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SYNTHESIS OF TERPENIC COMPOUNDS WITH ADVANCED FUNCTIONALIZATION VIA BIOMIMETIC METHODS

SPECIALITY 143.01 ORGANIC CHEMISTRY

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CONCEPTUAL LANDMARKS OF THE INVESTIGATION

Timeliness of the subject

Organic chemistry represents one of the basic areas of modern science. When we make an outline of the reasons which define the special place of this area of human knowledge, there are two general aspects that come into mind: its cognitive and creative power. Both aspects are quite clear. First of all, we strive in our endeavours to explain all the processes which surround us. Chemists see life through the prism of chemical reactions: reactions that occur in our own bodies, reactions that occur in the invisible micro-world, reactions that permanently affect our environment and finally, reactions that take place in the outer space. This cognitive function inevitably leads to our desire to create new matter, to produce materials and substances that we might consider useful for our lives. And the pivotal role of organic synthesis in this process is generally acknowledged. It is due to the practically infinite range of compounds which can be built on the basis of organic carbon chains. This unique circumstance turns organic synthesis into a creative adventure like a veritable Odyssey. Therefore, in order to "survive" and reach desired "lands" the organic chemist relies on a very simple but smart strategy: to reproduce what nature creates by all that sorrounds us, basing on the hypothesis that everything in the living world has a purpose and any chemical compound, wherever it is found, can be exploited to benefit our lives and existence. In fact, this strategic approach reflects one of the basic psychological features of humans as social beings: we build our lives by mimicking our environment. For organic chemists this means identifying natural targets and their replication.

Even more than that, promotion of this approach to a superior level includes not only the synthesis of certain compounds as ultimate goal. Much more profound is the identification of the biochemical paths that lead to the synthetic targets in the living cell and their following reproduction by chemical synthesis "*in vitro*". This apparent "ideal" established deep roots in the modern synthetic organic practice. It is called a ***biomimetic synthetic strategy***.

A careful examination of the chemicals that have firmly entered our lives will make us conclude that most of them are mimics of natural matter: from low molecular weight bio-regulators (pheromones, drugs, agrochemicals) to polymers and supramolecular aggregates (textiles, rubber and plastics). A comprehensive study of the examples illustrating this reality would certainly not fit the range of a bunch of books. The purpose of the current work is to provide the example of biomimetic approach in developing synthetic strategies relating to some important classes of terpenic compounds with complex structure and advanced functionalization [1],[2],[3],[4].

Overview of the state in the research field and identification of research problems

Terpenes represent an enormous family of natural compounds with an impressive diversity of both carbon backbones and heteroatom functionalization pattern. It is well known that this diversity is due to the last steps of terpene biosynthesis. This opinion has been confirmed by numerous biosynthetic studies which demonstrated that common precursors of all terpenic families are only several open chain oligomers of dimethylallylpyrophosphate (DMA-OPP): geranylpyrophosphate (Ger-OPP), farnesylpyrophosphate (Far-OPP), geranylgeranylpyrophosphate (Ger-Ger-OPP) and some other superior olygomers. Biosynthetic path towards these basic elementary representatives include two essential steps: the first is the synthesis of DMA-OPP by mevalonic (MP) or mevalonate independent (MIP) pathways, which along with its precursor - isopentenylpyrophosphate (IP-OPP) represent primary terpenic units which contain 5 carbon atoms (C_5).

The second biosynthetic step includes coupling of DMA-OPP and IP-OPP C_5 fragments which leads to open chain polyisoprenoids having the composition C_{10} (monoterpenes), C_{15} (sesquiterpenes), C_{20} (diterpenes), C_{25} (sesterterpenes), C_{30} (triterpenes) as well as more superior oligomers. The alcohols derived from the hydrolysis of the pyrophosphate functional group are the known geraniol, farnesol, geranylgeraniol and the series of superior oligomers called generically polyprenols.

Both these steps are similar (practically identical) in all living organisms, therefore they bring no structural diversity. It appears only after the next two biosynthesis steps, which are profoundly specific and play a crucial role in the explosive expansion of the possible terpenic structures.

These steps are acid-base catalized cyclization and isomerization reactions and degradation-functionalization reactions which take place predominantly on oxidative transformation. Enzymes that catalyze these transformations "*in vitro*" are cyclases and oxidases. From the mechanistic point of view, the terpene cyclases represent an interesting subject, since their action is accompanied by a huge variety of other transformations, which besides cyclizations may include hydride shifts, Wagner-Meerwein and other skeleton rearrangements.

To date, there are two basic mechanisms of terpene cyclisations. The first mechanism is given by the ability of the double bond to act as a nucleophile and to interact in a S_N2 fashion with the –OPP group, leading to its elimination and formation of a new C-C bond. This type of cyclizations is catalyzed "*in vivo*" by so-called class I cyclases.

The second mechanism includes a cascade of reactions initiated by a selective protonation of the double bond, followed by an electrophilic attack of the formed carbonium ions to the other double

bonds of the aliphatic chain. This type of cyclizations are catalyzed "*in vivo*" by the so-called class II cyclases.

Both mechanisms involve formation of intermediate carbonium ions, which can stabilize either by proton elimination, skeletal rearrangements or addition of other nucleophiles. Here is the point where the spectacular structural diversity of terpenic structure comes into play.

And finally, the last step that defines the structural diversity of terpenic compounds is based on selective enzymatic functionalizations, processes that are usually of oxidative nature leading to the introduction in the molecules of diverse functional groups, first of all oxygenated ones, but not limited to that. Enzymes responsible for these transformations are basically oxidases, and as a result of their action the carbon skeleton is "decorated" by a plethora of heteroatomic functional groups.

All the enumerated biosynthetic processes have inspired organic chemists to devise synthetic methods which selectively transform the substrates exactly in the same way as enzymes do, that is to mimic the biosynthesis. The most difficult component of this approach relates, first of all, to the biosynthetic mechanisms and their investigation represents a major problem in molecular biology and bioorganic chemistry, connected, first of all, to the identification and isolation of individual enzymes responsible for each step of individual terpenic compound biosynthesis.

The scope and objectives of the thesis

Due to the fact that the great majority of high value terpenoids which are interesting for diverse practical applications have a complex carbon skeleton and advanced degree of functionalization with heteroatoms, the main aim of the current work was the elaboration of synthetic schemes to acces diverse classes of terpenoids by a random combination of oligomerization, cyclization, rearrangement and targeted functionalization. In order to attain this goal, an array of specific objectives has been set, which defined the structure and contributed to the realization of the current work. These objectives are as follows:

- Application of oligomerization processes for the synthesis of linear α,ω-bifunctionalized terpenic compounds with the controlled configuration of the double bonds, as well as with specific functionalization in the chain;
- Investigation of direct selective functionalization of open chain terpenoids to α,ω-bifunctionalized products;
- Investigation of biomimetic cyclizations of α,ω-bifunctionalized linear terpenoids;

- Investigation of biomimetic cyclizations of terpenic compounds with functional groups intercalated in the chain interior;
- Application of degradation-rearrangement processes for the synthesis of some families of cyclic terpenoids.
- Application of oxidative processes, including radical spatial ones for remote post-cyclization functionalization of C-H unactivated bonds;
- Application of unconventional media such as ionic liquids or aqueous solutions for performing biomimetic transformations;
- Synthesis of some natural terpenoids or their advanced precursors on the basis of elaborated biomimetic transformations.

Methods of scientific research

The research performed within the current work has been based on the methods of modern synthetic organic chemistry, which include performance of chemical transformations "*in vitro*" on laboratory scale, isolation of individual reaction products and their structural identification basing on the modern methods of analytical chemistry. These are thin layer chromatography, column chromatography, high performance liquid chromatography, gas chromatography, nuclear magnetic resonance spectrometry, infrared spectroscopy, mass spectrometry and elemental analysis. For optically active compounds of natural origin, confirmation of the absolute stereochemistry was realized by circular dichroism studies.

Scientific novelty and originality

Due to the complexity of the cellular biosynthetic mechanism, the current thesis has forwarded the hypothesis that successive biosynthetic steps like olygomerization, cyclization and functionalization of terpenes can intercalate in the living systems in a random order, leading to terpenes of complex structure. In order to tackle this hypothesis, the current work has aimed a flexible alternation of terpene functionalization with cyclization/olygomerization reactions, once it is not clear what is the real order of biochemical events in the cells. This strategy that mimics the biosynthetic steps in a random order possess a relevant potential for the synthesis of new classes of terpenic compounds with complex structure and broad spectrum of properties.

Application of this approach to the superacidic cyclization of terpenic substrates functionalized either at the extremities or in the middle of open chain allowed to control the selectivity of cyclization process. In this way, a functional group attached to the ω-extremity of the chain allowed to selectively initiate the cyclization process from an internal double bond, inhibiting in such a way the terminal one. On the other hand, the placement of a functional group in the chain interior allowed a selective suspension of the cyclization cascade. In both cases the reaction products were partially cyclized terpenoids with prenyl moieties pendant to the (poly-) cyclic skeleton.

In the same time, application of a degradation approach in synthetic schemes allowed access to some families of terpenic compounds with rearranged skeletons, including natural products isolated from terrestrial and marine organisms.

And last but not least, the feasibility of using radical processes for post-cyclization functionalization of tetracyclic sesterterpenoids was demonstrated: it was shown for the first time that functionalization of scalaranic compounds can be made selectively in cycle B by substitution of nonactivated hydrogens for chlorine, followed by successive elimination of hydrochloric acid and other transformations of the formed double bond.

Application of oxidative degradation processes based on ozonolysis led to elaboration of efficient and environmental friendly methods for the synthesis of degraded labdanic compounds with industrial relevance.

Conceptually novel scientific results for basic and applied science achieved

The current thesis has demonstrated the viability of the successive combination of different biomimetic processes for the synthesis of terpenic compounds with diverse structures. The relevant complexity of biogenetic paths, which lead to the enormous structural diversity of terpenoids, has prompted us to launch the hypothesis of the flexible combination of biosynthetic steps within biomimetic synthesis strategies. This approach has been defined as *Random Biomimetic Synthesis*. As a result of verification and valorization of thesis hypothesis, the synthesis of representatives from 15 different classes of terpenic compounds has been realized.

Theoretical significance

The major theoretical relevance of the current work is based on the hypothesis of random biomimetic synthesis, which can be successfully applied in planning of synthetic schemes towards natural products with complex structure. Additionally, application of a new biomimetic mechanism

for cyclization of linear terpenic compounds by selective protonation of an internal double bond and in- depth study of compounds formed in nature via such a mechanistic pathway has led to the identification of a supra-family of cyclic terpenic compounds with pendant terminal prenyl groups [5],[6].

Another relevant theoretical aspect of the work is defined by revealing the major influence of functional groups from the terpenic skeleton on the cyclization/rearrangement reactions "*in vitro*". It allows elaboration of very efficient synthetic ways towards complex terpenoids. Addition of post-cyclization functionalizations enlarges even more the organic chemist's toolbox for generation of the entire structural diversity of terpenoids, paving the way to profound studies of terpenoids' utility in general.

Applied value of the work

Verification and implementation of the hypotheses presented in this work has led to the synthesis of the representatives of the following classes of terpenic compounds:

1. Bifunctionalized monoterpenic compounds with geraniol skeleton;
2. Norsesquiterpenic compounds with austrodoranic skeleton;
3. Bifunctionalized sesquiterpenic compounds with farnesol skeleton;
4. Sesquiterpenic comounds with *seco*-eudesmanic skeleton;
5. Homosesquiterpenic compounds with the bicyclic skeleton of halimans;
6. Polyfunctionalized diterpenic compounds with geranylgeraniol skeleton;
7. Diterpenic compounds with sacculatanic skeleton;
8. Diterpenic compounds with rearranged spongianic skeleton;
9. Sesterterpenic compounds with geranylfarnesol skeleton, analogues of polyprenols;
10. Bifunctionalized sesterterpenic compoinds with bicyclogeranylfarnesol skeleton;
11. Sesterterpenic compounds with cheilanthanic skeleton;
12. Sesterterpenic compounds with rearranged cheilanthanic skeleton;
13. Polyfunctionalized sesterterpenic compounds with scalaranic skeleton;
14. Polyfunctionalized triterpenic compounds with bicyclofarnesylfarnesol skeleton;
15. Polyfunctionalized triterpenic compounds with the bicyclic skeleton of neopolypodatetraens.

These include secondary metabolites isolated from terrestrial and marine sources, pheromones, precursors of compounds with relevant biological activity and also substances known for their use as aroma constituents in perfumery and cosmetic industry.

The most important aspect in this context is represented by the fact that the raw material for the majority of described synthetic schemes were compounds isolated from vegetal sources available in the Republic of Moldova at industrial scale, which allows to project their diverse practical applications. In particular, a major practical interest has the elaborated integrated scheme for the synthesis of scalaranic and cheilanthanic compounds, basing on sclareol, available from the wastes of sage essential oil production.

And finally, initiation of a program directed to the use of unconventional media for biomimetic transformations has let us patenting an efficient method for the synthesis of sclareoloxide [7] – an important compound which found implementation in tobacco industry [8],[9] with the direct contribution of the author.

The main scientific results presented for public defence

During the research process defined by the current thesis objectives the following scientific results have been obtained:

1. The synthesis of α,ω-bifunctionalized terpenic compounds by the direct oxidation of open chain substrates;
2. The synthesis of α,ω-bifunctionalized terpenic compounds by oligomerization of α,ω-bifunctionalized fragments;
3. The synthesis of terpenic compounds with selective functionalization in the chain interior by oligomerization of α,ω-bifunctionalized fragments;
4. The synthesis of polyprenol-like terpenic compounds by a two-step oligomerization;
5. The selective initiation of the cyclization cascade in α,ω-bifunctionalized sesqui- and diterpenic substrates from the internal double bonds. Biomimetic synthesis of *seco*-eudesmanic sesquiterpenoids and sacculatanic diterpenoids;
6. The selective suspension of cyclization cascade in substrates with functionalization in the chain interior. Biomimetic synthesis of cheilanthanic sesterterpenoids;

7. The synthesis of cyclic terpenic compounds with pendant prenylation by post-cyclization oligomerization;
8. Elaboration of skeletal rearrangement processes for the synthesis of terpenic compounds with perhydrindanic, *abeo*-cheilanthanic, halimanic and neopolypodatetraenic structures;
9. Application of oxidative degradation processes for the synthesis of compounds with perhydrindanic and oxa-heterocyclic skeletons;
10. Selective functionalization of sesterterpenic compounds belonging to scalarane family by remote radical processes;
11. Application of ionic liquids as reaction media for biomimetic cyclization of terpenoids.

Implementation of scientific results

Implementation of the above mentioned scientific results has been expressed in the synthesis of some natural compounds or close precursors. The most important are the following:

- α-terpineol – an important monoterpenic component of vegetal ethereal oils;
- 9-hydroxygeranyldiacetate – a component of the Australian predaceous bug pheromone;
- 6-hydroxygeranylgeraniol – a secondary metabolite isolated from fungi of *Boletinus cavipes* species and having biological activity expressed in macrophage cells peroxidase inhibition;
- 19-acetyl-sacculata-11,19-diol – immediate precursor of natural 19-hydroxysacculat-11-al;
- austrodoral – a secondary metabolite with an important ecological role isolated from the Antarctic nudibranchs *Austrodoris Querguelensis*;
- austrodoric acid – a secondary metabolite izolated from *Austrodoris Querguelensis*;
- an advanced precursor of norrisolide – a compound with cytotoxic activity related to an unique mechanism of action based on the Golgi irreversible fragmentation, isolated from nudibranchs *Chromodoris Norrisi*;
- sclareoloxide –heterocyclic bis-norditerpenic compound of industrial importance.

Approval of scientific results

Approval of scientific results of the current work has been ensured by a broad participation to the international scientific meetings with presentations of the most important achievements on the thesis subject in the form of posters and oral communications. The following can be mentioned: International Symposium “Chemistry & Biology of Marine Organisms”, Kolympari, Crete, Greece

(**2003**), the series of international conferences "Achievements and perspectives of modern chemistry", Chisinau (**2003**, **2007**, **2009**, **2014**), the Ukrainian conference on organic chemistry, Odessa (**2004**), the XIth MaNaPro congress, Sorrento, Italy (**2004**), international symposium "Advanced Science in Organic Chemistry", Sudak/Miskhor, Ukraine (**2006**, **2010**), the series of international conferences of the Chemical Society of Romania, Rmn. Vâlcea (**2006**, **2010**), international conference "Netzwerktagung der Alexander von Humboldt-Stiftung", Darmstadt, Germany (**2008**), international conference Humboldt-Kolleg „Cooperation and Networking of Universities and Research Institutes – study by doing research" NANO-2011, Chisinau (**2011**), the XXIII-rd session of scientific communications "Progresses in the science of organic and macromolecular compounds" within the framework of Iaşi Academic Days, Iaşi (**2011**), The International Simposium-Conference "Ecological Chemistry 2012", Chişinău (**2012**), the Phytochemical Society of Europe conference "Phytochemicals in Medicine and Pharmacognosy", Piatra Neamţ (**2014**). Additionally, a series of presentations related to the implementation of the random biomimetic synthesis concept has been performed on the invitation of international collaboration partners, including Institute of Biomolecular Chemistry, Naples, Italy (**2004**, **2012**), Institute of Organic Chemistry, Regensburg University, Germany (**2008**), Fraunhofer Research Center, Straubing, Germany (**2009**), Center for Marine Science of the University of North Carolina, Wilmington, USA (**2005**, **2015**).

Publications related to the thesis

The research presented in the current doctor habilitate work have been broadly published in national and international specialized scientific journals, including:

- One article in an international collective book;
- 4 review articles in ISI-quoted journals, including one article as sole author;
- one review article as sole author in national journals, cat. A;
- 17 articles in ISI-quoted journals;
- 3 articles in national journals, cat. A, including one article as sole author;
- 18 communications at international scientific conferences, including 4 oral plenary communications and 3 contributions as sole author;
- 3 patents.

Thesis volume and structure

The doctor habilitate thesis comprises 238 pages of main taxt and includes 122 figures. The work has 5 chapters, final conclusions and recommendations. The bibliographical list comprises 266 titles.

Keywords

Organic chemistry, organic synthesis, terpenoids, cyclization, rearrangement, functionalization, ozonolysis, biomimetic, prenylation.

THESIS CONTENT

The work presented to the scientific community includes 5 chapters, the first one relating to the review of literature data and the following 4 chapters, presented under the common title "Methods for the synthesis of terpenic compounds according to the random biomimetic principle", integrating the results of author's own experimental investigations on the thesis subject.

Chapter 1. Organic synthesis methods towards some classes of terpenic compounds which incorporate condensed and partially oppened cyclic systems

The literature review aimed the profound study of several terpenic families with specific structural features and heteroatom functionalization pattern, produced in the host organisms by less usual biogenetic mechanisms. The results of this study has been broadly published in national and international editions in the form of review articles [5],[10],[11],[12].

Chapter 2. Syntheis of terpenic compounds with multiple functionalization via oligomerization or direct functionalization

2.1. Direct functionalization of open chain terpenoids

An important selective functionalization method of linear terpenoids at the terminal extremity is based on a biomimetic post-oligomerization functionalization. Mono-, sesqui- and diterpenic derivatives have been used as substrates. It is clearly understood, that a selective functionalization of such substrates represents a challenge to organic synthesis, because the use of olefinic bonds reactivity is difficult, once the molecule is a polyene. Therefore, a selective SeO_2-mediated allylic oxidation has been applied succesfully only in the case of monoterpenes [13],[14],[15],[16],[17] and sesquiterpenes [18].

For the diterpenic substrates this path proved to be inefficient, due to the multitude of allylic positions and low selectivity of terminal oxidations. Alternatively, we have used a functionalization method based on a so-called Van Tamelen epoxidation procedure, epoxide cleavage and re-olefination of the ω- extremity of the diterpenic chain [19],[20]. This terminal functionalization approach is presented in the retrosynthetic scheme below (figure 1). Accordingly, the selective oxidation of the terminal methyl group in compond **1** has been achieved in **4** synthetic steps, starting from the acetylated derivative **2** of comercial geranylgeraniol **3**, which was selectively epoxidized to the oxiran **4**, cleaved with periodate and re-olefinated with formyl,methyl-methilenetriphenylphosphoran.

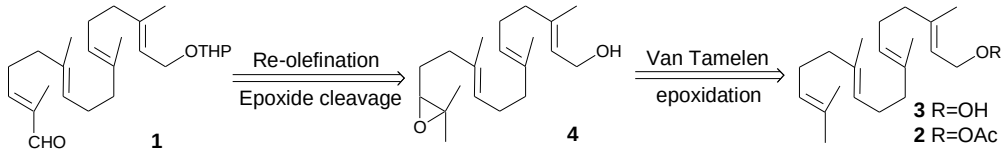


Figure 1. Retrosynthetic scheme for the synthesis of α,ω-bifunctionalized diterpenoids by direct oxidation.

2.2. Oligomerization approach in the synthesis of terpenes with multiple functionalization

The need for an „*in vitro*" terpene oligomerization is dictated by the fact that basic terpenic raw materials represent lower oligomers. The economically relevant renewable resources are firstly the wood processing wastes. The major part of these wastes are monoterpenes. The use of higher available representatives, such as abietic acid, sclareol or manool needs oligomerization procedures as well, in order to get access to sester- and triterpenes. That's why elaboration of synthetic procedures that allow efficient connection of inferior terpenic units represents a major priority in this field.

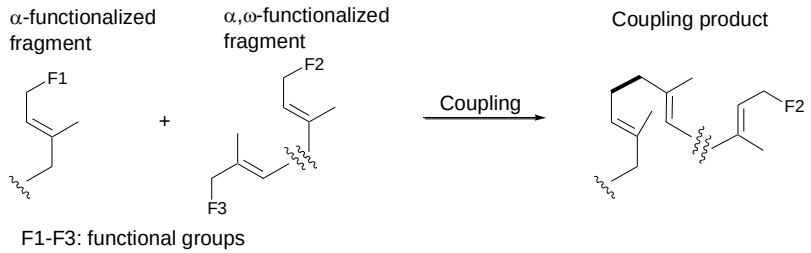


Figure 2. Oligomerization strategy of terpenes by synthesis.

The most convenient strategy is also based on a modular biomimetic approach, which includes connection of a terpenic fragment functionalized at the head terminus (α-functionalization) with the second fragment posessing double functionalization at both α– and ω– extremities of the chain (figure 2). Due to practical reasons, the α-functionalized fragment integrates an advanced complexity,

including cyclic structures, chirality or heteroatomic functional groups. As a rule, the α,ω-bifunctionalized fragment is a simple C_5 or C_{10} unit. Functional groups which activate the coupling process (F1 and F3) are selected in such a way so that to constitute a donor-acceptor synthon pair, which can combine and form a new C-C bond. Consequently, coupling of terpenic units of diverse nature can be acheived with a controlled regioflexibility by a rigurous selection of these terminal functional groups.

The preferable solutions for the synthetic equivalents of donor synthons are lithiated phenylsulfones and for the acceptor synthons – organic halides or carbonyl compounds. We have succesfull made use of this set of functional groups due to a set of advantages. First of all, introduction of phenylsulfonyl and halogenide moieties can be easily acheived for the major part of terpenic substrates basing on routine synthetic techniques. The yields of coupling reactions vary from good to excellent and the coupled product integrates the phenylsulfonyl group, which can be further manipulated in different ways: either substituted for hydrogen in a reductive process, eliminated to olefins or oxidized to carbonyl compounds. In such a way, two monoterpenic fragments **5** and **6** have been used in order to get access to α,ω-bifunctionalized diterpenic compounds [13],[14],[15]. These building blocks integrated the phenylsulfonyl group at the α-end and respectively the chlorine atom at the ω-end of the coupling partner chain (figure 3). The coupling product **7** was obtained with an excellent yield and its transformation to the *trans*-16-hydroxygeranylgeraniol **8** included reductive elimination of phenylsulfonyl group and acidic cleavage of tetrahydropyranyl protection. Diol **8** is a natural compound which have been identified in the fungus of *Boletinus cavipes* genus. It shows an unique inhibition activity of peroxides formation in macrophage cells.

In an analogous manner, the farnesyl chloride **9** has been homologated with a C_{10} bifunctionalized residue **10**, which contains the phenylsulfonyl group at the ω-extremity of the chain [16],[17]. As a result, the sesterterpenic compound **11** functionalized in the polyenic chain interior with the phenylsulfonyl group has been obtained (figure 4).

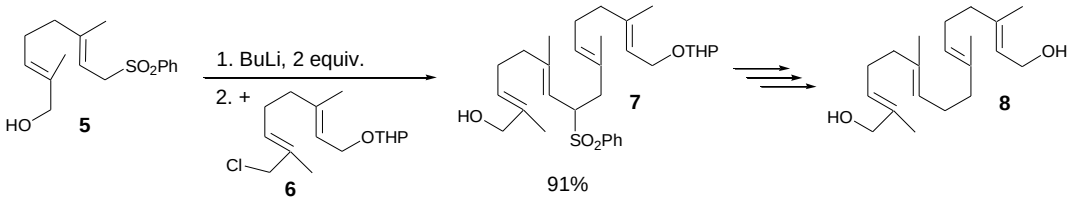


Figure 3. Synthesis of *trans*-16-hydroxygeranylgeraniol by homologation of inferior precursors.

Applying the same methodology to the optically active drimenylbromide **12** instead of farnesylchloride **9**, a bicyclic coupling product **13** has been obtained [21]. It integrates both a pendant lateral chain and functionalization in the chain interior. The result of a single synthetic operation has brought about an increased molecular complexity given by the bicyclic structure, pendant lateral chain, selective functionalization and chirality.

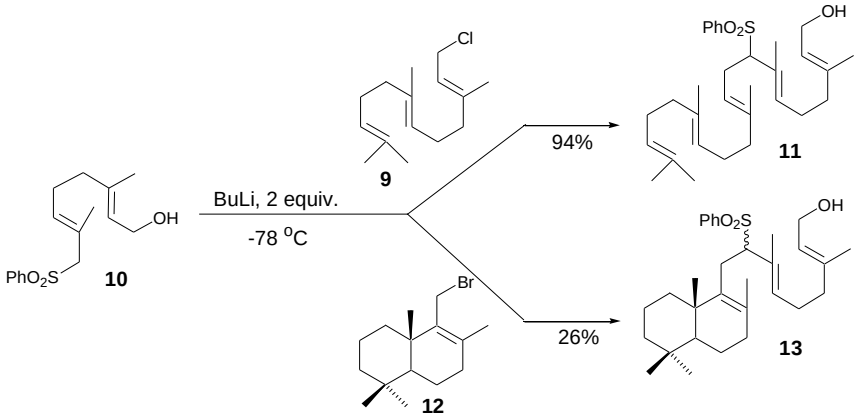


Figure 4. Synthesis of sesterterpenic derivatives by homologation of inferior precursors.

A recent example that relates to the synthesis of higher terpenoids with complex structure is represented by bicyclic compounds **14** and **15** [22]. These are terpenic derivatives resulting from oligomerization of bicyclic diterpenic sulfone **16**, obtained from manool **17**. The coupling partner in this case was the monoterpenic bifunctionalized aldehyde **18**, synthesized from geraniol **19** *via* its benzyl ether **20** and alcohol **21**. The whole synthetic sequence is represented in figure 5.

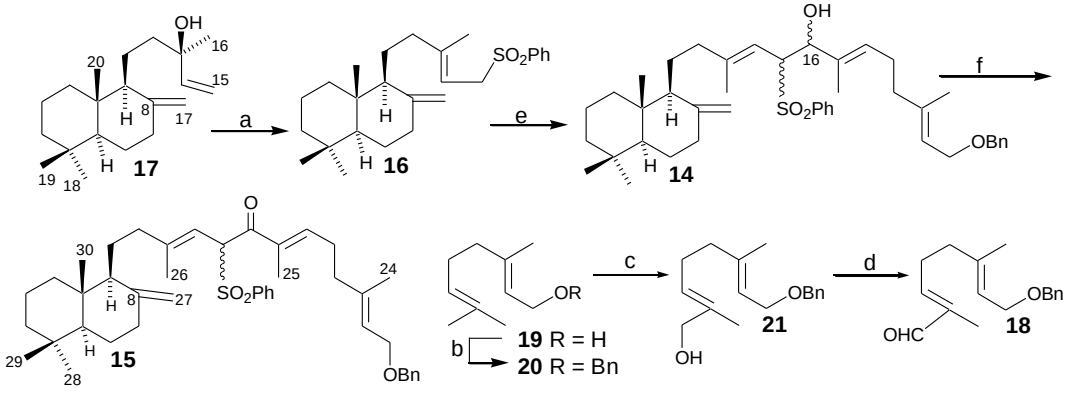


Figure 5. (a) *1*. PBr_3/Et_2O; *2*. $NaSO_2Ph$/DMF, 74% over two steps; (b) NaH, BnCl, TBAI, CH_2Cl_2, r.t., 12 h, 92%; (c) SeO_2, EtOH, reflux, 3h, 45%; (d) PCC, CH_2Cl_2, r.t., 1.5h, 70%; (e) *n*-BuLi/THF, then +**18**, 66%; (f) Swern oxidation, 73%.

A more specific oligomerization example relates to the synthesis of compounds with cheilanthanic skeleton in opticaly active form. Gaining access to these cheilanthanes, especially considering the β-oriented lateral chain which is broadly spread in natural sources, a synthesis method based on a post-cyclization prenylation has been elaborated [23]. The method can be also addressed as biomimetic, since an enzymatic cyclization of Ger-Ger-OPP and following addition of another isopentenyl pyrophosphate (IP-OPP) molecule can lead to the tricyclic structure of cheilanthanes.

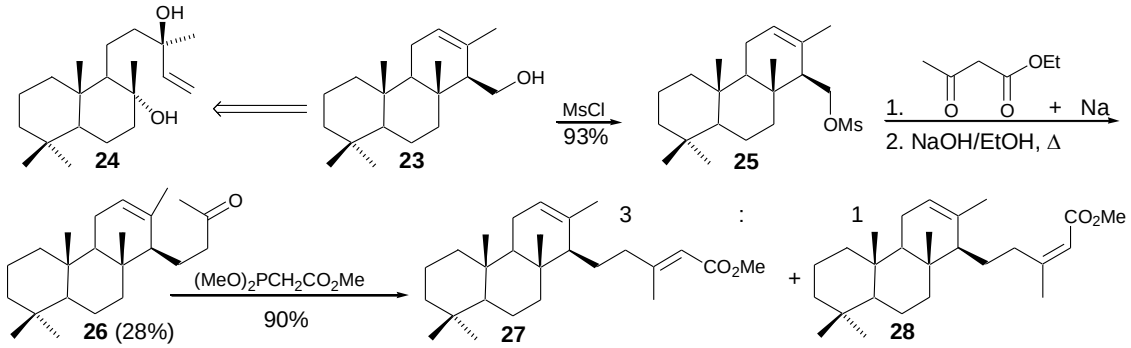


Figure 6. Sinthesis of chailanthanes in optically active form *via* post-cyclization oligomerization.

The starting material in this synthetic pathway was the known *ent*-isocopalic compound **23**, readily available from commercial sclareol **24** over a short sequence of transformations (figure 6). Accordingly, the transformation of the free hydroxyl group in **23** to a better leaving group by mesilation and following alkylation of mesilate **25** with ethylacetoacetate-derived enolate provided the expected keto ester, which decarboxilated under basic hydrolysis to the methylketone **26**. It is noteworthy mentioning that this step was the critical one in the whole synthetic scheme, the yield of the ketone **26** being relatively low. The unwanted secondary product was the conjugated diene resulting on the mesic acid elimination under basic conditions. Making use of tosyl moiety as a leaving group has diminished the coupling product yield further, making us draw the conclusion that steric hindrance represents the main cause of the parallel elimination process and consequently of the modest yield of the desired methylketone **26**.

Fortunately, the last step of olefination with thimethylphosphonoacetate took place smoothly, which allowed access to the esters **27** and **28** of cheilanthanic structure.

3. SYNTHESIS OF CYCLIC TERPENIC COMPOUNDS BY SELECTIVE CYCLIZATION SEQUENCES

3.1 Synthesis of partially cyclized terpenic compounds by a selective biomimetic initiation of the cyclization cascade

Elaboration of selective methods for polyprenic chain functionalization made possible following application of the resulting compounds in biomimetic-like cyclizations. The major challenge of this type of transformations is connected to the need of controling selectivity, once the diversity of reaction pathways and the number of possible products from a single substrate encrease dramatically along with the number of isoprene units in the molecule. Therefore, cyclization methods have evolved to the use of lower reaction temperatures and application of stronger acid promotors. It is clearly understood that running the reaction at lower temperature allows diminishing the conformational mobility of substrate, that is in fact a mimic of enzyme action, which practically locks the substrate conformation, making the process totally specific. Solid acids like zeolites and acidic ion exchange resins have been also successfully used to solve the problem. Their advantage consists in the posibility of substrate organization and promotion of cyclization sequences at temperatures close to ambiental. Unfortunately, the selectivity of solid acids versus substrate structure is based mostly on semi-empiric principles, limiting somehow the process versatility. More practical from this point of view proved to be superacids [1], which are able to initiate cyclization processes for a broad range of terpenoids with different functional groups at lower temperatures.

The significant progress in this area was possible due to the identification of the influence on the cyclization process exerted by additional functional groups, placed at specific positions of the linear substrate. Depending on the donor-acceptor character of these functional groups and their attachment positions, it was possible to influence the cyclization process pathway *via* selective initiation or suspension of cyclization cascade. The pioneering work in this context was connected to the unexpected result of a monoterpenic α,ω-bifunctionalized substrate superacidic cyclization, which contrary to expectations did not cyclize according to the iononic pathway but *para*-menthanic instead [24]. It turned out that an additional acetoxyl- functional group placed at the terminal extremity of the monoterpenic chain has an inhibition effect on the cyclization promotion from this terminal double bond. Lately, this effect has been demonstrated on the example of a longer substrate, namely the sesquiterpenic α,ω-bifunctionalized derivative **29** [18]. This substrate, due to the same functional group effect has been selectively protonated at the internal double bond launching a monocyclization

to form a sesquiterpenic compound **30** with the pendant terminal prenyl unit belonging to the *seco*-eudesmane series (figure 7).

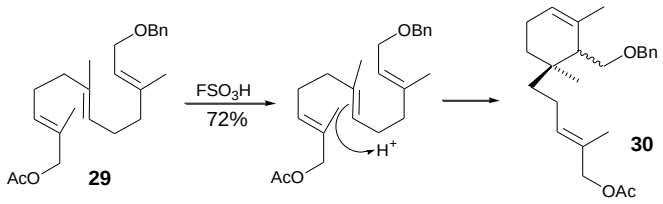


Figure 7. Biomimetic sinthesis of compounds with *seco*-eudesmanic skeleton.

This extraordinary cyclization mechanism has been further explored with the aim of biomimetic synthesis of sacculatanic diterpenoids [19],[20],[25]. In this line, the superacidic treatment of the diterpenic derivative **31**, having selective protection of the terminal alcoholic functional group, resulted in the isolation of a bicyclic major reaction product **32** having the sacculatane carbon skeleton (figure 8).

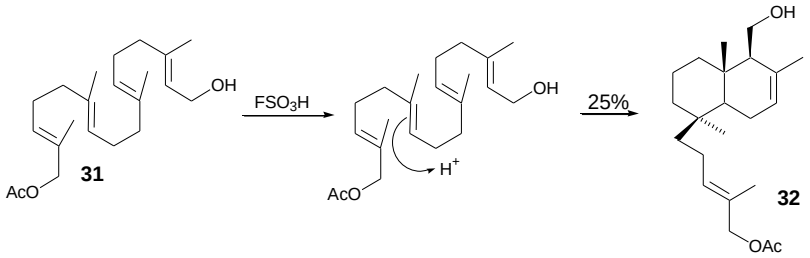


Figure 8. Biomimetic synthesis of compounds with sacculatane skeleton.

Inspite of the relatively modest yield of the cyclization process (cca. 25%), the value of this example is given by its unique mechanism, which demonstrates the principle of functional group participation in directing the selectivity of cyclization cascade. Under similar reaction conditions, substrates with the same chain lengths but lacking the terminal acetoxyl- functional groups transform to totally cyclic products, having no pendant prenyl units [1].

3.2 Synthesis of partially cyclized terpenic compounds by a selective biomimetic suspension of cyclization cascade

A totally different cyclization pathway has been revealed on the investigation of terpenic substrates containing double bonds with alternating configurations (*trans- vs. cis-*). The impetus for this investigation was the remarkable family of natural ruber-like isoprenoids – polyprenols. These compounds represent intermediate oligomers of DMA-OPP containing from 5 to 11 isoprenic

residues. Normally, they are identified in plants and are considered biogenetic precursors of condensed polycyclic substances isolated from fossil sediments [26]. Having in mind this hypothesis and aiming its verification, we have initiated a research program on superacidic isomerization of simpler polyprenols. The most representative substrates with di-*trans*-poli-*cis* double bond configuration have been selected.

As it was expected, all investigated substrates, independently on the chain length (from C_{25} to C_{55}) have shown a good reactivity on treatment with the cyclization agent – fluorosulfonic acid at low temperature (-50 ^{o}C ÷ -78 ^{o}C). But reasonable conclusions on the reaction course could be only drawn on the basis of experiments with inferior substrates, having the chain of five isoprenic residues [27],[28]. For longer chain substrates the complexity of the reaction products composition hampered isolation of individual reaction products and their structural identification. Due to the fact that currently there are no reliable sources of short natural polyprenols, we have realized the chemical synthesis of C_{25} substrates, basing on a sequential C_3+C_2 oligomerization method in order to lengthen the chain of commercial geranyllinalool **33** with one isoprenic residue (figure 9). This two step oligomerisation method was preferable, since a Carrol rearrangement of **33** with ethylacetoacetate has brought about an increased yield of ketone **34**, having the *cis*-configuration of the newly formed double bond. Olefination of this ketone with trimethylphosphonoacetate provided the esters **35** and **36**, which were studied in superacidic cyclization reactions. The selection of the esteric group at the α-extremity of the molecule was dictated by its advanced stability under superacidic treatment, as well as by the fact that polyprenols with the free hydroxyl group are less soluble in the solvents used for such transformations and tend to sediment at lower temperatures.

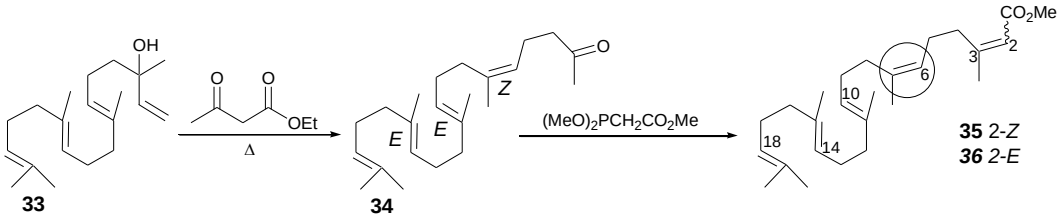


Figure 9. Synthesis of polyprenol-like compounds having internal double bond *cis*-configuration.

Cyclization of both substrates **35** and **36** occurred efficiently on treatment with fluorosulfonic acid (figure 10). Predominant reaction products in both cases were tricyclic compounds **37** and **38**, respectively. These compounds belong to the cheilanthane family and their biomimetic synthesis proved to be a very efficient preparative tool. In fact, the use of substrates **35** and **36** as synthetic

precursors has led to the identification of an unique effect of double bonds configuration influence on the propagation of the biomimetic-like cyclization cascade. Due to the presence in these substrates of internal double bonds with *cis*-configuration it was possible to suspend the cyclization cascade to tricyclic compounds. This functional group plays an important role in the conformational behaviour of the substrate and stops the cyclization sequence *via* a steric but less electronic effect.

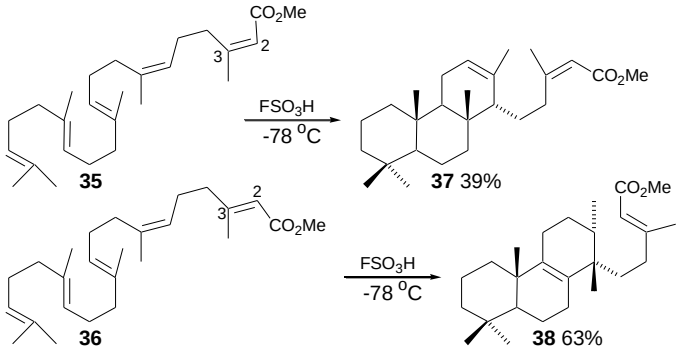


Figure 10. Superacidic cyclization of polyprenol-like substrates. Biomimetic synthesis of cheilanthanes.

This surprising conclusion has led to the idea of using more accessible bicyclic substrates as starting materials for cheilanthane synthesis, wich are readily available in optically active form [29]. The labdanic diterpenoid manool **39** was the candidate of choice. It is relatively available from different vegetal sources and can be also easily obtained from the commercial sclareol **34** by synthesis. The latter compound is produced on industrial scale in Moldova from the wastes of *Salvia Sclarea* essential oil production.

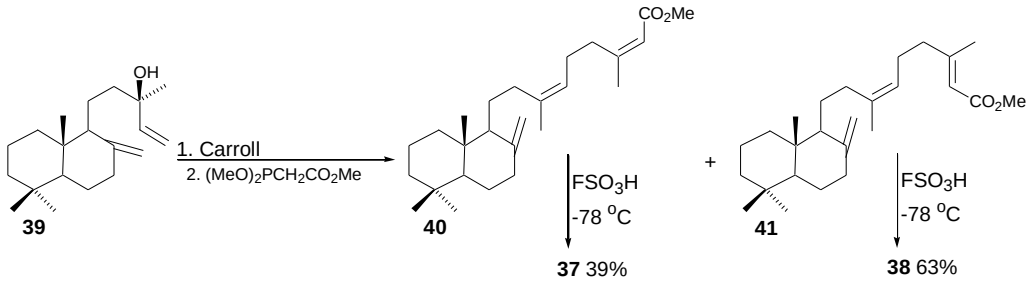


Figure 11. Biomimetic synthesis of cheilanthanes in optically active form.

Transformation of manool **39** to the cyclization substrates **40** and **41** was realized in a similar manner to the path described above for geranyllinalool (C_3 + C_2 homologation). Accordingly, the Caroll rearrangement with ethylacetoacetate and Horner-Wadsworth olefination with trimethylphosphonoacetate has led to the desired esters (figure 11). Their cyclization proceeded under

the same conditions described for the open chain esters **35** and **36**, with the only difference that in this case the reaction products **37** and **38** were optically active compound but not racemic, as in the case of the cyclization of linear substrates.

This method represents a complementary contribution to an alternative cheilanthane synthesis elaborated by us in a separate work [23]. It has an advanced synthetic value due to simplicity of transformations and reduced number of steps. Besides, it can be regarded as a reasonable synthetic method for tetracyclic scalaranic sesterterpenoids, namely the ester **42**, which is a secondary product after this transformations, along with cheilanthanes **37** and **38** (figure 12).

More exactly, our conclusion from this study was that the stereochemistry of secondary scalaranic compounds is not influenced by the *E-Z* configuration of the internal double bond in the cyclization substrate. This has allowed elaboration of an integrated process for the simultaneous synthesis of both cheilanthanes and scalaranes. Its value stems on the posibility of separation of the reaction products without chromatography. Accordingly, after the cyclization of the mixture of substrates **40** and **41**, the crude reaction product is submitted to alkaline hydrolysis. Under selected conditions, scalaranic esters do not hydrolize and cheilanthanic acids can be separated by their isolation in the acidic part. The remaining neutral part represents intact scalaranic esters.

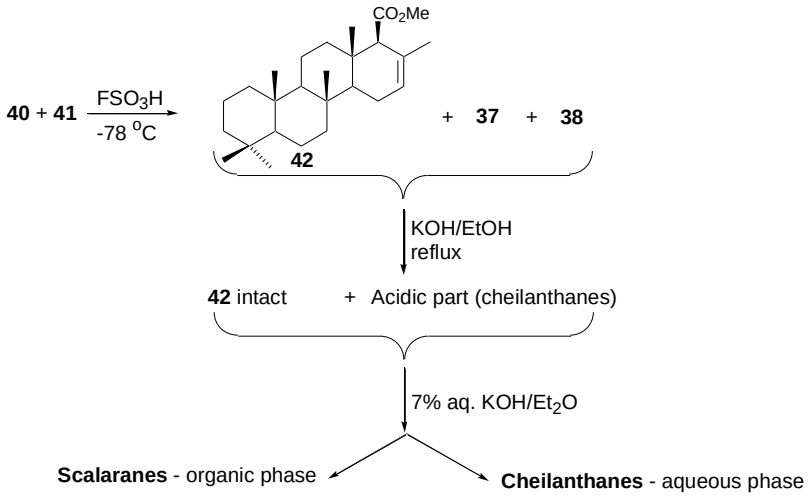


Figure 12. Integrated process for the preparative synthesis of cheilanthanes and scalaranes in optically active form.

The obtained cheilanthanic compounds have a major practical value since available natural sources do not allow exploitation of natural chailanthanes for advanced studies. In particular, it is the

case of compounds with the rearranged cheilanthanic skeleton similar to compound **38**, which have few known representatives in natural sources.

Another eloquent method for the selective control of cyclization cascade by its suspension has resulted from the study of superacidic isomerization of terpenic compounds with phenylsulfonyl groups intercalated in the aliphatic chain. Their synthesis has been presented in the sections above. Generally, it is very difficult to forsee the behavior of such complex substrates in superacidic isomerization reactions. Previous studies [1] have clearly shown that phenylsulfonyl functional groups tolerate well superacidic medium and once attached to the α-end of polyprenic chain lead to a complete cyclization (figure 13, substrate **A**, reaction **I**)

But in the case of integrating the phenylsulfonyl group within the chain interior the situation complicates. Two scenarios can be identified. The less probable scenario assumes no interference of the phenylsulfonyl groups with the cyclization cascade initiated in the superacid media. Under these circumstances, a substrate of structure **B** (figure 13, reaction **II**) on superacidic treatment would have brought about to totally cyclized compounds of still relevant synthetic value due to the integration of an additional functional group in the cyclic structure, amendable to following transformations. But it is hardly beleavable that such an electron-withdrawing functional group like phenylsulfonyl moiety will not influence the neighboring double bonds in the chain, diminishing their nucleophilicity and contributing in such a way to the suspension of the cyclization cascade.

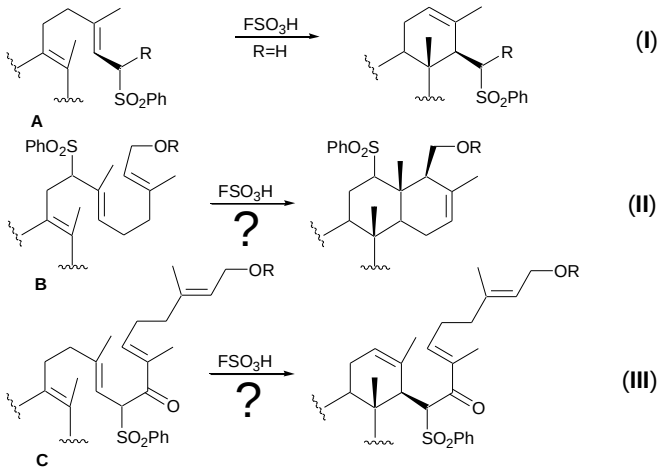
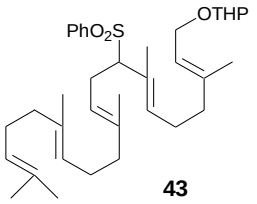


Figure 13. Hypothetic versions of superacidic isomerization of substrates witn phenylsulfonyl groups.

Under such a scenario, one can expect a substrate of general structure **C** (figure 13, reaction **III**) transforms on superacidic treatment to a cyclic compound with a pendant isoprenic residue. Such a

result would be also of great interest, since it could allow acces to similar natural compounds like cheilanthanes discussed above.



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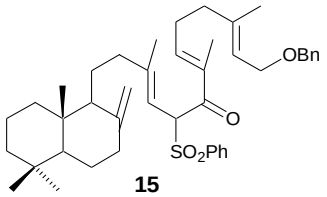
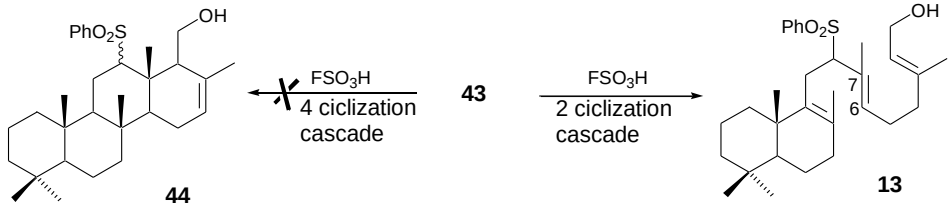


15

We decided to elucidate the subtle peculiarities of such substrates reactivity under superacidic treatment and performed the synthesis of compound **43** and **15**, similar to phenylsulfones **B** and **C** depicted in figure 13. The both substrates have been submitted to superacidic isomerization under standard conditions and the results were totally surprising.

Firstly, the superacidic isomerization of compound **43** was investigated [17],[21]. Integration of the phenylsulfonyl group in the interior position of the polyenic chain was envisaged as a way to reach an extra-functional group in a probable tetracyclic product **44**, obtained under superacidic cyclization and considering a non-interference of the phenylsulfonyl moiety with the cyclization cascade (figure 14). But this hypothesis was not confirmed. Polyene **43** treatment with an excess of fluorosulfonic acid at the temperature of -78 ^{o}C has provided a major reaction product of bicyclic structure **13**, which forms on the suspension of the cyclization cascade under the electron-withdrawing action of the phenylsulfone intercalated in the middle of the chain.



44 **13**

Figure 14. Superacid isomerization schemes of sesterterpenic substrate **43**.

This result can be explained by a simultaneous protonation of two centers in the molecule of the substrate **43**: the terminal double bond and the phenylsulfonyl group (figure 15). In this way, a two cyclizations cascade is initiated from the terminal double bond, which can not advance to tri- and tetracyclizations due to the protonation of the phenylsulfonyl group and drastic decrease of the $\Delta^{6,7}$ – double bond nucleophilicity under a strong allylic effect. As a result, the bicyclic product **13** is obtained on cyclization suspension and elimination of the protecting group under acidic media.

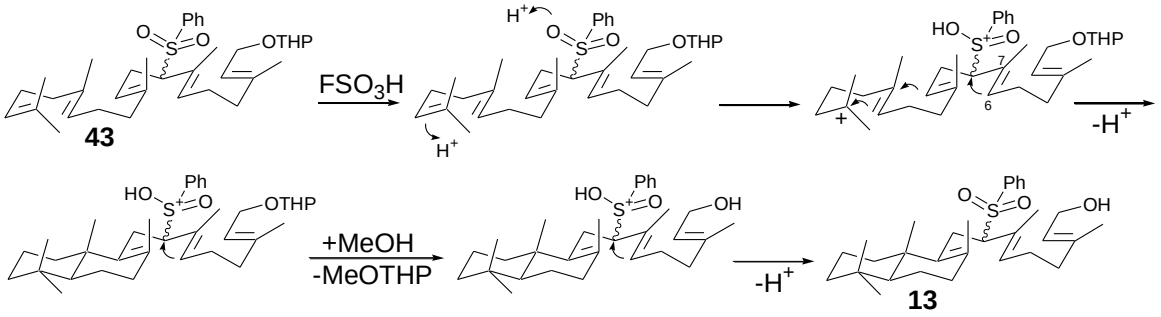


Figura 15. The mechanism of suspending the cyclization cascade by a phenylsulfonyl group intercalated into the polyenic chain.

3.3 Synthesis of cyclic terpenic compounds in non-conventional media. Superacidic cyclization in ionic liquids

One of the most recent research directions which has evolved along with the current thesis realization is connected to the exploration of new and unconventional media for biomimetic transformations. It is well known that currently the implementation of green (sustainable) chemistry principles represents a global development priority. Depletion of natural resources, the negative impact of chemical pollutants on human health and state of the environment, the tough competition on global markets require from organic chemists elaboration of sustainable synthetic processes which use raw materials from renewable resources and generate minimum wastes and secondary products within highly efficient catalytic processes. Therefore, in the context of terpenoids investigation we have set as a special goal to identify opportunities for new solvent systems exploration, which would represent less danger for the environment, while having kept the solvation abilities of classic solvents. The pioneering work in this area was the use of ionic liquids as media for biomimetic cyclizations [30],[31]. This investigation demonstrated the ionic liquids compatibility with superacidic media and concluded that under these conditions biomimetic cyclization of some representative terpenic substrates takes place in a similar way as previously shown with classic solvents. Two known ionic liquids have been involved: 1-buthyl-3-methylimidazolium tetrafluorobarate and hexafluorophosphate (BMIM-BF_4/BMIM-PF_6). Sesquiterpenic farnesol, its acetate and phenylsulfone, as well as methylfarnesoate have been cyclized efficiently as solutions in these ionic liquids on the action of fluorosulfonic acid. Cyclic products yields over 70% have been observed in the case of farnesylphenylsulfone and methylfarnesoate on the use of BMIM-BF_4 as solvent.

4. APPLICATION OF THE REARRANGEMENT BIOMIMETIC PROCESSES FOR THE SYNTHESIS OF SOME TERPENIC FAMILIES

As it was pointed out in the introductory part of this work, rearrangement processes also represent a frequent tool in the biosynthetic cellular machinery. Out of these, one can mention ring contractions and enlargements, atom and functional group migrations. These extremely complex processes mimic by chemical synthesis methods also represented one of the important goals of the current work.

4.1 Rearangement processes involving ring contractions. Synthesis of austrodoric acid and austrodoral

One of the richest sources of rearranged terpenic compounds are marine organisms, which permanently inspire organic chemists by the enormous diversity of unusual molecular architectures isolated mainly as secondary metabolites. An example can be spongianic compounds isolated from spongi, which along the normal skeleton **45** include a series of related compounds having rearranged skeletons (figure 16). An example is norrisolide **46**, isolated from the nudibranchs *Chromodoris norrisi* and identified with an unique biological activity consisting in irreversible fragmentation of Golgi aparatus in the mamalian cells. The biosynthetic origin of this highly oxygenated compound has been postulated to include a series of skeleton rearrangements and oxidative degradations of a spongianic skeleton.

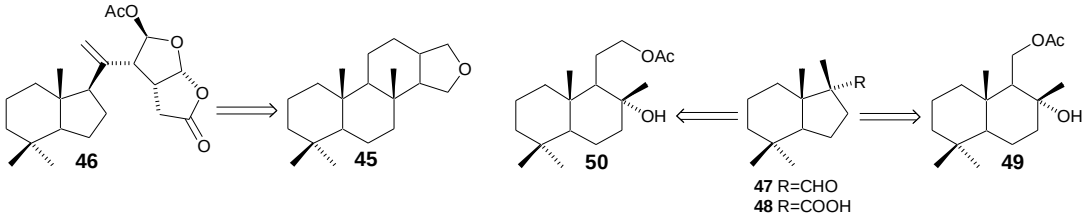


Figure 16. Possible biogenetic precursors of some terpenoids of marine origin.

Austrodoral **47** and austrodoric acid **48** are *nor*-sesquiterpenic compounds with a simplier structure, isolated from the dorid nudibranchs *Austrodoris kerguelenensis*. Their biogenesis has been also connected to a ring contraction process involving the B-cycle of drimanic **49** or homodrimanic **50** compounds, which are broadely spread in marine or terrestrial organisms.

We have elaborated a biomimetic procedure for the synthesis of acid **48** basing on this biogenetic hypothesis and starting from homodrimanic compounds [32],[33]. The sequence of transformations that finally conducted to the natural product **48** is represented in figure 17. Briefly,

the homodrimanic acetoxyalcohol **50** was dehydrated selectively, then epoxidated with a peroxoacid to the acetoxyepoxide **51**. The key step was the rearrangement of this epoxide under the influence of an acidic inducer, in this case a Lewis acid, which on the epoxide opening launched a ring B contraction leading to the acetoxyketone **52** of perhydrindanic structure. This transformation represented a first example of a direct ring contraction of homodrimanic substrates and a confirmation of the biogenetic hypothesis laid on the basis of austrodorane family.

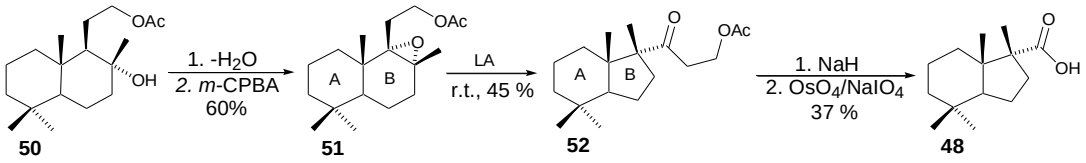


Figure 17. Biomimetic rearrangement of a homodrimanic substrate. Synthesis of austrodoric acid.

Transformation of ketone **52** into the acid **48** included two simple steps which aimed cleavage of two carbon atoms by acetic acid elimination and oxidation of the resulting ketoolefin with osmium tetraoxide in the presence of sodium periodate. The spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) of synthetic product corresponded in all aspects with those of an authentic sample isolated from *A. kerguelenensis* nudibranchs.

Determination of the absolute stereochemistry of austrodoral **47** and accumulation of larger amounts of this compound for biological activity testing experiments both required planning of a parallel synthetic study for the synthesis of this aldehyde. Regretfully, direct conversion of austrodoric acid **48** or its methyl ester to austrodoral **47** has not been successful, most probably due to steric hindrance around the angular position. Therefore, aiming the synthesis of aldehyde **47** we have decided to exploit an alternative synthetic path, starting from the substrate **49** of drimanic structure [34]. The elaborated synthetic scheme included two alternative paths (a) and (b), represented in figure 18.

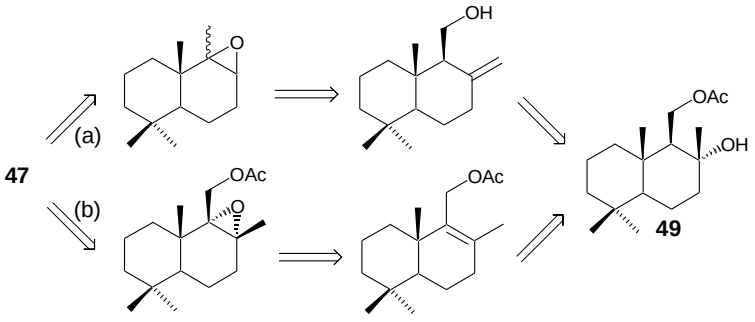


Figure 18. Alternative retrosynthetic schemes elaborated for the synthesis of austrodoral **47**.

Implementation of path (a) from this scheme have not provided the expected result since the rearrangement products formed on methyl group migration from the angular position adjancent to the heteroatomic functional group. But the realization of the second path (b) instead, allowed the succesfull synthesis of natural aldehyde **47**. The sequence of corresponding transformations is represented in figure 19.

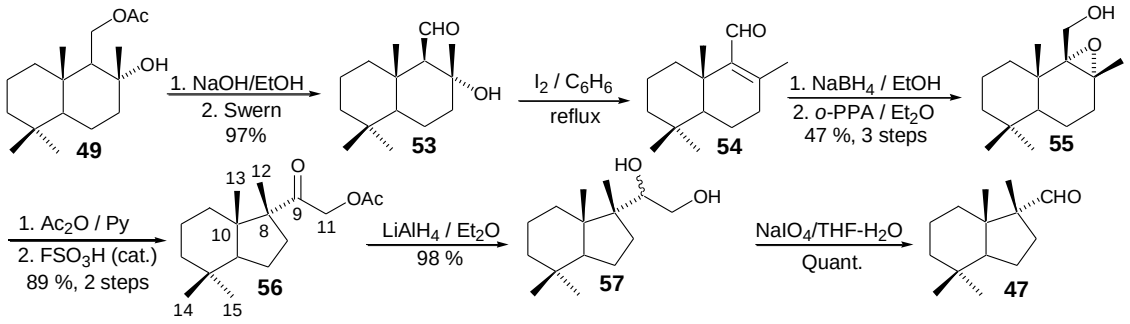


Figure 19. Biomimetic rearrangement of a drimanic substrate. Synthesis of austrodoral.

The synthesis has started from the drimanic oxyacetate **49**, which dehydration was thought to occur in a similar way as acheived with homodrimanic analogue **50** (figure 17). But it was not the case and **49** showed totaly inert under dehydration conditions. This transformation was finally acheived over a longer path *via* the hydroxialdehyde **53**, obtained on the hydrolysis of **49** followed by Swern oxidation. Accordingly, treatment of **53** with iodine in benzene at reflux resulted exclusively to the tetrasubstituted aldehyde **54**. The latter compound on reduction and epoxydation furnished epoxyalcohol **55**. Its following acetylation resulted in the corresponding epoxyacetate which was a suitable substrate for the key-step of ring contraction. Different acidic initiators have been investigated for this transformation and fluorosulfonic acid turned to be the most convenient one, promoting conversion to the rearranged ketone **56** under catalytic conditions and with a quantitative yield. Reduction of ketone **56** and periodate cleavage of diol **57** led to the desired aldehyde **47**. All spectral data (^{1}H NMR, ^{13}C NMR, IR, MS, $[\alpha]_D$) of the synthetic compound **47** matched in all respect those of the natural product. The synthetic austrodoral **47** was submitted to a preliminary investigation of its biologically active profile, including ichtiotoxicity *Gambusia affinis* tests. The sample showed an extreme toxicity in concentrations as low as 10 ppm, which confirms initial hypothesis of the ecological role of this secondary metabolite in the chemical defence of producing nudibranchs.

4.2 Rearangement processes involving functional group migrations

Examples of deeper skeletal rearrangements are present in diverse synthetic applications of terpenoids, in spite of the difficulties connected to control a cascade of events affecting reaction course and selectivity. They represent a generally accepted biosynthetic pathway to diverse natural compounds and their mimicking also provides an efficient synthetic tool. In particular, the ring contraction reaction that we have successfully exploited for the synthesis of austrodoric acid includes a relevant biomimetic approach. The key step of the synthesis was a ring contraction of the homodrimanic substrate **51** under the action of a Lewis acid.

The relatively moderate yield of target perhydrindane **52** (cca. 45 %) made us to deeper investigate the secondary products obtained on the acid induced rearrangement of the epoxide **51**. The incursion into the reaction peculiarities has led to the identification of all secondary products, which turned out to be rearrangement products too, but with both different structure and reaction mechanism. This result has stimulated our interest to the posibility of a selective control over both parallel homodrimanic epoxide rearrangement pathways [35].

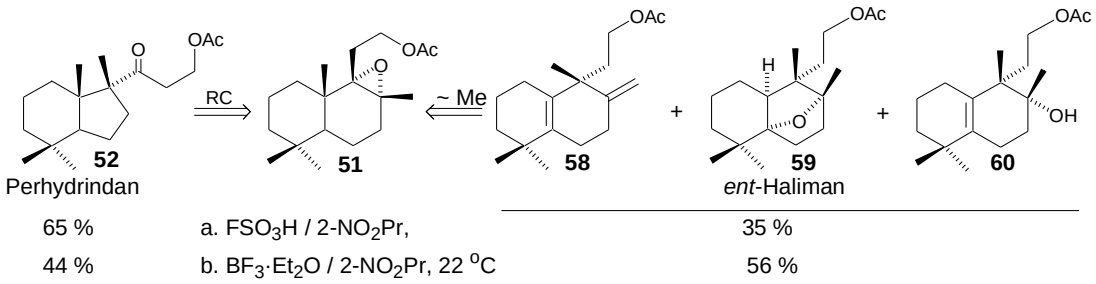


Figure 20. Biomimetic rearrangements of homodrimanic substrate **51**.

The identified secondary products resulted after a deeper skeletal rearrangement (figure 20). It included a cascade of hydride and methyl ions migrations, followed by proton elimination or heterocyclization, leading to compounds **58**-**60** with the structure of bicyclic system of *ent*-halimanic compounds. Reaction conditions modification, including the temperature, nature of acidic reagent and solvent, allowed to reach a moderate control of reaction selectivity either towards the ring contraction product or products of bicyclic halimanic skeleton.

This example integrates two different biogenetic pathways leading to compounds of perhydrindanic and halimanic structure. The striking difference between the reactivity of homodrimanic acetoxyepoxide **51** and its drimanic analogue has been explained by the lateral chain

length effect on the stability of intermediate carbonium ion species which are involved in both paths of skeletal rearrangement.

Triterpenoids represent a group of compounds with one of the broadest skeletal deversity in the row of natural compounds, including over 100 structures identified from natural sources. The interest towards the biological activity of triterpenoids is permanently fuelled by their relevant antiinflamatory, antitumor, anti-HIV, insecticide properties, as well as their efficiency in treatment of vascular and metabolic deseases.

In the continuation of our efforts oriented to the synthesis of terpenoids with complex skeleton basing on the random biomimetic concept, the reactivity of a triterpenic bicyclic adduct **15** has been investigated [22]. It includes two heteroatomic functional groups intercalated in the linear lateral chain and basing on our results with the similar substrate **43**, which also has a phenylsulfonyl moiety integrated in the isoprenic chain [17],[21], superacidic isomerization of the bicyclic sulfone **15** represented a obvious interest. Once we have observed an effect of functional group influence on the electrophilic isomerization of **43** and if this effect acts in substrate **15**, then a single cylization step (the following would be inhibited by the presence of strongly electron withdrowing keto- and phenylsulfonyl functional groups) could lead to the tricyclic compound **61**, having one prenyl (geranyl) unit pendant, similar to tricyclohexaprenols (figure 21). But this hypothesis was not confirmed in this case. The identified reaction product **62** turned out to be a bicyclic compound as well as the starting substrate, but unlike **15**, its carbon backbone has suffered a major rearrangement involving successive hydride ion shift and a methyl migration from the angular position.

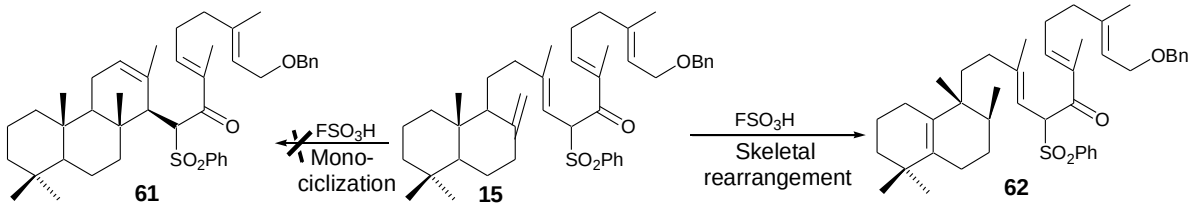


Figure 21. Total inhibition of polyenic chain double bonds by intercalated functional groups.

In conclusion, the presence of two functional groups intercalated in the chain interior has led to a total inhibition of the double bonds belonging to such a terpenic substrate, favouring a more advanced process of skeletal rearrangement instead. The structure of the rearranged compound **62** was elucidated basing on spectral data. It is noteworthy mentioning that this triterpenic polyfunctionalized derivative can be viewed similar to triterpenoids of neopolypodatetraene series, in particullar on

considering its bicyclic fragment. The former has been isolated from a squalene-hopene cyclise mutant strain of a procariotic bacteria *Alicyclobacillus acidocaldarius* F365A.

5. APPLICATION OF THE OXIDATIVE - DEGRADATION BIOMIMETIC PROCESSES FOR THE SYNTHESIS OF SPECIFICALLY FUNCTIONALIZED TERPENES. REMOTE C-H FUNCTIONALIZATIONS

The last chapter of the work relates to the chemical transformations which bring about structural diversity of terpenoids through different heteroatomic functional groups. Introducing "decoration" to the carbon backbone formed *via* oligomerizations, cyclizations or rearrangements is performed by virtue of various oxidative processes mediated *in vivo* by enzymes of cytochrome P450 family. On the other hand, reproduction of these transformations by chemical synthesis is still a relevant challenge, provided the difficulties connected to the selective reactivity of non-activated C-H bonds. Strong oxidants, based mostly on radical intermediates, can provide feasible solutions to tackle successfully this problem. The related processes are often accompanied by skeletal degradations, which also represent convenient tools in complex synthetic schemes.

We have undertaken substantial efforts in the direction of selective installment of heteroatomic functional groups in terpenes of different families, basing on oxidative transformations and radical processes. Strong oxidizing species like ozone or peroxoacids have been used, along with free radical species generated either by thermal or photochemical means. The detailed discussion of these examples is presented below.

5.1 Synthesis of the perhydrindanic fragment of norrisolide

The vast repertoire of structures that have so far been identified from marine invertebrates frequently have no comparable equivalent in terrestrial organisms. In addition, during the last years, a very high potential for marine natural products as sources and/or leads to drugs has been evidenced to cover a wide range of pharmacological effects, including antineoplastic, analgesic, immunomodulating, anti-inflammatory activities. One of the impediments that hampers following investigations of marine natural products as therapeutic agents is their limited availability from natural sources. That's why considerable efforts have been undertaken to provide access to these compounds by chemical synthesis.

Discovery of an efficient path for the synthesis of the bicyclic perhydrindanic system allowed us to elaborate a synthetic scheme towards an advanced precursor of norrisolide **46**, which structure

represents an interesting combination of the lipophilic perhydrindanic fragment and the highly oxygenated bicyclic furofuranic system. The devised retrosynthetic strategy is represented in figure 22.

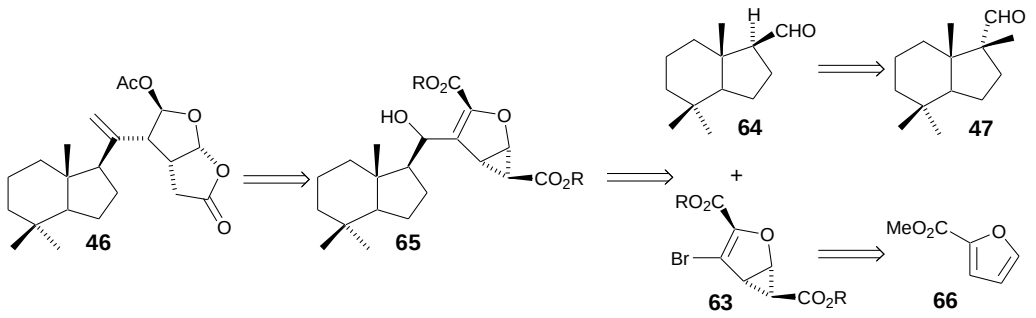


Figure 22. Retrosynthetic strategy for the synthesis of norrisolide.

The basic element of the suggested scheme is coupling of structural fragments **63** and **64** leading to the adduct **65**, which includes all carbon atoms of the furofuranic fragment of **46**, being an immediate precursor of the latter. The bromide **63** is known as an important building block for the synthesis of spongianic diterpenes of rearranged structure and it has been obtained on an asymmetric cyclopropanation of methylfuroate **66** basing on the described literature procedure. We have planned to synthesize the second coupling fragment, aldehyde **64**, from its superior oligomer austrodoral **47**, which was made available by us according to the method described above. Transformation **47** → **64** was envisaged *via* a degradative Baeyer-Williger oxidation, followed by a regioselective elimination of formic acid and hydroboration-oxidation of the resulting exocyclic double bond. Further fragments coupling was planned through lithium - bromine exchange in **63** and *in situ* treatment with aldehyde **64**.

The steps which led to the synthesis of aldehyde **64** and its further coupling are represented in figure 23 [36],[37]. Accordingly, austrodoral **47** was submitted to Baeyer-Williger oxidation and the resulting formate ester **67** was hydrolyzed to the alcohol **68**. The former was dehydrated to the mixture of olefins **69**. This step represented a major difficulty for two reasons. First of all, regioselective dehydration to the exocyclic isomer is relatively difficult to attain, since in such reactions formation of a thermodynamically more stable trisubstitute isomer predominates as a rule (Zaitzev rule). In addition, testing of different dehydration agents for this transformation has shown a secondary process involving migration of the neighboring methyl group from the angular position, which in some cases was predominant.

Despite these unfavorable circumstances, it was possible to selectively acheive the desired olefin making use of Swern reagent as a dehydration agent. Successive hydroboration was performed with the mixture **69**, resulting to alcohols **70** and **71**, which have been oxidized as a mixture as well, making possible separation of the resulting desired aldehyde **64** from the secondary ketone **72**.

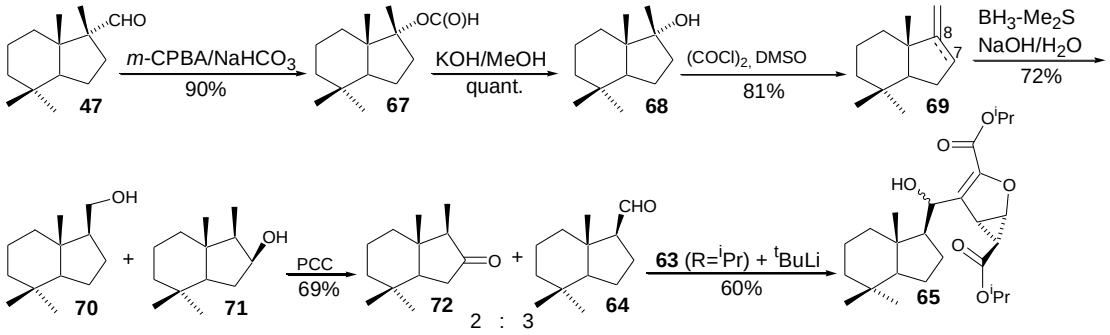


Figure 23. Norrisolide precursor **65** synthetic scheme.

Coupling of aldehyde **64** with the cyclopropanic fragment **63** was realized by the treatment of the latter with a double excess of *tert*-BuLi at low temperature (-115 ^{o}C) for 15 minutes, followed by interacting with **64** and usual work up. The coupling product **65** was isolated and its structure confirmed by spectral methods.

In such a way, on the application of a ring contraction strategy, followed by a degradative oxidation a complex adduct **79** has been synthesezed. It represents an imediate precursor in the synthesis of the natural product norrisolide **46** which posess interesting biological activity.

5.2 Biomimetic degradation processes based on ozonolysis

Oxygen-containing heterocycles are structural motifs widely found in natural products of different origins. A range of biologically active compounds such as *C*-nucleosides, ionophore antibiotics, acetogenins, and brevetoxins incorporate cyclic polyether moieties in their structural backbone. Consequently, considerable efforts have been undertaken to elaborate new efficient synthetic methods to access cyclic ethers of different ring sizes. Functionalized polyethers with elements of chirality are of special interest in synthetic organic methodology, because their synthesis often requires considerable effort. Over the time, different strategies have been undertaken aiming to access functionalized *O*-heterocycles. We have used a degradation approach in order to initiate a hetorocyclization involving an intramolecular process, assisted by an oxygenated functional group and intermediate ozonides derived from a dienic system ozonolysis.

As pointed out above, terpenoid degradations occur broadly in biogenetic schemes, therefore, adding oxidative degradation processes, in particular ozonolytic, to the toolbox of biomimetic synthesis, represented a relevant interest. It is well known that complex substrates with advanced functionalization yield "abnormal" ozonolytic products, obtained on the result of interaction of intermediate ozonolysis species: molozonides and especially carbonyloxides, which have an ionic character. This particular aspect has been demonstrated on the example of a norditerpenic diene **73** ozonolysis, which was additionally functionalized by a tertiary hydroxyl group [38]. Depending on the reaction temperature and the amount of ozone used, this diene ozonolysis resulted in different products (figure 24). At the lower temperature and excess ozone, the reaction product was the expected diol **74**. But on performing the reaction at 0 ^{o}C a surprising product was identified, confirming the formation of the intermediate bipolar carbonyloxide which on allylic isomerization cyclizes with the tertiary hydroxyl group and after borohydride reduction yield the tetrahydrofuranic hydroxylated derivative **75**.

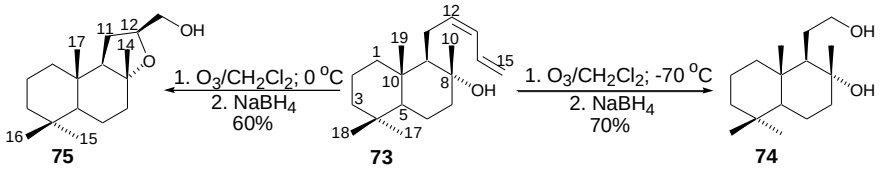


Figure 24. Selective ozonolysis assisted by a tertiary hydroxyl group.

Formation of alcohol **75** is possible only *via* the mol-ozonide **76** and Criegee intermediate – carbonyloxide **77** (figure 25). Stabilization of the latter by conjugation with the adjancent double bond leads to a partial charge distribution at the C-12 carbon atom, followed by a heterocyclization on the intramolecular attack of the tertiary hydroxyl group with the formation of heterocyclic compound **78**. Given the low stability of the vinyl hydroperoxides, it decomposes to the aldehyde **79**, which is reduced finally with sodium borohydride to the alcohol **75**.

As the result of these investigations a new method for the synthesis of functionalized perhydrofurans have been demonstrated. The procedure is based on a tandem ozonolysis – cyclization process which leads with an excellent yield to a heterocyclic compound containing a lateral chain for further functionalization. To the best of our knowledge, this is the first example of a conjugated diene ozonolysis with simultaneous cyclization involving an intramolecular hydroxyl group which ensures formation of the oxygenated heterocycle. Practical utilization of the newly synthesized compound represents the subject of further studies.

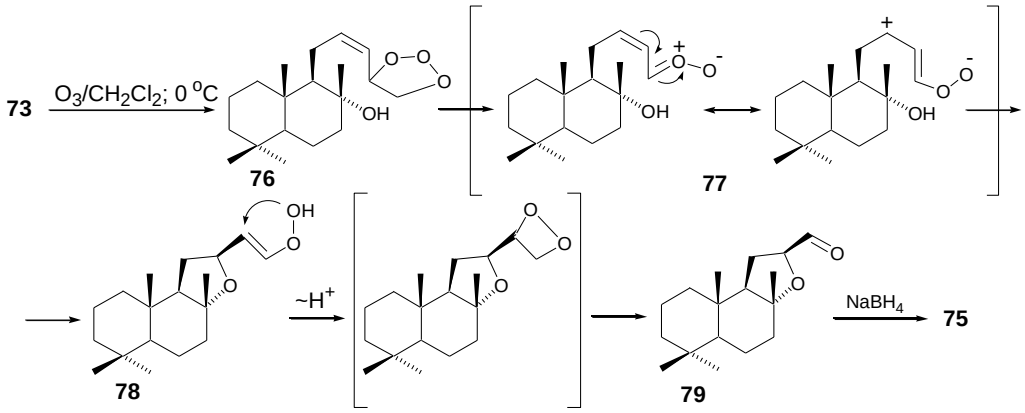


Figure 25. Suggested mechanism for the synthesis of the functionalized perhydrofurane **75**.

A relevant result from the point of view of practical utility represents the use of aqueous solvents for performance of terpenic compounds ozonolytic cleavage. An efficient method for the synthesis of sclareoloxide has been patented basing on these studies [7].

The main aspect of the respective investigations accounts for the use of water as an ozonolysis co-solvent, which allows application of redox catalytic cycles based on diverse inorganic compounds. Consequently, the use of aqueous solvents makes the workup procedure very simple and facilitates catalyst recycling. The conversion of the labdanic diterpenoid sclareol **24** to the industrial relevant sclareoloxide **80** has been performed in the discussed example [39],[40]. The transformation was realized with an excellent 97% yield (figure 26).

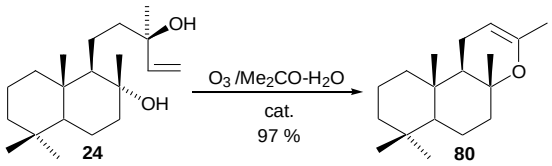


Figure 26. Ozonolytic cleavage os sclareol **24** under catalytical conditions.

The method novelty consists in the use of a co-oxidant which contributes to a higher rate of the lateral chain cleavage in the starting compound. Such ozonolysis strategies are known in the literature, a recent example being the use of lead (IV) tetraacetate (LTA) in suprastoichiometric quantities. The effect of this additive is expressed in C-C bond scission basing on the classical mechanism of α,β-dioxigenated compounds cleavage. This step limits the rate of the whole ozonolysis process and clearly contributes to the efficiency of successive transformations and sclareol degradation process in general.

But the use of LTA in suprastoichiometric quantities even with the final aim of accelerating lateral chain scission in substrate **24** is not adavantageous, firstly due to the lead (IV) compounds properties. For example, lead tetraacetate is an unstable compound of high toxicity and its use in industrial context is strongly discouraged, mainly because of its extreamely negative environmental impact.

Therefore, the substitution of LTA for lead diacetate has been considered under catalytic conditions, which is fairly sufficient for the lateral chain cleavage acceleration on ozonolytic treatment of diol **24**. Finally, this brings about excellent yields of sclareoloxide **80**.

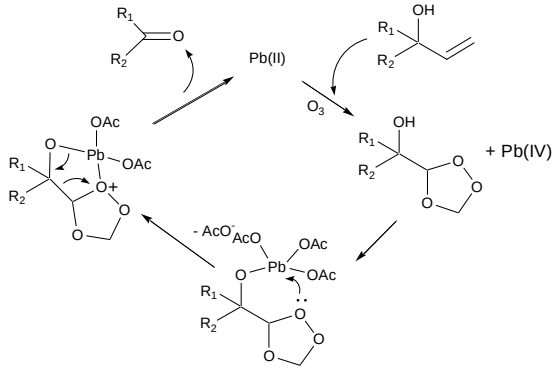


Figure 27. The suggested catalytic cycle for the Pb(II) catalized ozonolysis.

Although lead diacetate does not have the ability to cleave α,β-dioxigenated compounds, a parallel process of bivalent salt slow oxidation to LTA takes place under ozonolysis reaction conditions with ozone as oxidant. This is sufficient to initiate a catalytic cycle, significantly contributing to the lateral chain cleavage rate (figure 27).

Besides lead diacetate, hydrogen peroxide proved to be an efficient additive with minimal environmental impact. It is noteworthy mentioning, that running the ozonolysis reaction in aqueous media allows sometimes to avoid the use of traditional strong reducing or oxidyzing reagents in stoichiometric quantities, since water alone plays the role of an efficient reducing reagent for the intermediate ozonides.

5.3 Terpene modification by functionalization of inactivated C-H bonds. Radical relay remote functionalization of scalaranic compounds

A separate series of investigations presented in the current thesis is directly connected to the modulation of functional properties of terpenic compounds which are caused by heteroatoms incorporated in carbon backbones, formed after oligomerization-cyclization-rearrangement

sequences. Introduction of functional groups plays an important role in the interaction of terpenoids with biological matrix, and consequently brings about specific properties of the these molecules. Oxygenated functional groups represent the most frequent „decorations", as well as nitrogen and halogen atoms play an important role in terpene functionalization too.

The biomimetic approach can be implemented by two different pathways on terpenoid functionalization, once introduction of functional groups is addressed in a random order at different stages of terpene skeleton evolution, from oligomerization to cyclization and further rearrangements. The first pathway include pre-cyclization functionalization. In fact, as it was presented above, additional functional groups in a terpenic substrate inevitably influence the nature and selectivity of following processes both *in vitro* and *in vivo*. Practically, incorporation of additional functional groups in non-cyclic or partially cyclized terpenic compounds is more facile, since the double bonds of the isoprenic units can be efficiently exploited with the aim of additional functionalization. That's why we have used additional functionalization as a tool to control the direction of biomimetic processes, both involving electronic and steric factors. We succeded to demonstrate that diverse terpenic compounds with specific carbon skeletons and high complexity can be selectively obtained in such a way.

But this path still has disadvantages. The most relevant is caused by the dificulty to forsee the influence of the extra functionalities on the following substrate reactivity. Therefore, the second alternative pathway for the introduction of functional groups in the terpenic structure includes selective functionalization of the already assembled terpenic skeleton. Advantages of this post-cyclization process are firstly connected to the fact that cyclic terpenoids contain fewer reactive double bonds and the functionalization process can be performed more selectively, on the expense of lower reactivity. Besides, cyclic terpenoids possess more rigid conformations, which can contribute more efficiently to the steric control of functionalization process.

In order to exploit this alternative pathway, we have planned to study functionalization of tetracyclic compounds of scalarane structure making use of free radical methods [41],[42]. The ester **42** has been selected as a substrate and its synthesis has been reported previously by a oligomerization-cyclizaton sequence. The goal established for this investigation was to install an oxygenated functional group (**FG**) in the cycle B of tetracyclic system (figure 28). Due to the fact that this cycle contains only saturated C-C and C-H bonds which can be hardly transformed selectively, the only feasible way to effect selective functionalization was considered the so-called radical-relay halogenation (RRH).

The characteristic feature of this reaction is generation of a free radical in the substrate molecule, which must have a suitable functional group **R** as a „handle" for this radical. Once formed, the active radical species must functionalize remotely a nonactivated C-H bond which is sterically conveniently placed in the neighborhood of **R**. The functionalization position is determined both by steric and structural features of the substrate, since only tertiary hydrohen atoms show reactivity in this process and can be successfully involved in functionalizations.

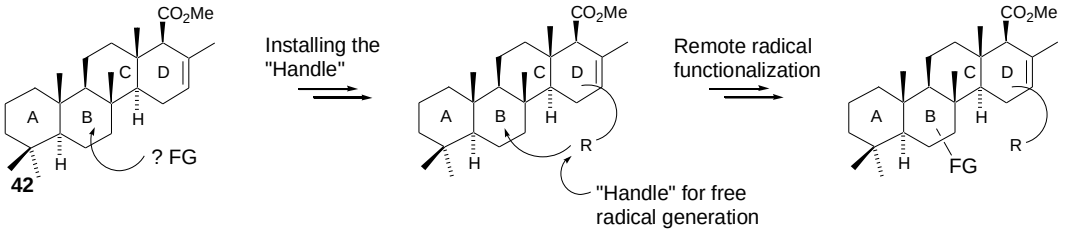


Figure 28. Remote radical halogenation strategy.

The figure 29 presents the real steps for implementation of remote radical halogenation and introduction of two additional functional groups in the scalaranic compound **42**. According to the scheme, the initial ester has been transformed to the allylic alcohol **81**, which served as a joint point for the radical „handle", generated aftewards. This „handle" has bee attached by an esterification reaction with the 3-iodophenylacetic chloroanhydride.

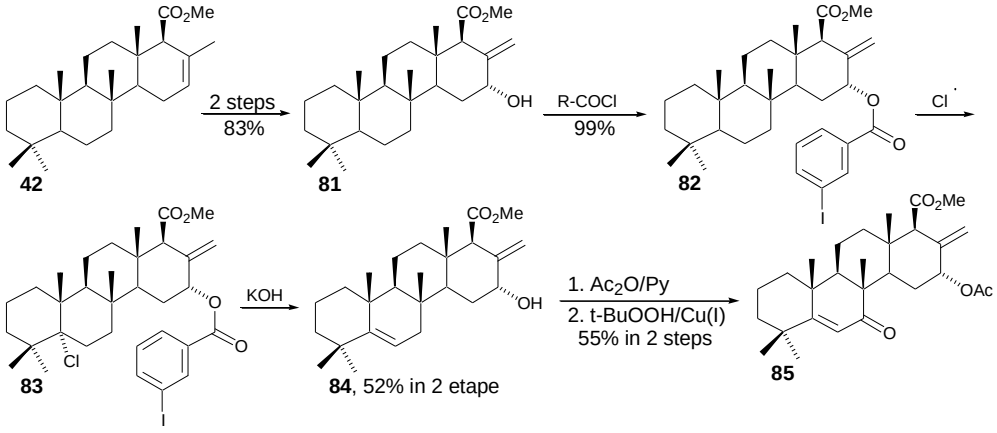


Figure 29. Functionalization of a scalaranic compound by remote radical halogenation.

The resulting ester **82** contains an iodine atom, which can add a chlorine, prone to specific transfer at the nonactivated hydrogen atom site in the tertiary position of B-cycle. The chlorine radical plays the role of an initiator, which efficiently substitute the above mentioned hydrogen from cycle B, forming the chlorinated derivative **83**. Following elimination of hydrochloric acid generates the

double bond in cycle B of ester **84**, which can be functionalized further by different means. In our case, we have performed an efficient allylic oxidation in order to introduce the oxygenated functional group in the structure of scalarane **85**.

The synthesis of cycle B-functionalized scalaranic compounds has been performed for the first time by chemical methods. It is noteworthy mentioning that in recent years several groups of researchers have also reported the synthesis of scalaranes functionalized at other positions of tetracyclic skeleton. But introduction of functional groups in the cycle B of scalaranic framework has currently no other alternatives.

GENERAL CONCLUSIONS AND RECCOMENDATIONS

The main concept presented in the current thesis relates to the principle of random biomimetic synthesis, applied to the natural products of terpenic structure. The basic idea of this concept relies on the hypothesis of intercalating biosynthetic steps in a random order within the whole chain of transformations leading to complex molecular architectures of terpenes. This relatively simple approach provides an efficient tool for modulation of the reactivity of terpenic substrates under conditions of classical organic synthesis. We have clearly demonstrated the interdependence of the sequential synthetic steps which mimic hypothetical biosynthetic paths from oligomerization of individual prenyl units, to cyclizations, rearrangements and oxidative integration of heteroatomic functional groups. The main conclusions can be enumerated as follows:

- Direct oxidative functionalization of open chain terpenoids was efficient in the case of mono- and sesquiterpenes. Van Tamelen epoxidation procedure has been demonstrated in the case of a diterpenic substrate. Two natural products with relevant properties have been obtained by direct oxidation, namely 8-acetoxygeranylacetate - a component of the pheromone of the Australian predaceous bug Oechalia schellenbergii and *trans*-16-hydroxygeranylgeraniol – an inhibitor of peroxide formation in macrophagous cells isolated from the fungus *Boletinus cavipes*.
- Higher terpenoids (di-, sester- and triterpenes) have been assembled predominantly via oligomerization protocols. Fragment coupling has been performed successfully basing on monoterpenic α,ω-bifunctional substrates and other building blocks of diverse complexity, including both open chain and cyclic systems. Allylic phenylsulfones represented convenient substrates for generation of donor synthons on lithiation. As coupling partners both allylic

halogenides and carbonyl compounds have been used. The obtained adducts represent examples of functional groups integration both at chain extremities and middle of the chain.

- An alternative oligomerization procedure based on a $C_3 + C_2$ strategy was shown effective for different substrates, including those with steric hindrances. The tricyclic skeleton of natural cheilanthanes was assembled in optically active form according to this strategy.
- Performing terpene functionalization before cyclization step allowed to control the selectivity of this challenging step. Selective initiation of cyclization cascade from an internal double bond has been achieved when the open chain substrate contained oxygenated functional groups at both α- and ω-ends. Superacidic cyclization of such substrates of sesquiterpenic series led to monocyclic compounds with terminal pendant prenylation of *seco*-eudesmanic structure. Diterpenic α,ω-bifunctionalized substrates have been cyclized into bicyclic compounds with terminal pendant prenylation of sacculatane family. It was the first reported biomimetic synthesis of sacculatanes.
- Intercalation of a specific functional group into the terpenic chain resulted in selective control over superacidic cyclization process, leading to a suspension of the cyclization sequence. The results included formation of partially cyclic compounds with the head units pendant. Open chain sesterterpenic substrates with a *cis*-configured internal double bond have been cyclized to cheilanthanes of regular and rearranged structure in racemic form. Bicyclic sesterterpenes of the same configuration in the lateral chain allowed access to above mentioned compounds in optically active form. Using the readily available bicyclic diterpenoid sclareol under this scenario resulted in the elaboration of an integrated process for the synthesis of sesterterpenes of both tetracyclic scalarane and tricyclic cheilanthane structure.
- Selective suspension of the cyclization cascade was achieved on the intercalation of a phenylsulfonyl functional group in the terpenic chain.
- Ionic liquids of methyl,butyl-imidazolinium series have been shown to represent suitable media for superacidic induced biomimetic-like cyclizations.
- A ring contraction biomimetic process of a homodrimanic epoxide has been applied as the key step for the synthesis of austrodoric acid – a secondary metabolite isolated from the nudibranch *Austrodoris Kerguelenensis*.

- A ring contraction biomimetic process of a drimanic epoxide has been applied as the key step for the synthesis of austrodoral – a secondary metabolite isolated from the nudibranch *Austrodoris Kerguelenensis*.
- Selective rearrangement of a homodrimanic epoxide resulted in the synthesis of compounds possessing the bicyclic skeleton of *ent*-halimanes.
- Intercalation of two electron-withdrawing functional groups into the linear chain of a bicyclic triterpenic substrate resulted in a total inhibition of three double bonds under superacidic cyclization conditions. A very selective skeletal rearrangement was achieved leading to a bicyclic compound - congener of the bicyclic family of natural neopolypodatetraenes.
- Oxidative degradation procedures have been applied for the synthesis of the bicyclic perhydrindane fragment of norrisolide – a rearranged member of spongiane diterpenoids. The potential application of this fragment was demonstrated on its coupling with a highly oxygenated cyclopropanated furan on the way to natural norrisolide synthesis.
- Ozonolytic degradations have been shown as useful tools for terpene functionalization. An unusual ozonolysis of a diene system led to the formation of a functionalized furan *via* a hypothetical mechanism based on the Criegee's intermediates.
- Ozonolytic degradation of sclareol under catalytic conditions in an aqueous solvent allowed for an efficient preparation of sclareoloxide. This degraded diterpene was successfully used as ingredient of various aromatic compositions for tobacco products.
- Functionalization of scalaranic framework has been achieved by a free radical process. The synthesis of cycle B – functionalized scalaranes has been reported for the first time.

To summarize, the current work presents application if a new concept in the biomimetic synthesis of terpenoids. It is based on the random combination of the chemical processes that mimic the known biosynthetic steps. As a result of this concept implementation it was possible to build in a flexible way diverse terpenic substances with a high complexity and functionalization pattern. The starting building blocks have been simple open chain substrates, as well as more complex, but still available cyclic structures, including those bearing chirality.

The flexible combination of the oligomerization-functionalization-cyclization-rearrangement processes allows exploring the reactivity of terpenic substrates in a very unusual and unexpected mode. As the result, diverse classes of terpenic compounds with complex structure have been

obtained. These represent a relevant interest as carriers of relevant bioactivities, being in the same time hardly available from natural sources.

Continuation of these studies can be considered for a broader spectrum of substances, with an extended range of heteroatomic functional groups intercalated in the oligomeric structure of terpenic framework and also under conditions of alternative processing conditions. More exactly, implementation of the novel methods for inactivated C-H functionalization represents currently a hot topic of research worldwide. Normally, such processes are devised under conditions of free radical chemistry application, frequently accompanied by transition metals catalysis. Such an approach is oriented to mimic the action of natural enzymatic oxidations, catalyzed by cytochrome P450 enzymes family. When conjugated to the use of nitrogen- or sulfur-containing functional groups incorporation, this approach can contribute to a more profound exploration of terpenic compounds in the context of medicinal chemistry research.

A relevant field of interest that refers to the use of nonconventional media for biomimetic transformations has been successfully tackled in the presented work. This relates both to aqueous solvents and also to other alternatives like ionic liquids and deep eutectic mixtures. We have demonstrated the positive impact of such systems on catalyst recycling in the case of processes with industrial perspectives, as well as in connection to the reduced environmental impact of low vapor pressure solvents. Given the broad availability of terpenic substrates from renewable resources, such a combination is perfectly in line with modern green chemistry approaches for a sustainable development.

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ADNOTARE

Numele de familie, prenumele autorului: KULCIŢKI Veaceslav.
Titlul tezei: Sinteza Compuşilor Terpenici cu Funcţionalizare Avansată prin Metode Biomimetice.
Gradul ştiinţific solicitat: Doctor habilitat în chimie.
Localitatea: or. Chişinău.
Anul perfectării tezei: 2017.
Structura tezei: Introducere, 5 capitole, dintre care primul reprezintă sinteza datelor literare, iar următoarele 4 capitole includ rezultatele cercetărilor experimentale proprii la subiectul tezei, urmate de concluzii generale şi recomandări, bibliografia cu 266 de titluri, 218 pagini de text de bază, 122 figuri şi 7 tabele.
Numărul de publicaţii la temă: Rezultatele obţinute au fost publicate în 42 lucrări ştiinţifice.
Cuvinte-cheie: chimie organică, sinteză organică, terpenoide, ciclizare, regrupare, funcţionalizare, biomimetic, prenilare.
Domeniul de cercetare: chimia organică.
Scopul şi obiectivele lucrării: În virtutea faptului că majoritatea compuşilor terpenici care reprezintă interes practic au schelete carbonice complexe şi funcţionalizare avansată cu heteroatomi, scopul primordial al acestei lucrări a fost elaborarea metodelor de sinteză a diverse clase de compuşi terpenici prin combinarea flexibilă a proceselor biomimetice de oligomerizare, ciclizare, regrupare şi funcţionalizare dirijată. Obiectivele specifice ale lucrării au inclus sinteza compuşilor terpenici din diferite serii oligomerice cu funcţionalizare diversă şi cercetarea lor în reacţiile de ciclizare, regrupare şi funcţionaluzare cu heteroatomi.
Noutatea şi originalitatea ştiinţifică: În lucrarea prezentă a fost demonstrată influenţa majoră a grupelor funcţionale din scheletul terpenoidelor asupra reacţiilor de ciclizare/regrupare *in vitro*. Aceasta a permis de a elabora căi de sinteză foarte eficiente a terpenoidelor complexe. Completarea acestor metode cu reacţiile de funcţionalizare spaţială post-ciclizare lărgerşte şi mai mult arsenalul de metode sintetice disponibile pentru generarea întregii diversităţi structurale a terpenoidelor, pregătind astfel terenul pentru studii profunde ale utilităţii compuşilor terpenici în ansamblu.
Rezultatele principial noi pentru ştiinţă şi practică obţinute: În cadrul tezei curente a fost demonstrată viabilitatea combinării succesive a diferitor procese biomimetice pentru sinteza compuşilor terpenici cu diverse structuri. Faptul complexităţii avansate a căilor biogenetice care conduc la diversitatea enormă a terpenoidelor a permis de a înainta ipoteza intercalării etapelor biosintetice în mod flexibil. Această abordare strategică a fost numită *Sinteză Biomimetică Aleatorie*. În urma verificării şi valorificării ipotezelor înaintate în cadrul îndeplinirii lucrării curente, au fost realizate sinteze ale reprezentanţilor a 15 diverse clase de compuşi terpenici.
Semnificaţia teoretică şi valoarea aplicativă a lucrării: Relevanţa teoretică primordială a lucrării se bazează pe lansarea principiului *Sintezei Biomimetice Aleatorii* în planificarea sintezelor compuşilor naturali cu structură complexă. De asemenea, studiul profund al compuşilor naturali a condus la identificarea unei noi super-familii de terpenoide ciclice cu grupe prenil terminale pendante. Implementarea rezultatelor ştiinţifice menţionate mai sus s-a exprimat în sintezele a 7 compuşi naturali sau precursori apropiaţi. De asemenea, iniţierea studilor reacţiilor de degradare ozonolitică în medii apoase a condus la brevetarea unei metode eficiente de obţinere a sclareoloxidului – compus important, utilizat în caltate de component al compoziţiilor de aromatizare.

ANNOTATION

First name, Last name: Veaceslav KULCIŢKI.
Thesis title: Synthesis of Terpenic Compounds with Advanced Functionalization via Biomimetic Methods.
Academic degree: doctor habilitate in chemistry.
Place: Chisinau, Moldova
Year of presentation: 2017.
Thesis structure: Introduction, 5 chapters, the first representing literature review and the next 4 chapters integrating the results of own investigations on the thesis subject, followed by general conclusions and recommendations, bibliography – 266 references, 218 pages of the main text, 122 Figures and 7 tables.
Number of publications: research results have been published in 42 scientific works.
Key words: Organic chemistry, organic synthesis, terpenoids, cyclization, rearrangement, functionalization, biomimetic, prenylation.
Field of research: Organic chemistry.
The aim and objectives of the thesis: Due to the fact that the majority of terpenic compounds which represent practical interest have complex carbon backbones and advanced functionalization with heteroatoms, the main aim of the current work was elaboration of synthesis methods for diverse classes of terpenic compounds by a flexible combination of major biomimetic processes, including oligomerization, cyclization, rearrangement and selective functionalization. The specific objectives of the work included the synthesis of terpenic compounds of different oligomeric series, having diverse functionalization pattern and their investigation in cyclization, rearrangement and heteroatom functionalization reactions.
Scientific novelty and originality of the research: A major influence of the functionalization pattern in the terpenoid skeletons on the cyclization/rearrangement reactions *in vitro* has been demonstrated in the present work. Addition of post-cyclization functionalization reactions to these synthetic transformations enlarge even more the arsenal of available synthetic tools for the generation of the entire structural diversity of terpenoids, preparing the ground for advanced studies on terpenic compounds utility in general.
Conceptually novel scientific results for basic and applied science achieved: The current thesis has demonstrated the viability of the successive combination of different biomimetic processes for the synthesis of terpenic compounds with diverse structures. The relevant complexity of biogenetic paths which lead to the enormous structural diversity of terpenoids has prompted us to launch the hypothesis of the flexible combination of biosynthetic steps within biomimetic synthesis strategies. This approach has been defined as *Random Biomimetic Synthesis*. As a result of verification and valorization of thesis hypothesis, the synthesis of representatives from 15 different classes of terpenic compounds has been realized.
Theoretical and application value of the research: The main theoretical relevance of the work is based on the coining the *Random Biomimetic Synthesis* principle in planning the synthesis of complex natural product. The deep study of natural products with some specific structural features, basing on the same biogenetical root, has led to the identification of a super-family of cyclic terpenoids with terminal pendant prenyl groups. Implementation of the above mentioned scientific results has been expressed in the synthesis of 7 natural products or close precursors. In addition, initiation of research on ozonolytic cleavage of terpenoids in aqueous solvents has led to patenting of an efficient method for the production of sclareoloxide – an important compound with a broad use as component of aromatization compositions.

АННОТАЦИЯ

Фамилия, имя автора: КУЛЬЧИЦКИЙ Вячеслав.
Название диссертации: Синтез Высоко-Функционализированых Терпеновых Соединений Биомиметическими Методами / **Соискание ученой степени:** доктора хабилитат химических наук / **Место защиты:** г. Кишинёв / **Год представления диссертации:** 2016 / **Структура диссертации:** введение, 5 глав, из которых первая является обзором литературы, а последующие 4 включают результаты собственых иследований на тему диссертации, а также общие выводы и рекомендации, библиография - 266 источников, 218 страниц основного текста, 122 рисунков и 7 таблиц / **Количество публикаций по теме:** результаты опубликованы в 42 научных работах / **Ключевые слова:** органическая химия, органический синтез, терпеноиды, циклизация, перегрупировки, функционализация, биомиметика, пренилирование / **Цель и задачи исследования:** Исходя из того что большинство терпеновых соединений которые представляют практический интерес имеют сложные структуры и высокую степень функционализации гетероатомами, главная цель настоящей работы была разработка методов синтеза различных классов терпеноидных соединений путем гибкого комбинирования биомиметических процессов олигомеризации, циклизации, перегрупировки и целенаправленой функционализации. Задачи исследования включили синтез терпеноидов из разных олигомерных серий с различной функционализацией и их иследование в реакциях циклизации, перегрупировки и дальнейшего функционализирования гетероатомами. **Научная новизна и оригинальность исследования:** В рамках настоящей работы было выявлено особое влияние функциональных групп на ход реакций циклизации/перегрупировки *in vitro*. Это позволило разработать высоко-эфективные пути синтеза сложных терпеноидов. Дополнение этого подхода методами пост-циклизационной пространственной функционализации, намного расширяет арсенал доступных синтетических приемов для генерации более широкого структурного разнообразия терпеноидов, приготавливая таким образом почву для применеия терпеновых соединений вообще. **Принципиально новые результаты полученые для науки и практики:** В настоящей работе была доказана возможность последовательного комбинирования различных биомиметических процессов для синтеза терпеновых соединений различной структуры. Факт повышеной сложности биогенетических путей которые приводят к огромному разнообразию структур природных терпеноидов, привел к выдвижению гипотеза интеркаляции биосинтетических этапов гибким способом. Данный стратегический подход был назван *Алеаторным Биомиметическим Синтезом*. В ходе проверки и применении гипотез выдвинутых в настоящей работе, были выполнены синтезы представителей 15 различных структурных групп терпеновых соединений. **Теоретическое и практическое значение работы:** Основная теоретическая значимость работы основывается на выдвижении принципа *Алеаторного Биомиметического Синтеза* в планировании синтеза природных соединений с сложной структурой. Также в ходе глубокого исследования природных терпеноидов с специфическими структурными особенностями привело к выявлению нового сверх-семейства циклических терпеноидов с пендантными терминальными пренильными групами. Внедрение вышеуказаных результатов выразилось в синтезе 7 природных соединений или их близких аналогов. Кроме того, начало иследований озонолитического расчепления в водных средах позволило запатентировать эфективный метод синтеза склареолоксида – важного соединения применяемого в качестве компонента ароматических композиций.

KULCIŢKI VEACESLAV

SINTEZA COMPUŞILOR TERPENICI CU FUNCŢIONALIZARE AVANSATĂ PRIN METODE BIOMIMETICE

SPECIALITATEA 143.01 CHIMIE ORGANICĂ

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