THE INSTITUTE OF CHEMISTRY

With manuscript of title
UDC: 547.596/.597:577.1 (043.3)

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SYNTHESIS OF POLYFUNCTIONALIZED TERPENIC DERIVATIVES *VIA* RADICAL AND CATIONIC REACTIONS

143.04 – BIOORGANIC CHEMISTRY, CHEMISTRY OF NATURAL AND PHYSIOLOGICALLY ACTIVE COMPOUNDS

Summary of the PhD thesis in chemical science

CHIȘINĂU, 2020

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The public defence of the thesis will take place on June 16, 2020, 14:00 in the session of the specialized scientific Council D 143.04-05 from the Institute of Chemistry (small hall, Institute of Chemistry, 3rd floor, Academiei 3 str., Chișinău, Republic of Moldova MD-2028).

The doctor thesis and the summary can be found in the Central Scientific Library ”*Andrei Lupan*” and on the web page of ANACEC (www.cnaa.md).

The summary of the thesis has been posted on May 14, 2020.

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CONCEPTUAL LANDMARKS OF THE INVESTIGATION

Timeliness of the subject

Natural products are an invaluable resource for the discovery of therapeutic agents, sometimes directly or more often as “natural product-derived” analogues. They have played an important role in guiding researchers to develop amazing compounds with promising biological activities. The achievement of selective chemical modifications of these complex natural structures is highly challenging. Thus, simple procedures involving a very limited number of steps should allow accessing new, complex analogues that might provide improved pharmacological properties. Since many complex terpenoids are becoming easily available *via* biotransformation processes, their modification may represent one of the most efficient and straightforward approaches for the development of drug and therapeutic candidates.

The total synthesis of natural products and analogues has proven over the years its efficiency for the discovery of optimization of drug candidates. However, this approach becomes extremely laboratory consuming and costly when complex natural products are targeted. Nowadays, an increasing number of natural products can be prepared efficiently *via* isolation processes. These products are becoming very attractive starting material for the preparation of analogues and derivatives. Therefore, the development of reactions, allowing site-selective modification of natural products is highly demanded. Due to the presence of several functional groups in most of the natural products, chemistry has to set very strict requirements in term of selectivity and reactivity. Despite their very high reactivity radicals tolerates a wide range of functional groups, and therefore may play an important role for site-selective modification of natural products. The potential of this approach is particularly significant when the natural products are readily available from natural sources or by biotransformation processes. Therefore, the isolation of terpenoids from plant wastes, such as sunflower and sage, has proven to be the most effective resource them in our research study.

As we know, terpenoids are one of the most numerous and important classes of natural compounds which are isolated from different natural sources. They have been used by humans in the food, pharmaceutical, and chemical industries. Whereas, due to their diverse biological activities, they have simulated intensive medicinal chemistry studies, culminating in sound results and relevant applications. For this reason, the chemical transformation of the relatively abundant natural substances is an important and promising direction of chemistry and is currently the subject of numerous theoretical and applicative investigations, and the

functionalization and modification of their carbon skeleton is a problem of major fundamental and applicative importance.

The aim of the thesis

Due to the presence of several functional groups in most of the natural products with promising biological activities, the aim of the current work was functionalization of the available terpenoids *via* radical reactions, especially, the introduction of the functional groups (-N_3, -CF_3, -I, etc.) which improve biological activities of the starting terpenic compounds, and the synthesis of hardly available compounds with halimane, hyrtiosane and *ent*-verrucosin skeleton by using cationic isomerization reactions.

The research objectives

- ✓ Application of radical reactions, such as hydroazidation, carboazidation and carbohydrogenation for the functionalization of terpenic compounds;
- ✓ Elaboration of methods of diversifying the structure of functionalized compounds radically;
- ✓ Introduction of the fluoride groups into terpenic compounds by the carbohydrogenation reactions;
- ✓ Conversion of the resulting azides into amines, amides, triazoles and guanidines which have a high potential for the biological activity;
- ✓ Synthesis of the functionalized terpenic compounds being key intermediates in the pharmaceutical and medicinal chemistry;
- ✓ Skeletal rearrangements of terpenes *via* cationic reactions in the production of the compounds with halimane, hyrtiosane and *ent*-verrucosin skeleton;
- ✓ Determination of the structure of resulting compounds through modern analysis, such as ^{1}H, ^{13}C, ^{19}F NMR, IR, HRMS and X-ray diffraction.

The research hypothesis

One of the current challenges of organic synthesis is the need to introduce various functional groups into the structure of interest compounds. This problem is increasingly important for the chemistry of natural compounds, which, on the one hand, are present in terrestrial or marine sources in very small amount, and on the other hand, their use as objects of applicative studies requires a flexible modification of the structure through the introduction of heteroatomic functional groups. For this reason, the elaboration of the methods for the efficient functionalization of the natural compounds in preparative quantities and will remain a major topical problem in organic synthesis.

The most often "requested" functional groups in the structure-activity studies, as we have noticed, are the oxygenated and nitrogen derivatives, which are important biomimetic functional groups. The presence of these functional groups offers a specific interaction of small molecules, with potential for biological activity, with biomacromolecules that represent mediators of biochemical processes in the living systems. In this context, obtaining the polyfunctional derivatives of terpenic compounds is a logical approach, as the importance of isoprene derivatives in cellular biochemical processes is well known.

The synthesis of the research methodology and justification of the research methods

All modern physico-chemical methods of analysis of the products were used to achieve the above objectives. The NMR spectra were recorded on a Bruker AVANCE-300 and on a Bruker AVANCE II-400. Infrared spectra were recorded on a Jasco FT-IR-4700 spectrometer and the values are reported in wave numbers (cm^{-1}). HRMS analyses and elemental composition determinations were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer using ESI and NSI mode. The X-Ray experiments are carried out using Oxford Diffraction (now Agilent) SuperNova equipped with Mo micro-source and Oxford cryosystem 700 for low/high temperature measurements.

All reactions were performed under nitrogen atmosphere, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) performed on SILICYCLE silica gel 60 Å (F-254) analytical plates followed by visualization under UV light (254 nm) or dipping in the different staining solutions: $KMnO_4$ (5 g), Na_2CO_3 (30 g), in H_2O (500 mL); ammonium molybdate (50 g), cerium sulfate (2 g), H_2SO_4 (conc. 100 mL) in H_2O (1000 mL). Sodium sulfate was used as a drying agent. Yields refer to chromatographically or spectroscopically pure compounds. Silica gel 60 Å (63-200 μm) was used for column chromatography. All commercial reagents have been used as received from the supplier.

Thesis overview

The thesis contains 111 pages of the main text, 65 figures, 6 tables, 203 references, annotation in three languages, list of abbreviations and symbols, introduction, 4 chapters: the first representing the literature review and next 3 chapters include the experimental results on the thesis, general conclusions and recommendations, declaration on the assumption of responsibility and author’s CV.

THESIS CONTENT

Chapter I. Functionalization and rearrangement of natural compounds *via* free radical and cationic induced reactions

1.1. The radical C-H functionalization of natural compounds

The first subchapter presents a literature review of the radical chemistry, exactly C-H functionalization of natural compounds using radical reactions [1]. Thus, in the structures of the terpenic compounds can be introduced different functional groups that can be further used as intermediates for the drugs in the medicinal chemistry.

1.2. The C-C and C-X bonds formation *via* atom transfer radical addition methodology

In the second subchapter were presented the most relevant publications of creating C-C and C-X bonds using atom transfer radical addition methodology (ATRA).

1.3. Recent examples of natural compounds synthesized *via* cationic reactions

In the last subchapter were presented recent syntheses of natural compounds by using cationic skeleton rearrangements that are found in vegetal sources in a small amount.

Chapter II. Radical transformations of *ent*-kaurane diterpenoids

Kaurane diterpenes have diverse biological activities and have been identified from numerous medicinal plants. Functionalization of *ent*-kaurane derivatives can lead to the formation of different products that may have more pronounced biological activities than the starting derivatives. In this chapter, methyl *ent*-kaurenoate and its derivatives have undergone radical transformations, such as hydroazidation, carboiodination, carboazidation and carbohydrogenation.

2.1. Hydroazidation of methyl *ent*-kaur-16-en-19-oate

Radical hydroazidation of **1** led to the formation of azide **2** in a good yield and its spectral data confirmed the selectivity of addition (Figure 2.1) [2].

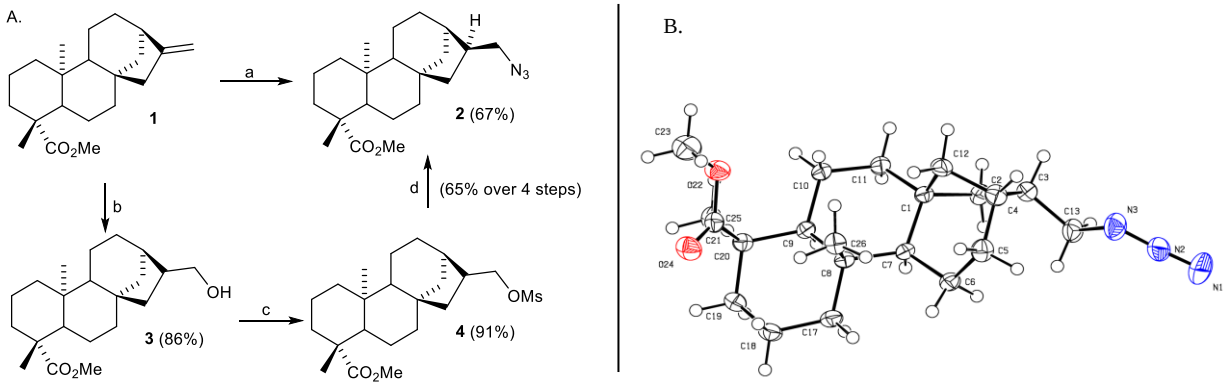

Fig. 2.1. A. Hydroazidation of methyl *ent*-kaurenoate. B. X-ray structure of azide 2.
Reagents and conditions: **a.** CatBH (3 equiv.), DMA (0.1 mmol), DCM; 3-$PySO_2N_3$ (3 equiv.), DMF, DTBHN (0.1 mmol); **b.** BH_3•Me_2S, THF; NaOH, H_2O_2; **c.** MsCl, Et_3N, DCM; **d.** NaN_3, DMF.

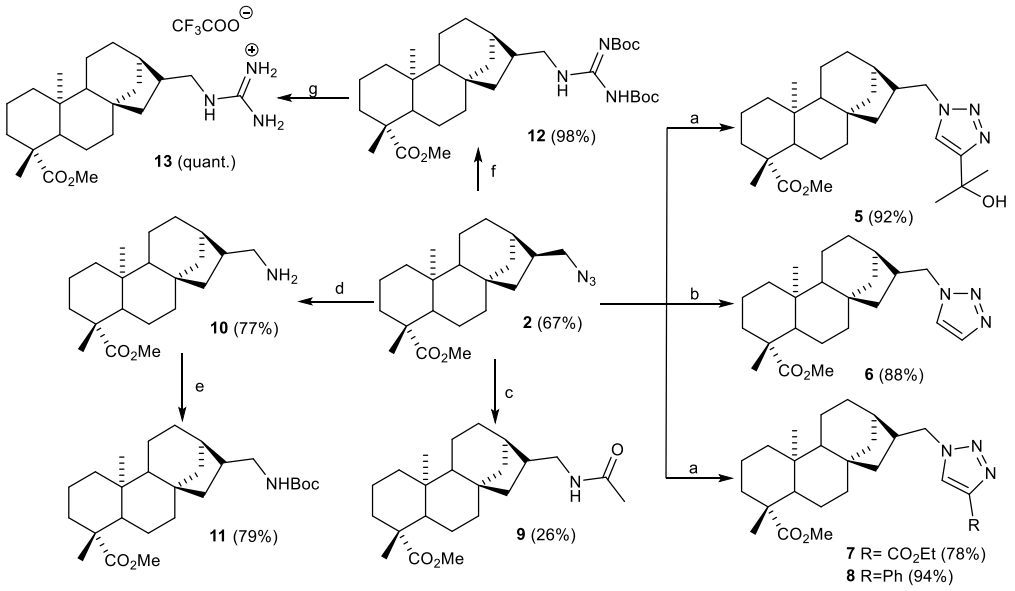

Fig. 2.2. Transformations of methyl 17-azido-*ent*-kaurenoate.
Reagents and conditions: **a.** CuI, DIPEA, AcOH, alkynes (1. $HC{\equiv}CC(CH_3)_2OH$, 2. $HC{\equiv}CCO_2C_2H_5$, 3. $HC{\equiv}CC_6H_5$), DCM; **b.** CuI, sodium ascorbate, DBU, propiolic acid, DMF; **c.** AcCl, Ph_3P, C_6H_6; **d.** Ph_3P, H_2O, THF; **e.** Boc_2O, Et_3N, THF; **f.** H_2, Pd/C, triflyl guanidine, DIPEA, EtOAc; **g.** TFA.

In our hands, the alternative procedure gave the azide **2** identical in all aspects with material obtained *via* radical hydroazidation. This is an additional proof of the suggested stereochemistry, which was finally demonstrated basing on the X-ray crystallographic analysis of **2** (Figure 2.1B). Following transformation of azide **2** included click reactions with a set of alkynes, obtaining triazoles (**5-8**), and its reduction under mild conditions to furnish amine **10** and amides (**9-11**) and guanidine **12**. The resulting di-boc-guanidine **12** was obtained in 98% yield, followed by deprotection with trifluoroacetic acid generated guanidine **13** (Figure 2.2). The triazoles **5-8** and amine **10** have been tested for cytotoxicity and toxicity on different bacteria and fish. Surprisingly, the amine **10** showed relevant cytotoxicity against several tumor cell lines, including Capan-1 (pancreatic adenocarcinoma) and NCI-H460 (pulmonary carcinoma) at 10^{-7} Mol/L concentrations (Table 2.1). A paralel zebrafish (*Danio rerio*) toxicity tests showed negligible *in vivo* toxicity of the title compound **10** [3].

Table 2.1. Cytotoxic activities of amine 10 against selected cell lines.

Compound	Conc. unit	IC_{50}								
		hTERT RPE-1	Capan-1	Hap-1	HCT-116	NCI-H460	DND-41	HL-60	K-562	Z-138
10	μM	7.7	0.8	1.8	1.1	0.7	1.7	2.0	8.3	1.2

2.2. Carboazidation and carboiodination of *ent*-kaurane derivatives

Radical carboazidation became a very useful tool for preparation of alkyl azides due to mild reaction conditions as well as good levels of chemoselectivity. Carboazidation reaction of methyl *ent*-kaurenoate **1** with ethyl iodoacetate led to full consumption of the starting material in only 2 h. The reaction product **15** was obtained in 83% yield. Therefore, *ent*-kaurenoic acid **14** treated with ethyl iodoacetate as a radical precursor and phenyl sulfonyl azide, afforded the azide **16** in 70% yield. Because the product was contaminated with hexabutylditin, azide was methylated with an ethereal solution of diazomethane. Carboazidation of methyl *ent*-kaurenoate **1** with 3 equiv. of triethylborane gave the desired product **15** in good yield (60%), and the reaction between *ent*-kaurenoic acid **14** and triethylborane afforded azide **16** in similar yields (Figure 2.3).

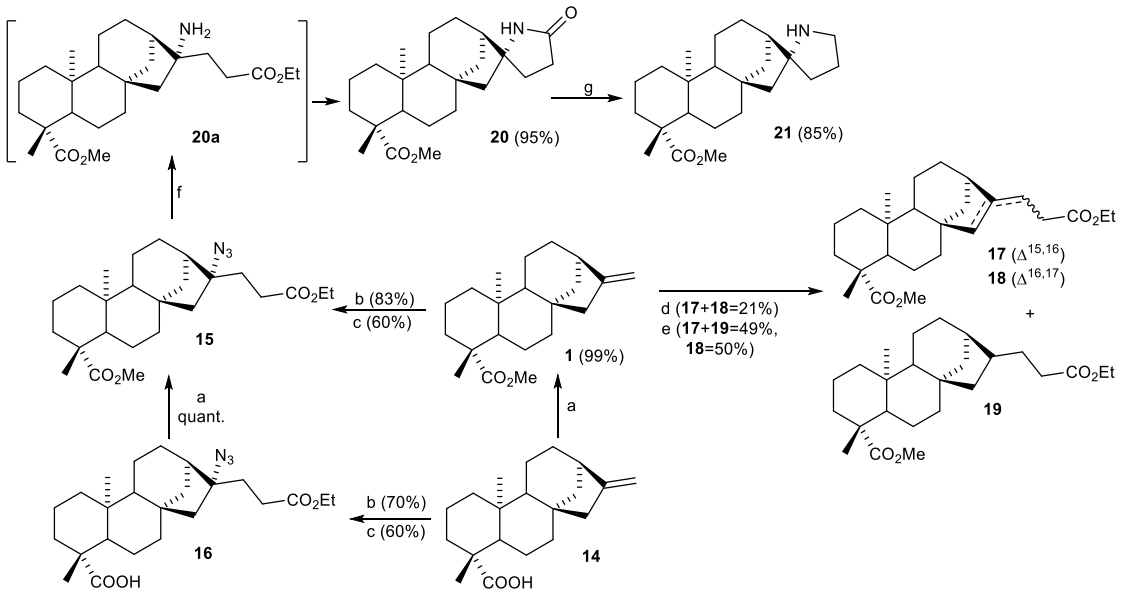

Fig. 2.3. Carboazidation and carboiodination of methyl *ent*-kaurenoate 1.

Reagents and conditions: **a.** CH_2N_2, Et_2O; **b.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 2 h; **c.** ICH_2CO_2Et (2 equiv.), $PhSO_2N_3$ (3 equiv.), Et_3B (3 equiv.), r.t., overnight; **d.** ICH_2CO_2Et, DLP, benzene, Δ, 24 h; **e.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 2 h; **f.** H_2, Pd/C (10% w/w), EtOAc, r.t., 48 h; **g.** $NaBH_4$, I_2, THF, Δ, 8 h.

Carboiodination reaction of methyl *ent*-kaurenoate **1** took place under two different conditions. First, treatment of **1** with ethyl iodoacetate in the presence of dilauroyl peroxide (DLP) as a radical initiator in refluxing benzene led to a complex mixture. Chromatographic separation of the crude afforded 21% of the mixture **17** and **18** and approximately 40% of starting material **1**. Unfortunately, the iodinated product has involved in a process of HI elimination, with the formation of unsaturated products **17** and **18** after 24 h of reflux.

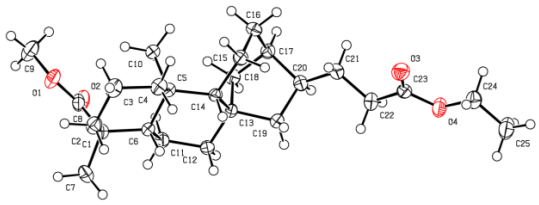

Fig. 2.4. X-Ray structure of compound 19.

Carboiodination using Bu_6Sn_2 as a radical transfer reagent and di-*tert*-butyl hyponitrite (DTBHN_ as radical initiator improves the yield of the reaction and led to the formation of a new product. The starting material was consumed within 2 h and the formation of a mixture of three products in 99% yield was observed. The unsaturated compounds **17** and **18** were obtained in 75% total yield. The saturated product **19** was formed in 24% yield and its structure was determined by X-ray diffraction (Figure 2.4). The azide **15** was converted into lactam **20** by simple hydrogenation with 1 atmosphere of H_2, was catalyzed by Pd/C in ethyl acetate. The stereochemistry was determined by X-Ray diffraction (Figure 2.5). The lactam **20** is reduced by sodium borohydride and iodine in THF, and converted into pyrrolidine **21** in 85% yield (Figure 2.3).

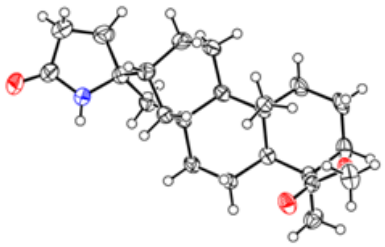

Fig. 2.5. X-Ray structure of compound 20.

As in the previous case of methyl *ent*-kaurenoate **1** transformations shown in Figure 2.3, methyl 15α-hydroxy-*ent*-kaurenoate **22** was used in the same carboazidation and carboiodination reactions. Treatment of **22** with ethyl iodoacetate, DLP as a radical initiator on heating at 95 ℃ in benzene led to the formation of a mixture of two compounds. Following acetylation of reaction products with acetic anhydride and DMAP in pyridine led to the formation of lactone **23** in 11% yield and unsaturated compound **24** in 24% yield. Unexpectedly, submission of **22** to radical carboazidation conditions led to the formation of the same products as in the carboiodination reaction in 22% yield. Carboazidation reaction of methyl 15α-hydroxy-*ent*-kaurenoate **22** with ethyl iodoacetate, triehtylborane (1M in THF) at room temperature led to the formation of a mixture *cis* **25** and *trans* **26** in a 1:1 ratio according to ^{1}H spectrum (Figure 2.6). The unsaturated compounds were easily separated by column chromatography.

Carboazidation of alcohol **22** was performed with iodoacetic acid as a radical precursor, phenyl sulphonyl azide as azide source and DTBHN as radical initiator, in refluxing benzene. The crude reaction product was methylated with an ethereal solution of diazomethane leading to compound **24** in 42% yield and the lactone **23** in 28% after cyclization. The structure of lactone was demonstrated based on X-ray diffraction (Figure 2.6). Azide **27** was further converted into lactam **28** by hydrogenation reaction under 1 atmosphere of H_2, catalyzed by Pd/C in ethyl acetate. The hydroxyl group was further protected using *tert*-butyldimethylsilyl chloride and

imidazole in dimethylformamide. The corresponding ether **29** was treated with ethyl iodoacetate, 3-$PySO_2N_3$ and DTBHN after which provided azide **30** in 73% yield. Treatment of azide **30** with TBAF in THF led to the formation of azide **31** in 51% yield (Figure 2.7).

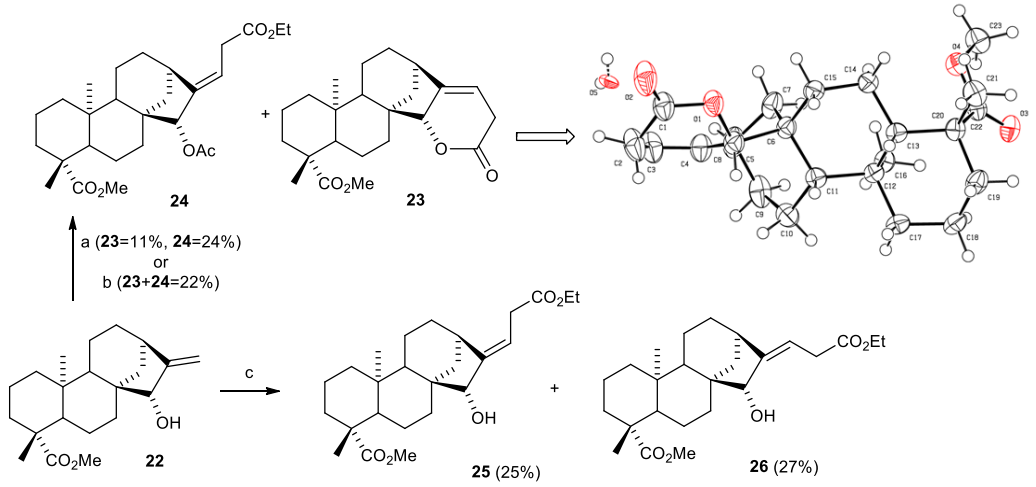

Fig. 2.6. Carboazidation and carboiodination of methyl 15α-hydroxy-*ent*-kaurenoate.
Reagents and conditions: **a.** ICH_2CO_2Et, DLP, benzene, Δ, 24 h then Ac_2O, DMAP, Py; **b.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 5 h then Ac_2O, DMAP, Py; **c.** ICH_2CO_2Et (2 equiv.), $PhSO_2N_3$ (3 equiv.), Et_3B (3 equiv.), r.t., overnight.

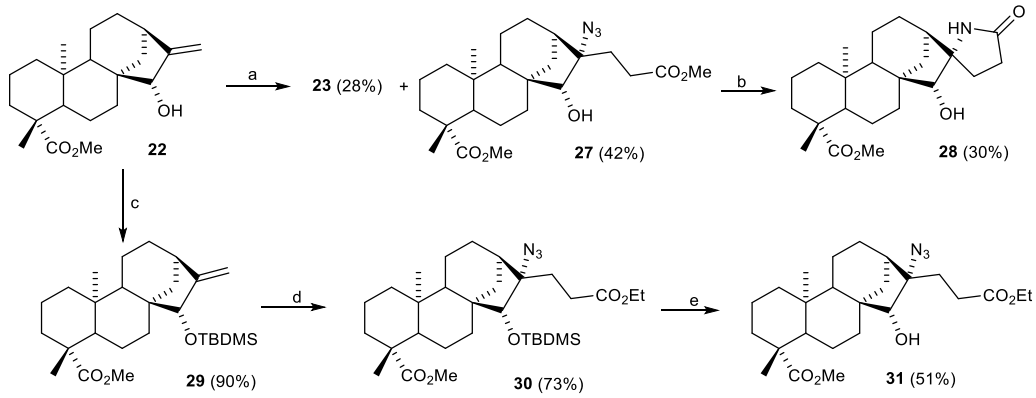

Fig. 2.7. Carboazidation and carboiodination of methyl 15α-hydroxy-*ent*-kaurenoate.
Reagents and conditions: **a.** ICH_2COOH (2 equiv.), Bu_6Sn_2 (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 5 h then CH_2N_2; **b.** H_2, Pd/C (10% w/w), EtOAc, r.t., 64 h; **c.** imidazole (4 equiv.), TBDMSCl (2 equiv.), DMF, r.t., 12 h; **d.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), 3-$PySO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 10 h; **e.** TBAF (3 equiv.), THF, r.t., 12 h.

2.3. Carbohydrogenation of *ent*-kaurane derivatives

Carbohydrogenation of methyl *ent*-kaurenoate **1** with iodo-radical precursor under very mild conditions, in the presence of triethylborane and air as a radical initiator and 4-*tert*-butylcatechol as a reducing agent afforded good results. The hydroalkylation of methyl *ent*-kaurenoate **1** with ethyl iodoacetate led to quick consumption of the starting material and the desired product **32** was obtained in 86% yield (Figure 2.8). The structure of compound **32** was

confirmed using the NMR data, HRMS and IR analysis. The reaction of olefin **1** with iodomethylphenylsulfone during 2 h gave the product **33** in 75% yield. Carbohydrogenation using isobornyl iodoacetate afforded the desired product **34** in 84% yield. Contrary to our expectations, the reaction with dihydrocholesteryl iodoacetate as a radical alkylating reagent was unsuccessful and 70% of the starting material was recovered after purification.

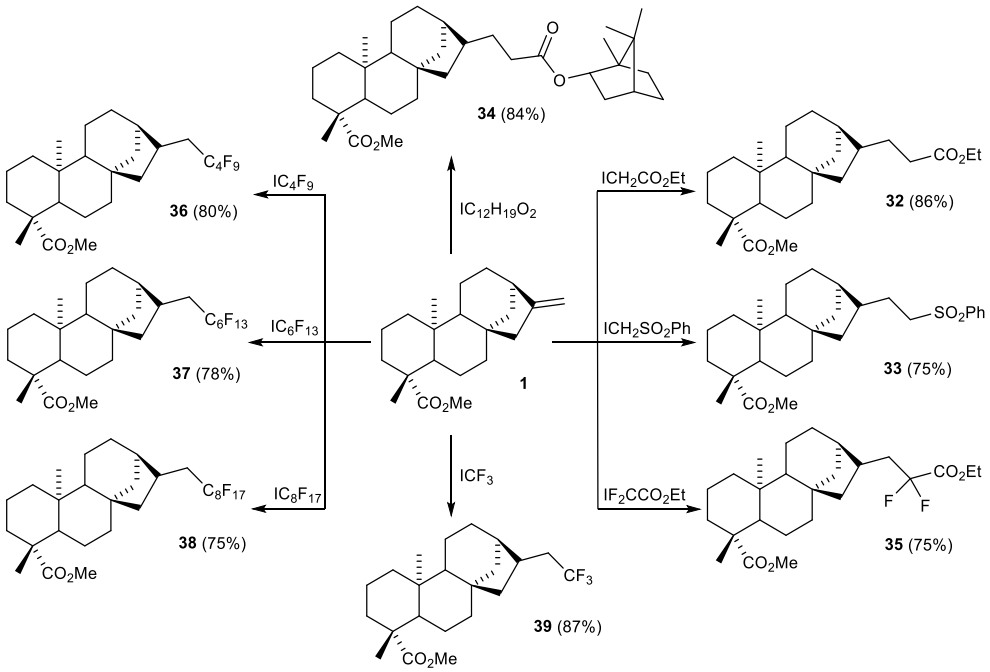

Fig. 2.8. Carbohydrogenation of methyl *ent*-kaurenoate.
Reagents and conditions: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

Treatment of ester **1** with ethyl difluoroacetate (1.2 equiv.), triethylborane (1.3 equiv.) and TBC (2 equiv.) as a radical reductant gave the product **35** in good yield (75%). Surprisingly, carbohydrogenation of methyl *ent*-kaurenoate **1** with perfluoroalkyl iodides afforded desired products (**36-39**) in excellent yields (Figure 2.8).

Unexpectedly, hydroalkylation of methyl 15α-hydroxy-*ent*-kaurenoate **22** led to the elimination of hydroxyl group and formation of the double bond in the cycle D. Treatment of the compound **22** with ethyl iodoacetate as a radical precursor and 4-methoxycatechol as a reducing agent afforded the product **40** in 40% yield and decomposition of the initial olefin. The reaction of **22** with ethyl difluoroiodoacetate led to the formation of compound **41** in 43% yield, whereas *iso*-bornyl iodoacetate afforded the product **42** in 50% yield. The structure of all isolated products was confirmed by spectral data. We proposed that on carbohydrogenation of methyl 15-hydroxy *ent*-kaurenoate **22** the protonation of hydroxyl group occurred under the action of the

slightly acidic 4-methoxycatechol, followed by water elimination and formation of the double bond (Figure 2.9).

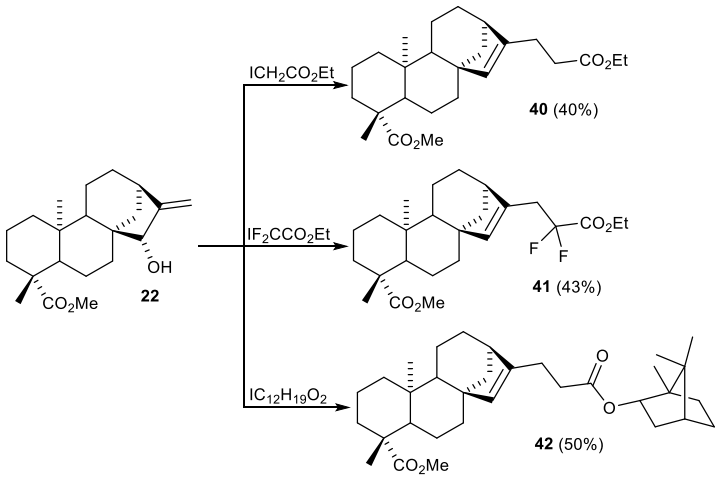

Fig. 2.9. Carbohydrogenation of methyl 15α-hydroxy-*ent*-kaurenoate.
Reagents and conditions: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

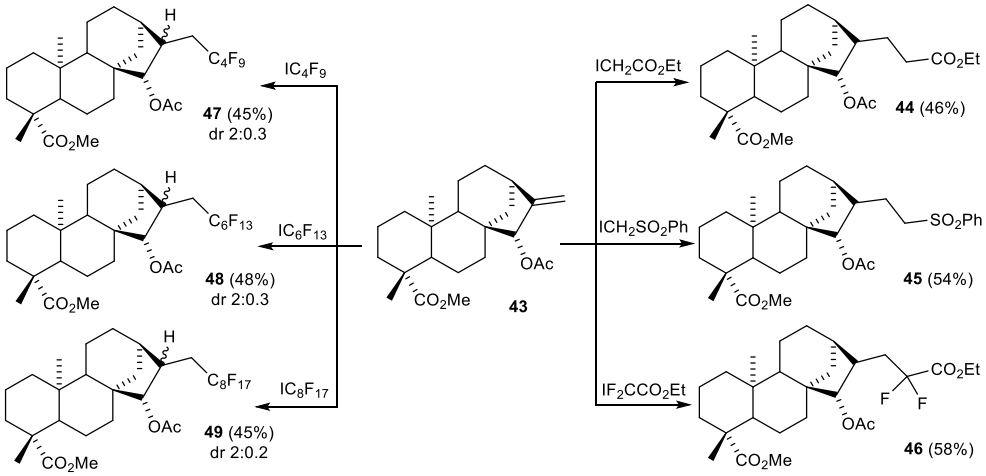

Fig. 2.10. Carbohydrogenation of methyl 15α-acetoxy-*ent*-kaurenoate.
Reagents and conditions: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

Carbohydrogenation reactions with methyl 15α-acetoxy-*ent*-kaurenoate **43** were not so selective and the yields were lower than when methyl *ent*-kaurenoate was used. Treatment of methyl 15α-acetoxy-*ent*-kaurenoate **43** with ethyl iodoacetate afforded the desired product **44** in only 46% yield (Figure 2.10). Hydroalkylation of **43** with iodomethylphenylsulfone provided the compound **45** in 54% yield. Reaction with ethyl difluoroiodoacetate as radical precursor and 4-methoxycatechol at room temperature afforded the difluoro product **46** in moderate yield (58%) [4]. Coupling of olefin **43** with perfluoroalkyl iodides led to formation of epimers (**47-49**) at C-16 position according to ^{1}H spectrum. The resulting epimers were not individually separated

(Figure 2.10). The hydroalkylation of olefin **43** with trifluoroiodomethane failed, only decomposition of the starting material was observed.

Chapter III. Radical transformations labdanic and isocopalic diterpenoids

3.1. Hydroazidation of *epi*-manoyl oxide

Anti-Markovnikov hydroazidation of **50** was performed according to the procedure reported by Renaud [5] and the azide **51** was obtained in 40% yield. Following transformation of azide **51** included its reduction under mild conditions to furnish amine **56** and click reaction with a set of alkynes. The structure of the obtained triazoles **52-55** was elucidated basing on spectral data (Figure 3.1).

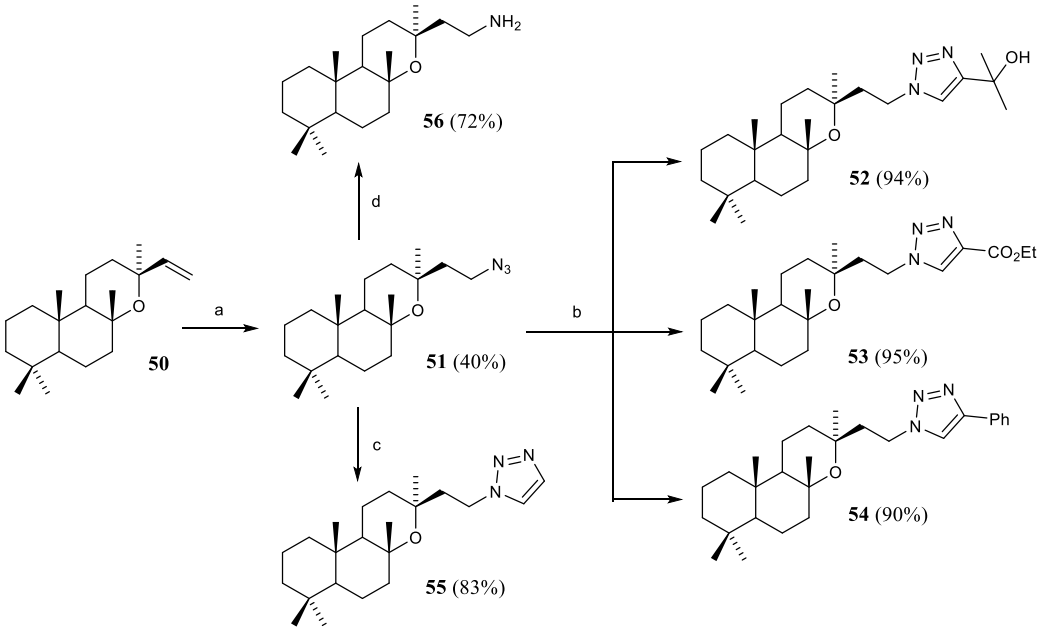

Fig. 3.1. *Anti*-Markovnikov hydroazidation of *epi*-manoyl oxide and versatility of azido group.

Reagents and conditions: **a.** HBCat, DMA, DCM; 3-PySO_2N_3, DTBHN, DMF; **b.** alkynes (1. HC≡C$(CH_3)_2$OH, 2. HC≡C$CO_2C_2H_5$, 3. HC≡CC_6H_5), CuI, DIPEA, AcOH, DCM, r.t.; **c.** propiolic acid, CuI, sodium ascorbate, DBU, DMF; **d.** H_2, Pd/C, EtOAc, r.t., overnight.

3.2. Carboazidation and carboiodination of manoyl oxides

Synthesis of natural products and their analogues provide a fruitful field for ATRA methodology and in our opinion this potential is underexplored. There is still prevalence in the scientific publications of ionic processes reported for assembling C-C bonds in complex molecular frameworks, although successful examples involving ATRA are also known in natural product synthesis. Sometimes radical additions represent the only solutions to overcome synthetic challenges connected to substrate reactivity and stereochemistry issues.

For the carboazidation or carboiodination reactions, we have chosen several alkylating agents with electron-accepting functional groups adjacent to a halogenated sp^3 carbon. The

character of these halides can be conveniently modulated based on their sterical bulk and halogen ability to radical transfer. Therefore, we have chosen iodoacetic acid and its esters, as well as iodomethylphenylsulfone and bromotrichloromethane for ATRA to both substrates **50** and **57**.

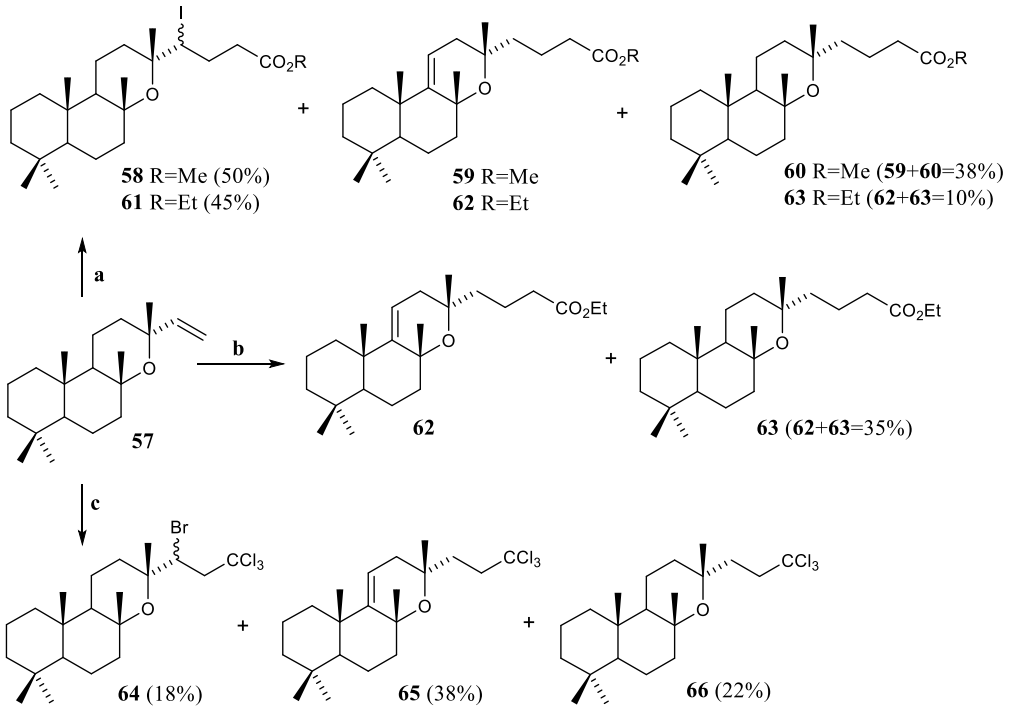

Fig. 3.2. Carboazidation and carboiodination of manoyl oxide.

Reagents and conditions: **a.** ICH_2CO_2H (2 equiv.) or ICH_2CO_2Et, DLP, benzene, Δ, then CH_2N_2 for acid; **b.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN, benzene, Δ, 8 h; **c.** $BrCCl_3$, DLP, benzene, Δ.

Treatment of **57** with iodoacetic acid led to the quick consumption of the starting material in the presence of dilauroyl peroxide (DLP) as a radical initiator in refluxing benzene. The reaction product represented a rather complex mixture. A tentative separation by flash chromatography failed, and to reduce the tail effect of the free carboxylic acids, methylation with an ethereal solution of diazomethane was performed. Chromatographic separation of obtained methyl esters resulted in the isolation of the expected 1,2-addition product **58** and a fraction containing alkylated compounds which lack the iodine in their structure. A careful examination of NMR data led to the conclusion that this fraction represents a mixture of two compounds, the major one being olefin **59**, which could be possibly formed after a 1,5-radical migration, followed by elimination (Figure 3.2).

The complex nature of reaction products suggested parallel substrate reactivity, due to acid-catalyzed transformations induced by free iodoacetic acid. To diminish this effect, reaction

of **57** with ethyl iodoacetate under the same conditions has been investigated. The conversion rate was slightly slower in this case, but reaction selectivity was improved. The main reaction product was isolated by flash chromatography and according to NMR data, its structure was assigned as iodide **61**. A minor fraction was also isolated, and the NMR data showed a mixture of esters **62** and **63**, like esters **59** and **60** derived from reaction of **57** with iodoacetic acid. All attempts to separate individual **62** and **63** failed. Surprisingly, interaction of oxide **57** with bromotrichloromethane occurred with a totally opposite selectivity. Bromide **64**, resulting from 1,2-addition, was minor in this case and the predominating products **65** and **66** have been isolated in individual form. On the other hand, the reaction of the same substrate under carboazidation conditions with ethyl iodoacetate and phenylsulfonyl azide as azide source led to the same mixture of esters **62** and **63**. No azide radical transfer was observed (Figure 3.2).

Performing carboiodination of **50** with iodoacetic acid and its esters (methyl and ethyl) under the DLP initiation conditions resulted in the formation of similar iodides **68**, **69**, **71** as major reaction products (Figure 3.3). Along with these major products, a minor fraction of iodides has been also isolated and its structural characterization led us to the conclusion that an unprecedented iodine migration has happened during alkylation, involving 3 successive 1,5-HAT and final addition of iodine at the distal methyl from cycle A of the substrate. Following our assumption that steric effects govern the radical translocations, we investigated alkylation of **50** under the action of a bulkier agent – iodomethylphenylsulfone. In this case the reaction was much more sluggish showing a modest conversion rate of 25%. However, the product distribution was in favor of the distal iodide **78**, which formed along with the alkylated sulfone **77**. Switching to the $BrCCl_3$ alkylation gave a better overall yield of radical translocation products. Moreover, the identification of products **74** and **75** deriving from all the successive radical shifts was made possible by a careful HPLC of the reaction products and following NMR studies.

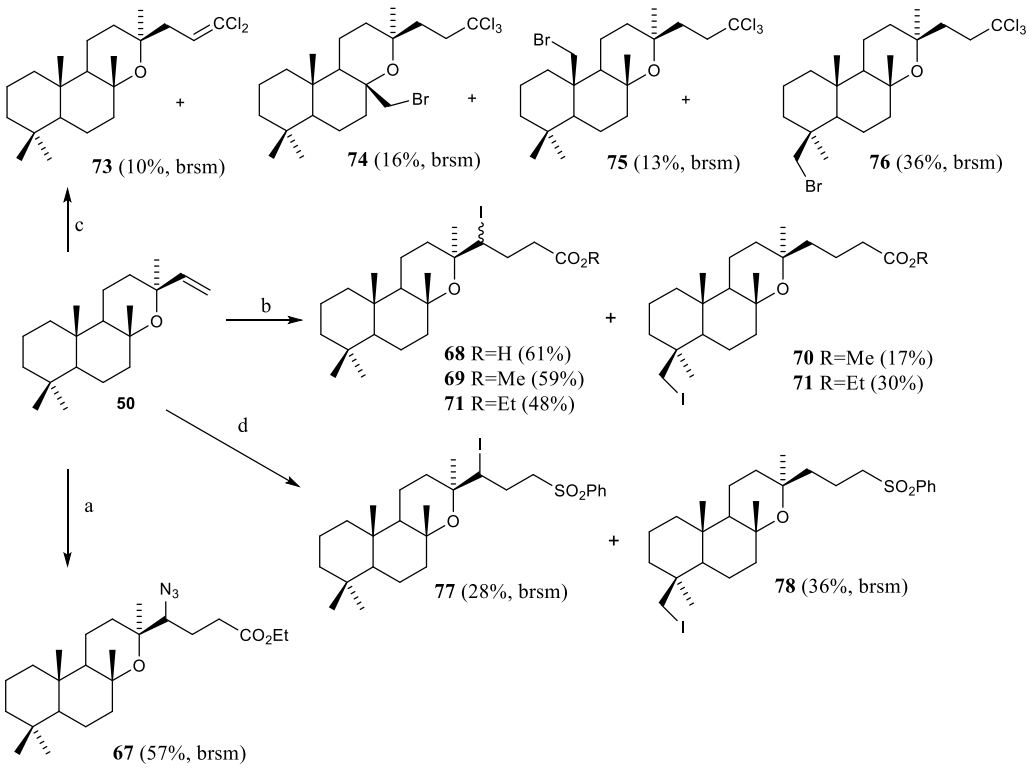

Fig. 3.3. Carboazidation and carboiodination of *epi*-manoyl oxide.

Reagents and conditions: **a.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), benzene, Δ, 7 h; **b.** ICH_2CO_2H (2 equiv.) or ICH_2CO_2Et, DLP, benzene, Δ, then CH_2N_2 for acid; **c.** $BrCCl_3$, DLP, benzene, Δ; **d.** ICH_2SO_2Ph (2 equiv.), DLP, benzene, Δ.

3.3. Carboazidation of natural compound Forskolin

Forskolin is a secondary metabolite isolated from *Coleus forskohlii* plant and shows a myriad of therapeutic activities, such as antihypertensive and broncho-spasmolytic [6]. Its main mechanism of action relates to the ability to penetrate the cell membranes and stimulate the enzyme adenylyl cyclase. A lot of work has been done on the chemical synthesis of **79** and diverse strategies have been demonstrated for its total and semisynthesis [7].

Carboazidation of forskolin with ethyl iodoacetate and pyridinsulfonyl azide under DTBHN initiation conditions resulted in the formation of azide **80** in 68% yield (Figure 3.4). Only one diastereomer was observed by carbon NMR. When comparing the ^{13}C NMR spectrum of forskolin azide with *epi*-manoyl oxide azide, we observed a peak at 70.5 ppm which corresponds to the CH-N_3 of compound **67** and a peak at 79.9 ppm for compound **80**.

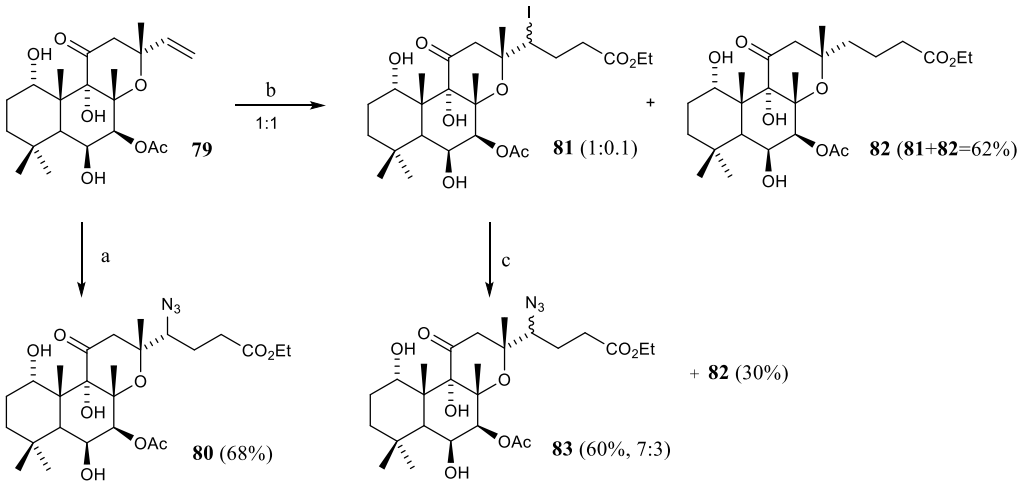

Fig. 3.4. Radical transformation of forskolin.

Reagents and conditions: **a.** ICH_2CO_2Et (2 equiv.), 3-$PySO_2N_3$ (3 equiv.), Bu_6Sn_2 (1.5 equiv.), DTBHN (0.03 equiv.), benzene, 6 h, Δ; **b.** ICH_2CO_2Et (1.2 equiv.), Et_3B (1.3 equiv.), 2 h, r.t.; **c.** NaN_3 (1.25 equiv.), DMF, 65 ℃. Δ.

Carboiodination of forskolin with ethyl iodoacetate and triethylborane (1M in pentane) in dichloromethane afforded epimeric-iodides **81** and reduced compound **82** in 62% combined yield. All attempts to separate individual compounds **81** and **82** failed. According to NMR data, the mixture of epimeric iodides **81** contains approximately 10% of minor epimer. The mixture of the iodide and reduced product was used in the next step without separation. Azidation with sodium azide in dimethylformamide at 65 ℃ overnight led to formation of azides **83** in 44 % yield with the ratio 70:30 and the reduced product **82** in 30% yield. The major compound in the azides mixture **83** coincides with the one from the carboazidation of the forskolin. Conversion of forskolin azide into lactam or simple amine failed. We tried conversion of azide **80** by hydrogenation reaction using two different catalysts Pd/C and $Pd/CaCO_3$. We assumed that the azido group is hindered due to the functional groups and the azide modification in the amine was unsuccessful.

3.4. Carbohydrogenation of manoyl oxides

The carbohydrogenation of olefin upon initiation with triethylborane and air in presence of *tert*-butylcatechol (TBC) as a reducing agent was performed. We have chosen several iodides as electron-poor radical precursors, such as ethyl iodoacetate, difluoroiodoacetate, terpenic iodoacetates and perfluoroalkyl iodides.

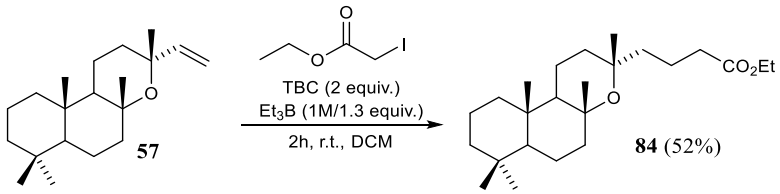

Fig. 3.5. Carbohydrogenation of manoyl oxide with ethyl iodoacetate.

Carbohydrogenation of manoyl oxide with ethyl iodoacetate, TBC and triethylborane in dichloromethane afforded the desired product **84** in 52% yield after 2 h (Figure 3.5). Unexpectedly, when we tried carbohydrogenation with ethyl difluoroiodoacetate, decomposition of the olefin was observed, and no desired product could be obtained. We then decided to do all the transformations only with *epi*-manoyl oxide, which probably is more stable due to its stereochemistry.

First, *epi*-manoyl oxide was treated with ethyl iodoacetate, 4-*tert*-butylcatechol followed by triethylborane in dichloromethane in an open-air flask to afford the desired product **85** in 58% yield (Figure 3.6). The reaction of olefin with iodophenyl sulfone provided the product **86** in moderate yield. We tried as well to perform C-C coupling with other isoprenic iodoacetates as radical precursor, such as acetyl-iodocholesterol and acetyl-iodoisoborneol. Unfortunately, carbohydrogenation reaction of **50** with both iodides failed and the starting material partially decomposed after 2 h. We then added different quantities of bases (0.2-0.5 equiv. of Na_2CO_3 and 2,6-lutidine) to the reaction mixture, but not improvement was observed.

The hydroalkylation of *epi*-manoyl oxide with perfluoroalkyl iodides ($CF_3(CF_2)_n$-I) with n = 0, 3, 5 and 7 afforded the products (**88**-**90**) in excellent yields (Figure 3.6).

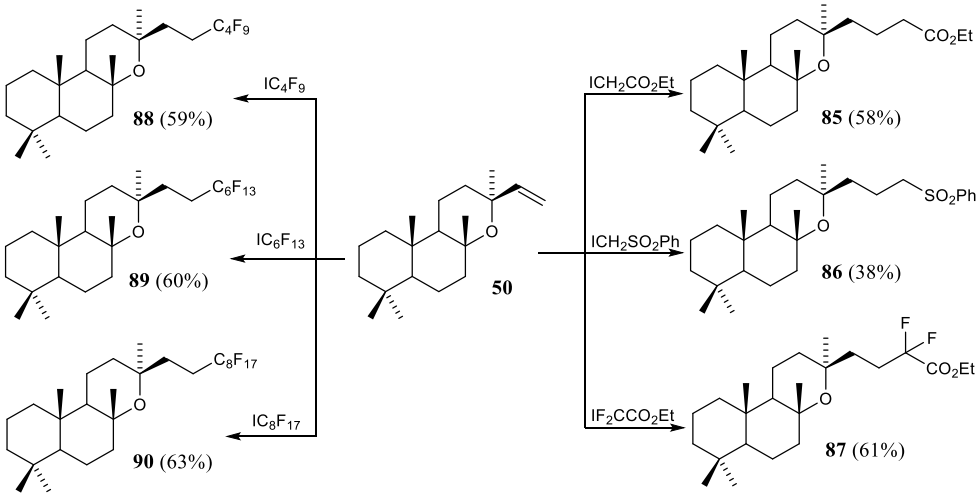

Fig. 3.6. Carbohydrogenation of *epi*-manoyl oxide.
Reagents and conditions: iodides (1.2 equiv.), olefin (1 equiv.), TBC (2 equiv.), Et_3B 1M in pentane (1.3 equiv.) in DCM, r.t., 2 h.

3.5. Carboazidation of isocopalic related diterpenoids

Spongiane diterpenoids are natural compounds isolated form sponges, corals and marine mollusks. Most of them play a key role as physiological mediators and are of interest for potential applications as therapeutic agents. These diterpenoids possess biological properties including antifungal, anti-inflammatory, cytotoxic and *anti*-HIV activities [8].

Methyl *ent*-isocopalate **91**, the tricyclic diterpene intermediate is used as a good precursor in the total synthesis of natural compounds. The first synthesis of *ent*-isocopalate was reported by Cimino [9], starting from grindelic acid in 5-steps (45% yield). Later, another approach to the synthesis of methyl *ent*-isocopalate was reported [10].

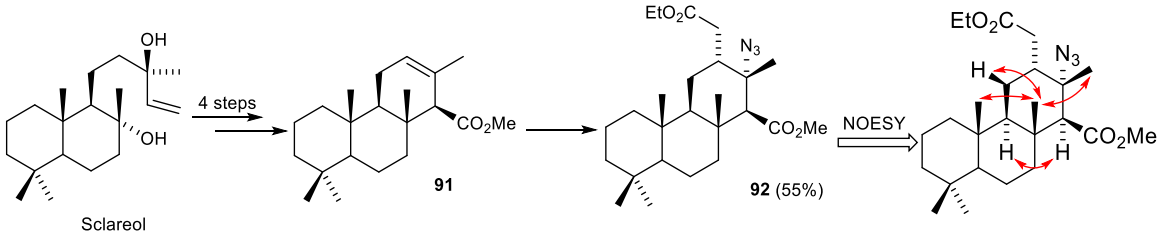

Fig. 3.7. Carboazidation of methyl *ent*-isocopalate and NOESY correlation of compound 92.

Reagents and conditions: ICH_2CO_2Et (2 equiv.), 3-$PySO_2N_3$ (3 equiv.), Bu_6Sn_2 (1.5 equiv.), DTBHN (0.03 equiv.), benzene, 10 h, Δ.

In the continuation of our studies, two other isocopalate diterpenoids **91** and **93** have been investigated as substrates for ATRA processes. Carboazidation of methyl *ent*-isocopalate **91** with ethyl iodoacetate and phenylsulfonyl azide under DTBHN initiation conditions resulted in the formation of azide **92** in 55% yield (Figure 3.7) [11]. The relative stereochemistry of azide **92** was determined based on NOESY NMR data which attests correlation between the hydrogen atoms at the 3H-21↔3H-18↔3H-17, 3H-18↔H-11 and H-9↔H-14 (Figure 3.7).

As we know, free hydroxyl group can interfere with radical chains and our alcohol was protected with a silyl group. Treatment of protected diterpenoid **94** with ethyl iodoacetate, pyridine-sulfonyl azide and DTBHN resulted in a 7:3 mixture of products. According to ^{13}C NMR spectra, two sets of carbons were registered and the major tertiary azide gave peak at 72.72 ppm and the minor at 70.37 ppm. Their individual separation was unsuccessful. Surprisingly, the subsequent removal of the TBDMS protection with TBAF led to one azide **96** in 40% yield. Stereochemistry of the tertiary azide **96** was not determined. Following hydrogenation of azide **96** resulted into lactam **97** in quantitative yield. Cyclization of amine group with carbonyl is faster than with hydroxyl group (Figure 3.8) [12].

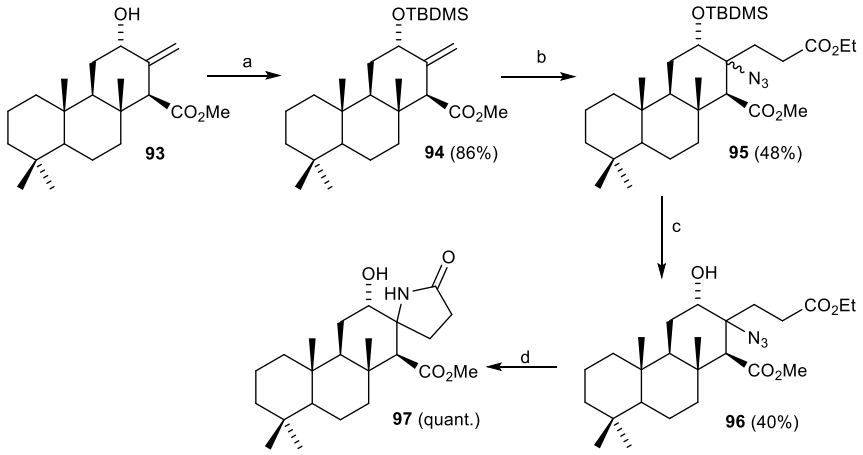

Fig. 3.8. Carboazidation of hydroxy *ent*-isocopalate.

Reagents and conditions: **a.** imidazole (4 equiv.), TBDMSCl (2 equiv.), DMF, r.t., 12 h; **b.** ICH_2CO_2Et (2 equiv.), Bu_6Sn_2 (1.5 equiv.), 3-$PySO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, Δ, 12 h; **c.** TBAF (3 equiv.), THF, r.t., overnight; **d.** H_2, Pd/C (10% w/w), EtOAc, r.t., 12 h.

Chapter IV. Synthesis of some terpenoids *via* cationic rearrangements

The broad range of terpenoids is due to the tremendous diversity of isomerization and skeletal rearrangements that can occur in the final steps of their biosynthesis. Based on biosynthetic hypotheses, it is possible to devise biomimetic approaches for the chemical synthesis of different groups of terpenoids which are scarcely available from natural sources, but which possess relevant properties. The best example of such an approach is the cation-induced cyclization of linear isoprenoids leading to different polycyclic compounds under efficient chemo-, regio- and stereocontrol [13]. Examples of deeper skeletal rearrangements, ring contractions and expansions are also present in diverse synthetic applications, despite the difficulties connected to control and cascade events affecting the reaction course and selectivity.

4.1. Synthesis of *ent*-verrucosin and hyrtiosane skeleton

Verrucosins A **98** and B **99** are two acylglycerols isolated for the first time from *Doris verrucosa* mollusks collected in the Mediterranean Sea (Figure 4.1) [14, 15]. Diterpenoids **98** and **99** are highly ichthyotoxic and have demonstrated *in vivo* bioactivity as morphogens in the *Hydra tentacle* regeneration assay and their parallel function as activators of rat brain protein kinase C was also described. It should also be noted that the synthesis of terpenoids with the verrucosin A and B carbon skeleton has not yet been achieved. The biogenetic pathway leading to **98** and **99** has been below suggested. We elaborated a synthetic scheme for the synthesis of bicyclic framework of *ent*-verucosins *via* a cationic-induces rearrangement of available iso-copalic derivatives.

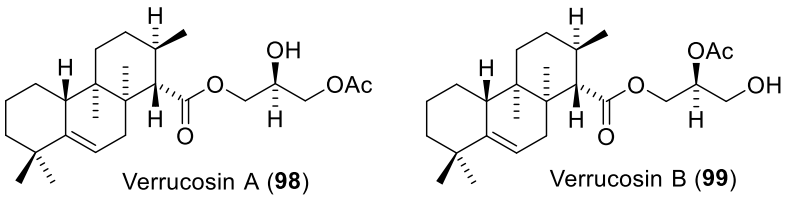

Fig. 4.1. Natural verrucosins A and B.

(-)-Sclareol served as a starting compound, which was converted into the methyl ester of *ent*-isocopalic acid **91**, according to the known procedure [16]. The latter compound was in turn transformed into the methyl ester of 12α-hydroxy-*ent*-isocopal-13(16)-en-15-oic acid **93** and 12α-hydroxy-*ent*-isocopal-13(14)-en-15-oic acid **100**, according to the reported two-step sequence [17]. Afterward, the mixture of alcohols **93** and **100** was treated with 6N H_2SO_4 in dioxane, which led to the formation of some lactone **101** (37%) along with major unreacted $\Delta^{13,14}$ alcohol **100** and a minor amount of the rearranged compound **102** in 7% yield (Figure 4.2).

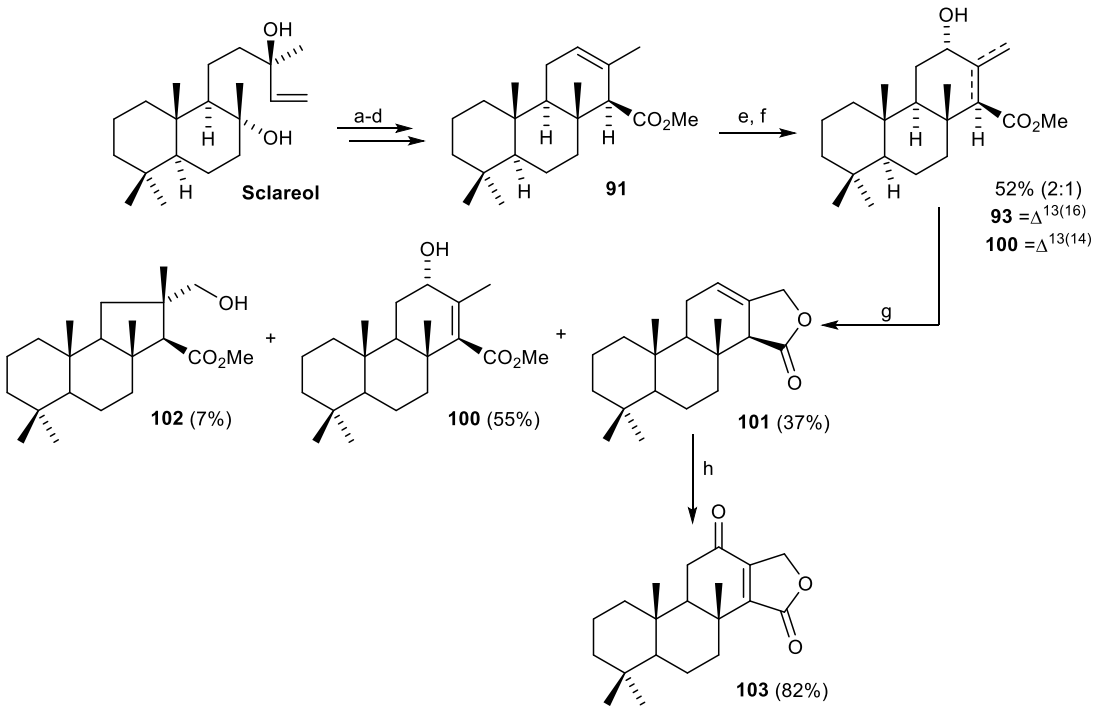

Fig. 4.2. Isomerization of isocopalic diterpenes.

Reagents and conditions: **a.** $KMnO_4$, Me_2CO, r.t., 12 h, 90%; **b.** I_2, PhMe, Δ, 3 h, 78%; **c.** $(MeO)_2P(O)CH_2CO_2Me$, PhH, MeONa, Δ, 2 h, 98%, (13E/13Z = 10:1); **d.** FSO_3H (5 equiv.), i-$PrNO_2$, -78 ^oC, 15 min, then Et_3N, 92%; **e.** m-CPBA, CH_2Cl_2, 0 ^oC, 12 h, 97%; **f.** Al(Oi-Pr)$_3$, PhMe, Δ, 24 h, 78%; **g.** H_2SO_4 6N, dioxane, Δ, 4 h; **h.** AcOH, Ac_2O, $Na_2Cr_2O_4$, C_6H_6, Δ, 48 h.

Then, oxidation of γ-lactone **101** with sodium chromate led to spongiane α,β-unsaturated keto-lactone **103** in 82% yield, functionalized in C-12 position (Figure 4.2) [18].

The reaction of ester **93** with *p*-toluenesulfonic acid in chloroform at reflux for 4 h afforded a 5:2 mixture of two compounds. The polar minor compound was identified by its spectroscopic data and other properties as the known diterpenic lactone **101** in only 4% yield and compound **104** in 67% yield (Figure 4.3). According to elemental analysis, IR and NMR spectra, the major compound **104** was identified as a diterpenic diene ester with the molecular formula $C_{21}H_{32}O_2$. The relative configuration of diene **104** was deduced from NOESY correlations of its reduction product, alcohol **105**.

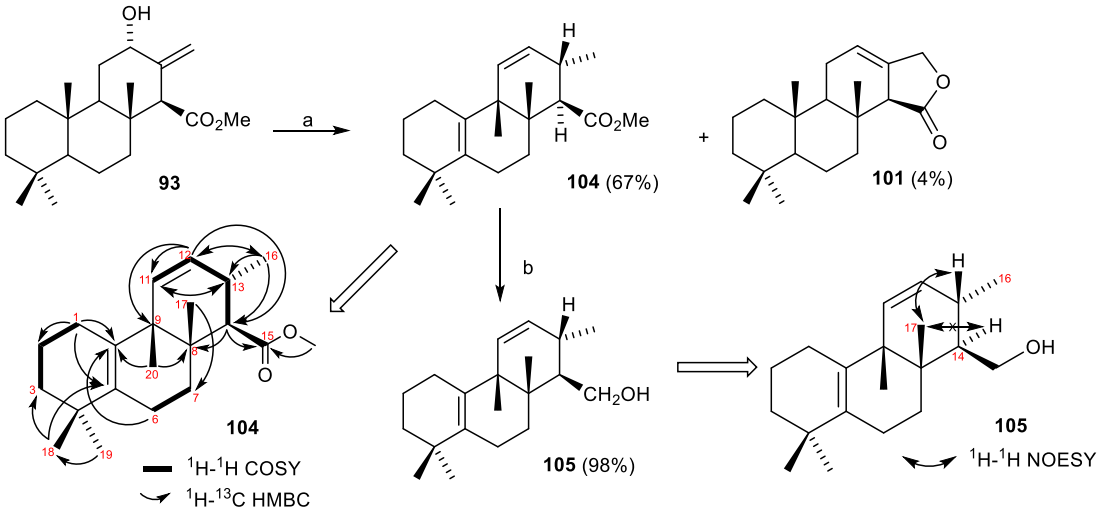

Fig. 4.3. Isomerization of diterpenic alcohol 93. COSY and HMBC correlations of compound 104 and NOESY of compound 105.

Reagents and conditions: **a.** *p*-TsOH/$CHCl_3$, Δ, 3 h; **b.** $LiAlH_4$, THF, Δ, 4 h.

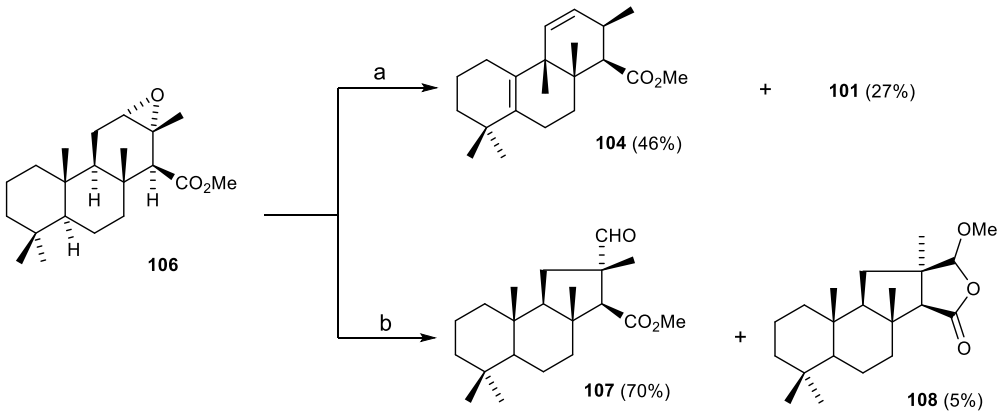

Fig. 4.4. Skeletal rearrangements of epoxide 106 under acidic conditions.

Reagents and conditions: **a.** *p*-TsOH/$CHCl_3$, Δ, 3 h; **b.** FSO_3H, 2-NO_2Pr, MeOH, -78 ^oC.

We demonstrated the synthesis of the diene **104** from epoxide **106** in the same conditions of the reaction as we did with alcohol **93** (Figure 4.4). In this case, the yield is lower than above, but the yield of *γ*-lactone **101** increased from 4% to 27%. The alternative transformations of

methyl ester under superacidic conditions gave the mixture of two rearranged diterpenoids. The isomerization of compound **106** in 2-nitropropan with 5 equiv. FSO_3H in mild conditions at -78 ^oC, led to the formation of the aldehyde **107** (70% yield) and compound **108** (5% yield) in only 30 min. The aldehyde **107** was also synthesized from epoxide **106** by Basabe et. al [19], but these authors used 50 equiv. of BF_3•Et_2O and high temperature compared with our mild conditions of the reaction. Surprisingly, the isomerization of epoxide **106** [20] under mild conditions gave the new compound **108** with a very interesting rearranged skeleton, which was not observed in the reaction with BF_3•Et_2O.

4.2. The acid-induced rearrangement of homodrimanic epoxide

The synthesis of austrodoric acid, a perhydrindanic sesquiterpenoid isolated from a *Austrodoris Querguelensis* has been reported starting from homodrimanic epoxide **111** [21]. When we used pillared clay for the rearrangement of **111** we obtained not the same compounds as in [21], but with a totally opposite selectivity. The prevailing rearrangement products **112-114** represented the bicyclic fragment of halimanes (Figure 4.5).

The starting material for the rearrangement reaction can be easily synthesized from commercially available sclareolide **109** *via* a short synthetic sequence [22]. The tertrasubstituted acetate **110** was treated with *meta*-chloroperbenzoic acid in dichloromethane led to the formation of epoxide **111** in 52% yield. The isomerization of epoxide **111** led to the formation of a mixture of several compounds. The reaction with Al-H-Na-Lar pillared clay as a heterogeneous catalyst, on heating in 2-nitropropane at 100 ^oC results in a substantial prevalence of the oxide **112** (75% yield), over olefin **113** (20%) and alcohol **114** (5%) (Figure 4.5).

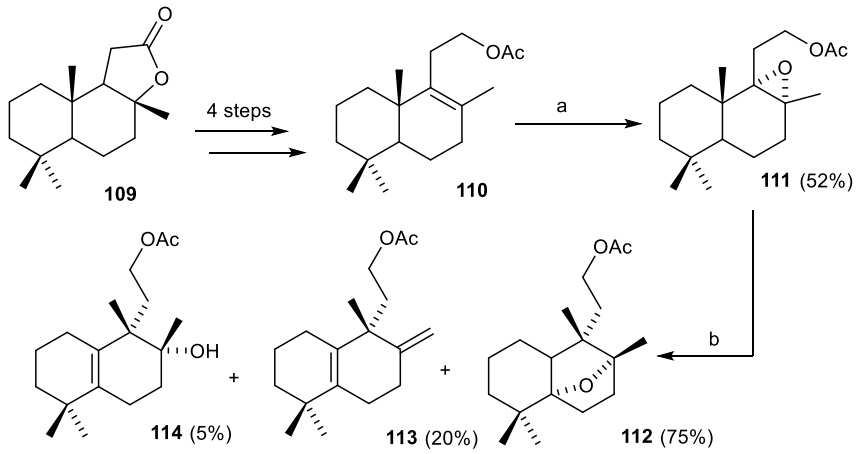

Fig. 4.5. Isomerization of homodrimane epoxide 111.
Reagents and conditions: **a.** *m*-CPBA, CH_2Cl_2, 0 ^oC, 12 h; **b.** pillared clay, 2-NO_2Pr, 100 ^oC, 2 h.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The main scientific problem addressed in the current thesis represents the expansion of structural diversity of some available terpenic scaffolds basing on free radical processes and cationic rearrangements. As it was shown in the chapters above, the solution of this problem was convincingly provided by an array of transformations that have been demonstrated with readily available terpenic substrates of *ent*-kauranic, labdanic, isoagatanic and homodrimanic structure, which generated a broad range of functionalized derivatives and rearranged carbon backbones. These transformations represented both free radical processes and cationic rearrangements, that is totally in line with formulated thesis goal, which has been convincingly achieved.

The conclusions presented below are based entirely on the author's contributions, and correlate perfectly with the thesis specific objectives. These also include some recommendations, which could provide further impetus for the development of the research in the field of late stage functionalization of terpenic compounds and contribute to the identification of potential applications of terpenoids and their derivatives.

1. The stereoselective, free radical, *anti*-Markovnikov hydroazidation of methyl *ent*-kaur-16-en-19-oate has been demonstrated. The elaborated procedure is based on the „one pot" strategy and allows the isolation of the corresponding primary azide with a high yield. Its parallel synthesis according to an alternative 4-steps pathway has revealed the advantage of the „one pot" strategy, which comprises less steps and provides a better yield. The structure of the obtained azide has been confirmed basing on X-ray crystallographic analysis [chapter 2, § 2.1].
2. The feasibility of preparation of 15α-hydroxy-*ent*-kaur-16-en-19-oic acid from sunflower wastes has been demonstrated. A series of new compounds with multiple functional groups has been synthesized basing on free radical transformations of methyl 15α-hydroxy-*ent*-kaur-16-en-19-oate. These include nitrogen and oxygen condensed and spiro heterocycles. Their structure has been determined unambiguously basing on X-ray crystallographic analysis [chapter 2, § 2.2].
3. The synthetic utility of free radical hydroazidations, carboazidations and carbohydrogenations has been demonstrated for the advanced functionalization of labile compounds belonging to labdanic and isocopalic series [chapter 3, § 3.5].
4. Basing on the 13-*epi*-manoyl oxide *anti*-Markovnikov hydroazidation new nitrogen-containing derivatives have been obtained for the first time, including 1,2,3-triazoles which represent amides bioisosteres [chapter 3, § 3.1].

5. The synthetic value of free radical carbohalogenation has been demonstrated for the generation of halogenated derivatives of manoyloxides. As the result, a series of halo-compounds having the tricyclic skeleton similar to natural, biologically active forskolin has been synthesized [chapter 3, § 3.2 and § 3.3].
6. The carboazidation reaction has been applied on labile diterpenic substrates of isocopalic structure, which have both exocyclic and endocyclic double bonds as reactive moieties. As the result, highly functionalized carbo- and heterocyclic derivatives have been synthesized. A method for the synthesis of isocopalic spiro lactams has been demonstrated for the first time [chapter 3, § 3.5].
7. Broadening the structural diversity of available isocopalic compounds has been demonstrated on the example of cationic isomerization of methyl isocopalate **93**, which led under acidic conditions to the one-step generation of tricyclic verucosin skeleton **104** [chapter 4, § 4.1].
8. Optimization of isocopalic skeleton rearrangement has been demonstrated on the identification of selective conditions for the direct transformation of methyl 12,13-epoxyisocopalate into compounds of verrucosinic structure [chapter 4, § 4.1].
9. The selective rearrangement of homodrimanic skeleton, involving a successive migration of the angular methyl and a hydrogen atom, has been demonstrated. In such a way, the energetic sink, corresponding to an alternative deprotonation process, has been avoided and a selective method for the synthesis of bicyclic fragment of *ent*-halimanic framework has been elaborated. The obtained rearranged compound represents an important platform for the synthesis of some natural products with relevant biological activity [chapter 4, § 4.2].

The most relevant findings of significant theoretical and practical value can be summarized as follows:

1. The selective functionalization of the *ent*-kauranic skeleton by free radical alkylation at C-17 carbon atom has been realized for the first time. Carboazidation and carbohydrogenation reactions represented an efficient tool for the synthesis of functionalized derivatives, including nitrogen-, oxygen- and fluorine-containing ones. The following transformations provided access to spiro heterocycles of *ent*-kaurane series. The chemical structure of these compounds has been unambiguously demonstrated basing on X-ray diffraction analysis. The total stereoselectivity of the observed ATRA process has been demonstrated basing on the steric effect of the *ent*-kauranic tetracyclic framework. This result represents a significant theoretical value and is a convincing proof

that free radical processes involving chiral terpenoids can be efficiently controlled by steric factors leading to highly selective transformations [chapter 2, § 2.2 and § 2.3].

2. The practical value of methyl 17-azido-16β-*ent*-kauran-19-oate **2** has been demonstrated by its following chemical transformations, which led to the synthesis of a series of nitrogen-functionalized derivatives, including 1,2,3-triazoles, amines and guanidines. These nitrogen derivatives have been submitted to a broad study of cytotoxic activity. As a result, a series of new compounds with relevant cytotoxicity and selectivity towards several tumour cell lines has been revealed. Methyl 17-amino-16β-*ent*-kauran-19-oate showed the most promising results and basing on these a patent application has been filed [chapter 2, § 2.1].
3. An unique, triple sequence of successive 1,5-hydrogen atom transfers has been demonstrated for the first time in radical chemistry, leading to remote functionalization of 13-*epi*-manoyl oxide with iodine and bromine at the *gem*-dimethyl position of cycle A [chapter 3, § 3.2].
4. The selective functionalization of forskoline has been achieved under protecting group free conditions. Application of carboazidation resulted in the synthesis of a nitrogen-containing derivative of forskolin with a good yield [chapter 3, § 3.3].
5. The application of free radical carbofunctionalization of *ent*-kauranic framework has been demonstrated under triethylborane initiation conditions. It avoids the use of toxic tin compounds under stoichiometric conditions and provides opportunities for environmentally friendly reaction conditions [chapter 2, § 2.2]. In line with this idea, montmorillonite pillared clay has been shown to efficiently catalyse the cationic rearrangements of the homodrimanic epoxide under heterogeneous conditions and catalyst recycling. The use of similar adsorbents, prepared from local mineral raw material, can provide an efficient avenue for the complex transformations of terpenic compounds in preparative amounts and minimal environmental impact [chapter 4, § 4.2].

The overall recommendation relates to the exploitation of the whole range of substances obtained synthetically in the current work and reaching the value of 90 new compounds, which could be submitted to a broader set of biologically activity tests in order to entirely reveal their application potential.

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ADNOTARE

Gîrbu Vladilena, ”Sinteza derivaților terpenici polifuncționalizați prin intermediul reacțiilor radicalice și cationice”, teză de doctor în științe chimice, Chișinău 2019.

Structura tezei: introducere, 4 capitole, concluzii generale și recomandări, bibliografie din 203 titluri, 111 pagini de text de bază, 65 figuri, 6 tabele, 1 anexă. Rezultatele obținute sunt publicate în 20 lucrări științifice.

Cuvintele-cheie: terpenoide, chimie radicalică, carboazidare, carbohidrogenare, hidroazidare, transpoziții cationice, compuși biologic activi.

Scopul lucrării: constă în funcționalizarea terpenoidelor cu heteroatomi de azot, oxigen sau halogen prin intermediul reacțiilor radicalice, astfel obținându-se compuși cu un potențial sporit de activitate biologică; modificarea terpenoidelor ușor disponibile cu ajutorul transpozițiilor cationice și generarea compușilor cu schelete regrupate.

Obiectivele cercetării: utilizarea reacțiilor de hidroazidare, carboazidare și carbohidrogenare radicalică în funcționalizarea diterpenoidelor naturale și sintetice; modificarea scheletului carbonic în derivații isocopalici și homodrimanici prin migrări cationice cu obținerea derivaților terpenici, analogii cărora se găsesc în natură în cantități mici; caracterizarea compușilor obținuți prin metode moderne de analiză.

Noutatea și originalitatea științifică: Pentru prima dată a fost demonstrată utilitatea adițiilor radicalice cu transfer de atomi pentru funcționalizarea compușilor diterpenici, cum ar fi derivații *ent*-kauranici, labdanici și isocopalici. Au fost sintetizați 90 compuși noi, unii manifestând activitate biologică pronunțată. Pentru prima dată, cu ajutorul transpozițiilor cationice au fost sintetizați compuși cu schelet halimanic, *ent*-verrucosinic și hirtiosanic.

Rezultatele obținute care contribuie la soluționarea unei probleme științifice importante în teză constau în introducerea simultană a grupelor funcționale de interes prin intermediul reacțiilor radicalice și obținerea compușilor de tip labdanic, *ent*-kauranic și isocopalic funcționalizați cu heteroatomi de azot, oxigen sau halogeni, unii demonstrând activitate biologică; au fost obținute o serie de sesquiterpenoide cu schelet halimanic, hirtiosanic și *ent*-verrucosinic, compuși cu valoare teoretică și aplicativă.

Semnificația teoretică a lucrării constă în aplicarea cu succes a transformărilor radicalice pentru lărgirea diversității structurale a compușilor terpenici cu structură complexă, demonstrarea influenței efectelor stereoelectronice asupra selectivității proceselor abordate și elaborarea unor căi eficiente de funcționalizare a substratelor selectate în baza baza reacțiilor radicalice și cationice.

Valoarea aplicativă a lucrării: viabilitatea chimiei radicalice pe substrate terpenice complexe; demonstrarea reacției click pe substrate diterpenice și utilizarea lor în studiile activității biologice.

Implementarea rezultatelor științifice: o serie de compuși obținuți în cadrul lucrării, au demonstrat activitate citotoxică selectivă. În baza acestor rezultate au fost înregistrate patru cereri de brevet.

ANNOTATION

Gîrbu Vladilena, "Synthesis of polyfunctionalized terpenic derivatives *via* radical and cationic reactions", PhD thesis in chemical science, Chișinău 2019.

Structure of the thesis: Introduction, 4 chapters, general conclusions and recommendations, bibliography of 203 references, 111 basic text pages, 65 figures, 6 tables, 1 annex. The results of the research have published in 20 scientific papers.

Key-words: terpenoids, radical chemistry, carboazidation, carbohydrogenation, hydroazidation, skeletal rearrangements, biologically active compounds.

The aim of the thesis: is functionalization of terpenoids with nitrogen, oxygen and halogen heteroatoms through radical reactions thus obtaining compounds with high potential biological activity; modification of readily available terpenoids *via* skeletal rearrangements and generation of compounds with rearranged skeletons.

Research objectives: the use of hydroazidation, carboazidation and carbohydrogenation radical reactions for the functionalization of natural and synthetic diterpenoids; modification of the carbonic skeleton in isocopalic and homodrimanic derivatives through cationic migrations to obtain the terpenic derivatives, the analogues of which are found in nature in a small amount; characterization of the compounds using modern methods of analysis.

Scientific novelty and the originality: For the first time, the usefulness of radical addition with atom transfer has been demonstrated for the functionalization of diterpenic compounds, such as *ent*-kaurane, labdane and isocopal derivatives. Ninety new compounds have been synthesized, some showing pronounced biological activity. For the first time, due to cationic transpositions, compounds with halimane, *ent*-verrucosin and hyrtiosane skeleton have been synthesized.

The results which can contribute to the solution of an important scientific problem in the thesis consist in the simultaneous introduction of functional groups *via* radical reactions and obtaining labdanic, *ent*-kauranic and isocopalic compounds functionalized with nitrogen, oxygen or halogen heteroatoms, some demonstrating biological activity; a series of sesquiterpenoids with halimane, hyrtiosane and *ent*-verrucosin skeleton, compounds with theoretical and applicative value have been obtained.

The theoretical value: consists in the successful application of radical transformations for broadening the structural diversity of terpenic compounds with complex structure, demonstrating the influence of stereoelectronic effects on the selectivity of the processes approached and developing efficient ways of functionalization of the selected substrates based on radical and cationic reactions.

The applicative value of the research is the viability of radical chemistry on complex terpenic substrates; demonstration of the click reaction on diterpenic substrates and their use in biological activity studies.

The implementation of scientific results: a number of compounds synthesized throughout the research demonstrated selective cytotoxic activity. Based on these results, four patent applications have been filed.

АННОТАЦИЯ

Гырбу Владилена, «Синтез полифункциональных терпеновых производных посредством радикальных и катионных реакций», диссертация на соискание учёной степени доктора химических наук, Кишинев, 2019.

Структура диссертации: введение, 4 главы, общие выводы и рекомендации, библиография, включающая 203 ссылок, 111 страниц основного текста, 65 рисунков, 6 таблиц, 1 приложение. Полученные результаты опубликованы в 20 научных работах.

Ключевые слова: терпеноиды, химия радикалов, карбоазидирование, карбогидрирование, гидроазидирование, катионные перегруппировки, биологически активные соединения.

Цель работы: состоит в функционализации терпеноидов гетероатомами азота, кислорода или галогена посредством радикальных реакций, получая таким образом соединения с высоким потенциалом биологической активности; модификация легко доступных терпеноидов при помощь катионных перегруппировок и получение соединений с перегрупированымы скелетами.

Задачи исследования: использование радикальных реакций гидроазидирования, карбоазидирования и карбогидрирования в функционализации природных и синтетических дитерпеноидов; модификация углеродного скелета изокопаловых и гомодримановых производных посредством катионных миграций для получения терпеновых производных, аналоги которых встречаются в природе в небольших количествах; охарактеризование полученных соединений современными методами анализа.

Новизна и научная оригинальность: Впервые была продемонстрирована полезность радикального присоединения с переносом атома для функционализации дитерпеновых соединений, таких как *энт*-каурановые, лабдановые и изокопаловые производные. Было синтезировано 90 новых соединений, некоторые из которых проявляют выраженную биологическую активность. Впервые с помощью катионных перегруппировок были синтезированы соединения с галимановым, *энт*-веррукосиновым и гиртиозановым скелетом.

Полученные результаты, которые способствуют решению важной научной проблемы в диссертации, состоят в одновременном введении представляющих интерес функциональных групп посредством радикальных реакций и получении лабдановых, *энт*-каурановых и изокопаловых соединений, функционализированных гетероатомами азота, кислорода или галогена, некоторые из которых проявили биологичекую активность; были получены серии терпеноидов с галимановым, гиртиозановым и *энт*-веррукосиновым скелетом, соединения с теоретической и практической ценностью**.**

Теоретическая значимость работы состоит в успешном применении радикальных реакции для расширения структурного разнообразия терпеновых соединений со сложной структурой, демонстрации влияния пространственных электронных эффектов на селективность изученных процессов и разработке эффективных способов функционализации выбранных субстратов на основе радикальных и катионных реакций.

Практическая ценность работы: надежность химии радикалов на сложных терпеновых соединениях; демонстрация реакции ”клик” на дитерпеновых субстратах и их использование в исследованиях биологической активности.

Внедрение научных результатов: ряд соединений, полученных в работе, продемонстрировали селективную цитотоксичность. На основании этих результатов были поданы четыре патентные заявки.

GÎRBU VLADILENA

SINTEZA DERIVAŢILOR TERPENICI POLIFUNCŢIONALIZAŢI PRIN INTERMEDIUL REACŢIILOR RADICALICE ȘI CATIONICE

143.04 – CHIMIE BIOORGANICĂ, CHIMIA COMPUȘILOR NATURALI ȘI FIZIOLOGIC ACTIVI

Rezumatul tezei de doctor în științe chimice

Aprobat spre tipar: 12.05.2020	Formatul hârtiei 60x84 1/16
Hârtie ofset.	Tipar ofset. Tiraj: 40 ex
Coli de tipar.: 2.1	Comanda nr. 83/17

Centrul Editorial-Poligrafic al Universitații de Stat din Tiraspol

Str. Iablocikin 5, Chișinău, MD 2069