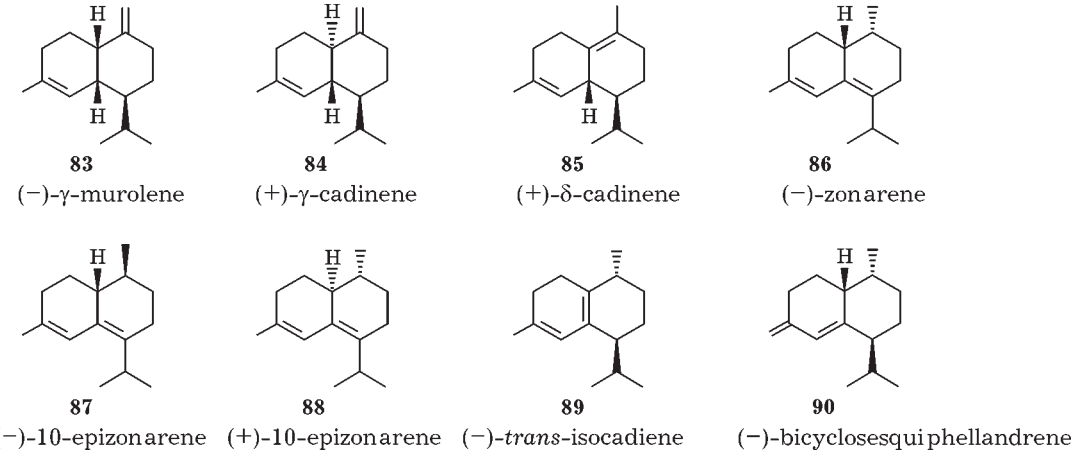
The type of cation centre generation reaction affects the structure of carbodications obtained from dienes and corresponding dihydrochlorides. In [20], starting from diene α-murolene **74** and murolene dihydrochloride **78** with identical skeletons and only one potentially possible position of the formed cation centres, under identical conditions isomeric stable carbodications **79** and **80** were generated (Scheme 11). It was established that slaking of the acid solution of dichloride **78** leads to the formation of diene **82**, while the transfer of the positive charge from $C_{(9)}$ atom to $C_{(11)}$ atom is performed through serial 1,2-hydride shifts, through the intermediate formation of monoschloro cation.

The transition from non-conjugated dienes **74**, **83–85** [22] (Scheme 12) that were extracted from the oleo-resin of *Pinus sylvestris* L., to conjugated dienes **86–90** was carried out through the interaction of the solutions of salts of stable cations with nucleophiles. Results of the investigation of rearrangements of isomeric dienes **74**, **83–85** in superacids not only allow one to reveal the features of their behaviour and determine the scheme of diene **74** transformations more precisely (see Scheme 10) but also can be used for preparative purposes because they allow using difficultly separable mixtures of isomeric sesquiterpenes for obtaining target products. For example, diene **87** may be obtained through isomerization of difficultly separable mixture of dienes **74** and **83** in HSO_3F at −70 °C.

It should be noted that deep molecular rearrangements that cannot be realized in normal media even under the most rigid conditions can proceed in superacid media. The solutions of the salts of stable ions can be heated to 100 °C and above, so the conditions for rearrangements with activation barrier about 30 kcal/mol and higher are provided. At the same



Scheme 11.

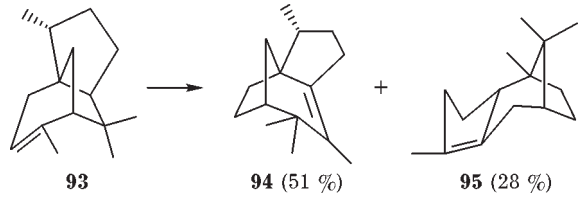


Scheme12.

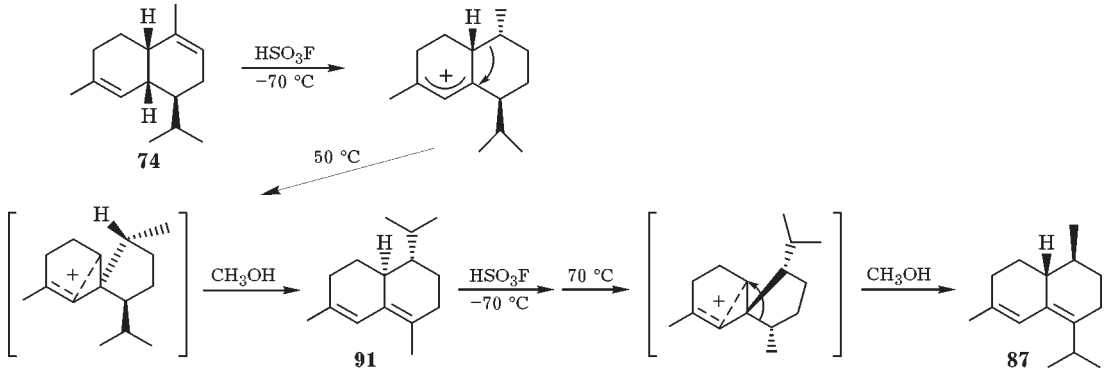
time, under the conditions of acid catalysts one usually does not succeed to perform molecular rearrangements of cationoid type that are performed in superacid media with the activation barrier about 20 kcal/mol. For example, under heating to 50 °C the solution of the salt of ion formed from compound **74** undergoes rearrangement with intermediate formation of spirocation (Scheme 13); compound **91** with daucalane skeleton was isolated as the sole product of transformation. Further heating of the solution of the salt of ion formed from compound **91** leads to one more overturn of the framework and to the formation of (−)-10-episonarene **87**.

For the transformations of sesquiterpene hydrocarbon β-alaskene **92** [24] with spiro[4,5]decane skeleton as example, the possibility of the intermediate formation of spirocyclic carbocation was demonstrated in previously discovered [23] rearrangement of allyl cations with cadaline skeleton (Scheme 14); the isolated compound **93** is an isomer of compound **91** an has the daucalane skeleton, too.

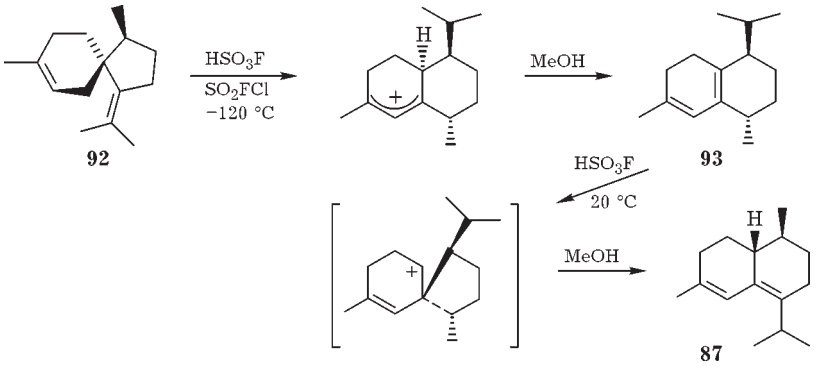
Along with bicyclic sesquiterpenes, we also studied the transformations of tricyclic terpenoids in superacids; products with the skeletons of natural terpenes and new compounds were isolated.



In [25, 26], rearrangements of tricyclic alkene α-cedrene **93** were studied; the transformation of the compound with cedrane skeleton **93** into isomeric substances with natural zyzaane **94** and patchulane **95** skeletons was carried out. The use of approaches described in [27, 28] for estimation of ΔH_f^0 and $\Delta G^{\neq}$ al-



Scheme13.



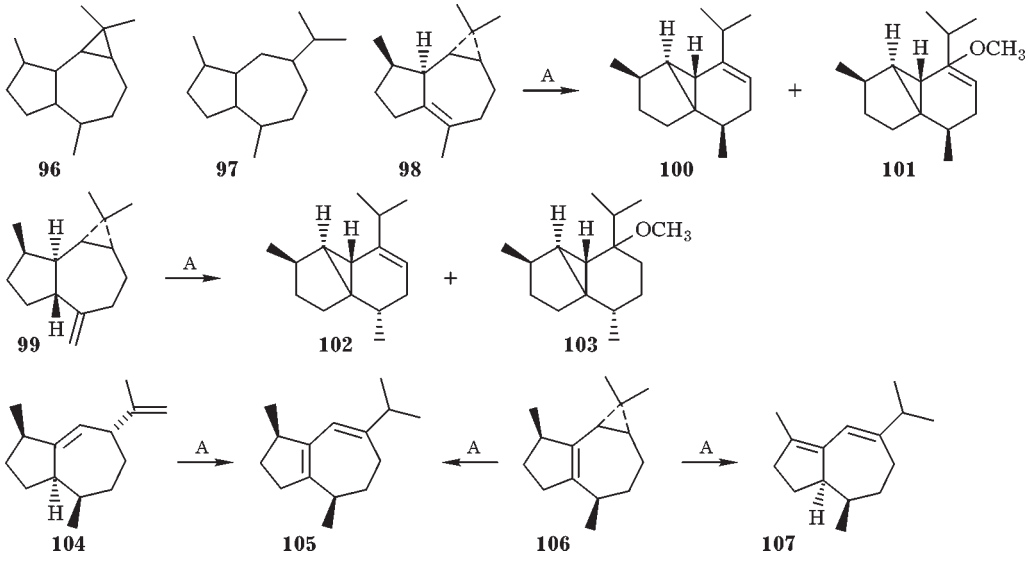
Scheme 14.

lowed proposing the most probable scheme of rearrangement for α-cedrene **93** in superacids in agreement with experiment.

Sesquiterpenoids possessing the aromadendrane type of framework **96** (Scheme 15) contain *hem*-dimethylcyclopropane ring attached to the hydroazulene skeleton.

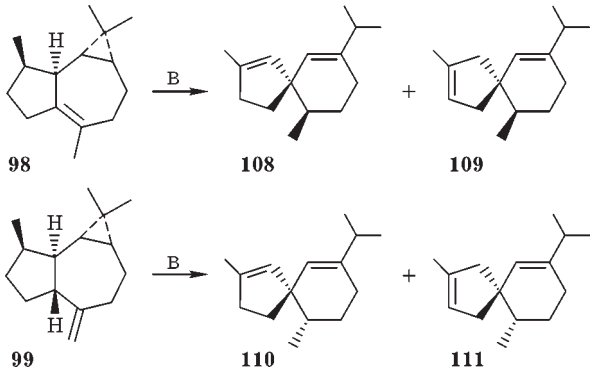
The majority of the compounds of this type are characterized by the presence of double bond, hydroxyl group, epoxide cycle, which determines their ability to form carbocation centre. As a consequence of this fact, acid-catalyzed transformations of aromadendrane terpenoids can proceed with intermediate formation of cyclopropylcarbynyl cations [29]. Another direction of the transformations of these compounds can include acid splitting of the C^2–C^3 bond of three-membered cycle with the final formation of sesquiterpenoids with guaiane type of framework **97** (see Scheme 15).

In [30, 31], the behaviour of aromadendrane terpenes (+)-ledene **98** and (+)-aromadendrene **99** in superacids was studied; it was demonstrated that the major products of their transformations are represented by previously nondescribed compounds **100**–**103** with natural cubebane framework. The formation of compounds **100**–**103** with cubebane framework from olefins **98** and **99** with natural aromadendrane framework at very low temperatures can serve as a chemical confirmation of the possibility of biogenetic connection between these types of compounds. It was also shown in [30] that under the same conditions γ-gurhunene **104**



Scheme 15.

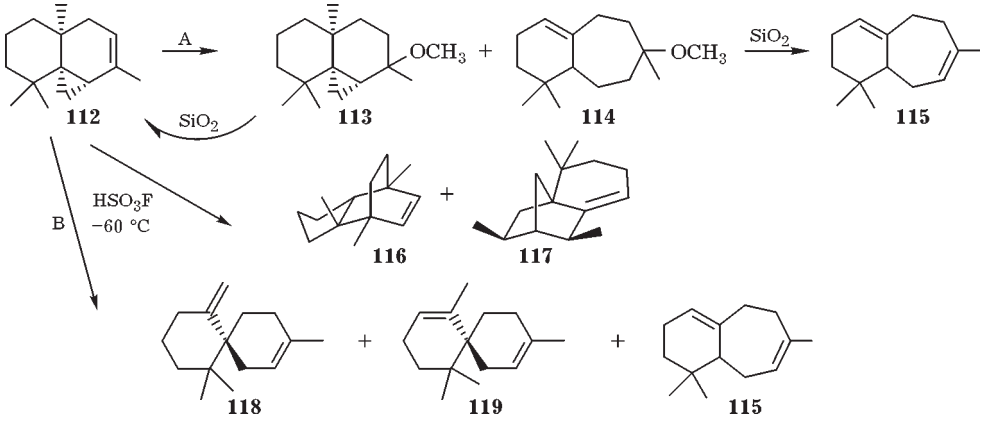
is transformed mainly into diene **105**; isomeric isoledene **106** is transformed into diene **105** (50 %, GLC) and diene **106**. So, it was demonstrated that the result of transformations of compounds **98** and **99** with aromadendrane framework in superacids at low temperatures differs from that for isomeric sesquiterpenes **104** and **105**. In the first case, the substances with natural cubebane framework are formed (**100**–**103**), while in the second case – various dienes with guaiane framework (**105**, **107**). These rearrangements from natural substrates **98**, **99**, **104** and **106** were carried out for the first time. During transformation in solid superacid TiO_2/SO_4^{2-}, sesquiterpenes **98** and **99** form spirodienes with spiroaxane frameworks **108**, **109** and **110**, **111**, respectively.



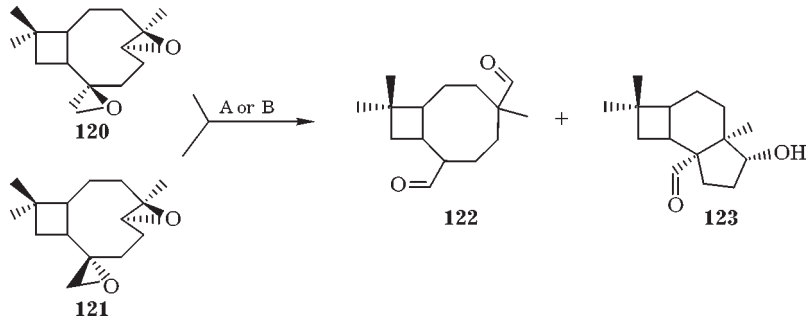
Compounds with aromadendrane, cubebane and spiroaxane frameworks occur in some sponge species [32, 33]; in combination with the discovered transformations of olefins **98** and **99** into compounds **100**–**103** and **108**–**111**, it may be expected that aromadendrane, cubebane and spiroaxane terpenoids are connected with each other biogenetically.

Along with the above considerations, the behaviour of (–)-thujopsene **112** containing the cyclopropane fragment was studied in liquid superacids (HSO_3F–SO_2FCl) and on solid ones (TiO_2/SO_4^{2-}). New tricyclic hydrocarbons were isolated during investigation (Scheme 16).

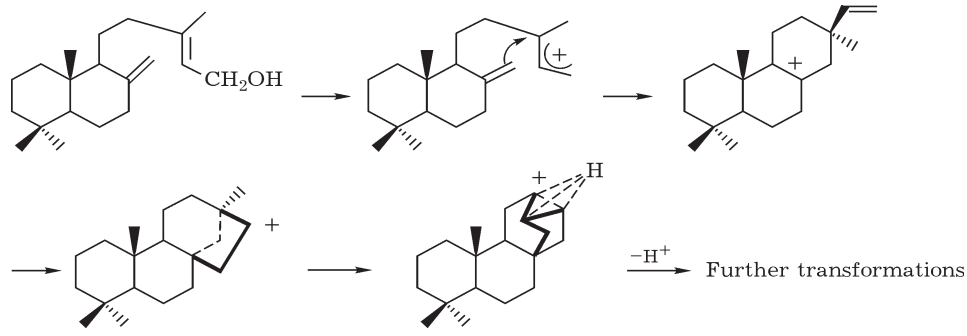
One can see that the dissolution of compound **112** in the mixture of HSO_3F–SO_2FCl at low temperature does not involve deep rearrangements of the thujopsene framework; compounds **113** and **114** that are formed after slaking of the acid solution are transformed into initial compound **112** and diene **115**, respectively, during passing through a column with silica gel. The dissolution of compound **112** in the system HSO_3F–SO_2FCl at –60 °C followed by slaking with a mixture of CH_3OH–$(C_2H_5)_2O$ leads to the formation of reaction mixture containing mainly tricyclic compounds (1R,2S,6R,7S)1,2,7,9-tetramethyltricyclo[5.2.2.-$0^{2,6}$]undec-8-ene **116** (31 %) and (1S,7S,8S, 9S)2,2,7,9-tetramethyltricyclo[6.2.1.$0^{1,6}$]undec-5-ene **117** (19 %). The transformations of alkene **112** on solid superacid TiO_2/SO_4^{2-} leads to the formation of a mixture of spirocompounds β-chamigrene **118** (37 %) and α-chamigrene **119** (30 %); in smaller amounts pseudowiddrene **115** is formed (25 %). So, changing experimental conditions (HSO_3F or TiO_2/SO_4^{2-}), from natural sesquiterpene thujopsene **112** one can in the directed manner obtain either compounds with tricyclic framework **116** and **117** or natural spirocyclic compounds **118** and **119**.



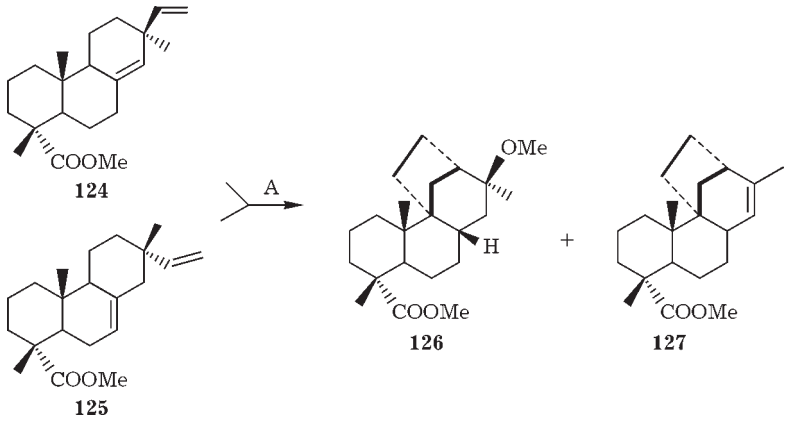
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

The initial substrates for the generation of carbocations may be not only epoxides but also diepoxides of terpenoids. In [35], the transformations of distereomeric diepoxides **120** and **121** of widespread natural sesquiterpene caryophyllene were studied in various acid media, under the conditions of both homogeneous and heterogeneous catalysts (Scheme 17).

Both in the presence of HSO_3F and on solid superacid TiO_2/SO_4^{2-}, a mixture of dialdehyde **122** having the bicyclo[6.2.0]decane framework and tricyclic aldehydoalcohol **123** at a ratio of 2 : 1 is formed.

DITERPENOIDS

In diterpenoid chemistry, Wenkert put forward the hypothesis that tetracyclic diterpenoids with different types of framework are formed from bicyclic compounds according to Scheme 18 [36].

However, numerous attempts to reproduce these *in vitro* syntheses of tetracyclic diterpenoids from tricyclic ones were unsuccessful.

In [37] (Scheme 19) using superacid media, cyclization of the esters of isopimaric (**124**) and pimaric (**125**) acids into tetracyclic compounds **126** and **127** with natural stimarane framework was carried out for the first time.

Synthetic approaches involving superacids in terpenoid chemistry were further developed in the works of other authors who studied the synthesis of complicated molecules of natural biologically active compounds of different classes [38–42].

CONCLUSION

The major factors allowing us to govern the multistage, multi-route cationoid molecular rearrangements were analysed: 1) the nature of the acid environment; 2) the type of the reaction of cation centre generation in primarily formed cation; 3) temperature of the generation of stable carbocations; 4) temperature of defreezing the acid solution before slaking. It was shown that taking the revealed regularities into account it is possible to perform directed synthesis of optically active natural compounds and the compounds with the new type of framework, the products of deep rearrangement of initial substrates. In some cases the use of superacids in the synthesis of terpenoids is reasonable because, as a rule, the reaction proceeds rapidly, in one stage. As a result of the transformation, one product is formed or a non-complicated mixture of compounds allowing separation by means of column chromatography on available sorbents (Al_2O_3 or SiO_2) and isolated of pure poorly available natural compounds.

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