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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**

**PhD thesis in chemical science**

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# SINTEZA DERIVAŢILOR TERPENICI POLIFUNCŢIONALIZAŢI PRIN INTERMEDIUL REACŢIILOR RADICALICE ȘI CATIONICE

**143.04 – CHIMIE BIOORGANICĂ, CHIMIA COMPUȘILOR NATURALI ȘI FIZIOLOGIC ACTIVI**

**Teză de doctor în științe chimice**

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CONTENTS

**Annotation** **7**

**List of tables** **10**

**List of figures** **10**

**List of abbreviations and symbols** **13**

**Introduction** **14**

**1. FUNCTIONALIZATION AND REARRANGEMENT OF NATURAL COMPOUNDS *VIA* FREE RADICAL AND CATIONIC INDUCED REACTIONS** **18**

1.1 The radical C-H functionalization of natural compounds **18**

1.2 The C-C and C-X bonds formation *via* atom transfer radical addition methodology **26**

1.3 Recent examples of natural compounds synthesized *via* cationic reactions **40**

1.4 Conclusions to chapter 1 **43**

**2. RADICAL TRANSFORMATIONS OF *ENT*-KAURANE DITERPENOIDS** **45**

2.1 Hydroazidation of methyl *ent*-kaur-16-en-19-oate **45**

2.2 Carboazidation and carboiodination of *ent*-kaurane derivatives **48**

2.3 Carbohydrogenation of *ent*-kaurane derivatives **54**

2.4 Conclusions to chapter 2 **59**

2.5 Experimental part **60**

**3. RADICAL TRANSFORMATIONS OF LABDANIC AND ISOCOPALIC DITERPENOIDS** **81**

3.1 Hydroazidation of *epi*-manoyl oxide **81**

3.2 Carboazidation and carboiodination of manoyl oxides **82**

3.3 Carboazidation of natural compound Forskolin **88**

3.4 Carbohydrogenation of manoyl oxides **89**

3.5 Carboazidation of isocopalic related diterpenoids **91**

3.6 Conclusions to chapter 3 **93**

3.7 Experimental part **94**

**4. SYNTHESIS OF SOME TERPENOIDS *VIA* CATIONIC REARRANGEMENTS** **114**

4.1 Synthesis of *ent*-verrucosin and hyrtiosane skeleton **114**

4.2 The acid-induced rearrangement of homodrimanic epoxide **120**

4.3 Conclusions to chapter 4 **123**

4.4 Experimental part **123**

**4. OVERALL CONCLUSIONS AND RECOMMENDATIONS** **129**

**5. REFERENCES** **133**

**6. ANEXX** **151**

**7. DECLARATION ON THE ASSUMPTION OF RESPONSIBILITY** **152**

**8. AUTHOR'S CV** **153**

## 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.

## LIST OF TABLES

**Table 2.1.** Cytotoxic activities of amine **143** against selected cell lines (p. 47)

**Table 2.2.** Optimization of hydrogenation reaction of azide **147** (p. 51)

**Table 2.3.** $^{19}F$ NMR of compounds **168-171** (p. 56)

**Table 3.1**. NMR data for compounds **201** and **202** (assigned basing on $^{1}H$, $^{13}C$, DEPT, HSQC, HMBC, COSY-45, NOESY NMR experiments) (p. 86)

**Table 4.1.** $^{1}H$ and $^{13}C$ data of compound **237** in $CDCl_3$ (p. 117)

**Table 4.2.** $^{1}H$ and $^{13}C$ of compounds **247**, **248** and **249** (p. 122)

## LIST OF FIGURES

**Figure 1.1.** *A.* The C-H azidation of complex molecules *B.* Plausible mechanism (p. 20)

**Figure 1.2.** Iron-catalyzed C-H azidation of natural compounds (p. 21)

**Figure 1.3.** Plausible mechanism of C-H azidation (p. 21)

**Figure 1.4**. *A.* The transition-metal-free oxidative C-H azidation of complex molecules. *B.* The suggested mechanism (p. 23)

**Figure 1.5.** Late-stage diversification of azides (p. 23)

**Figure 1.6.** *A.* and *B.* The electrochemical C-H oxidation of complex molecules. *C*. The putative mechanism (p. 25)

**Figure 1.7.** The synthesis of 2-oxo-yahazunone from oxo-sclareolide (p. 26)

**Figure 1.8.** Cobalt-catalyzed Markovnikov hydoazidation of olefin (p. 27)

**Figure 1.9.** *Anti*-Markovnikov hydroazidation of olefins. Proposed mechanism (p. 28)

**Figure 1.10**. Synthesis of (+)-rodocaine (p. 28)

**Figure 1.11**. Radical *anti*-Markovnikov hydroxyazidation of bioactive molecules (p. 29)

**Figure 1.12**. Proposed mechanism of *anti*-Markovnikov hydroxyazidation reaction (p. 29)

**Figure 1.13**. Diazidation of natural compounds (p. 30)

**Figure 1.14.** Carboazidation of olefins using different conditions of the reactions (p. 31)

**Figure 1.15.** The proposed mechanism for the tin-mediated carboazidation reaction (p. 31)

**Figure 1.16.** Application of the radical carboazidation reaction in total synthesis (p. 32)

**Figure 1.17.** The carboazidation reaction of estrone derivative *via* blue LED (p. 32)

**Figure 1.18.** The plausible mechanism of azidoperfluoroalkylation reaction (p. 33)

**Figure 1.19.** The azido sulfonylation reaction of alkenes and the proposed mechanism (p. 34)

**Figure 1.20.** The ATRA bromination reaction (p. 35)

**Figure 1.21.** The reductive radical difluoroalkylation-thiolation of compound with sugar moiety (p. 35)
**Figure 1.22.** Iodoperfluoroalkylation of olefin **76** (p. 36)
**Figure 1.23.** The chlorotrifluormethylation of terminal olefins (p. 37)
**Figure 1.24.** The chlorotrifluoromethylation of cholesterol (p. 37)
**Figure 1.25**. The electrocatalytic proposed mechanism of the chlorotrifluoromethylation reaction (p. 38)
**Figure 1.26.** The synthesis of metalloproteinase inhibitor (p. 39)
**Figure 1.27.** The three-component coupling of alkenes (p. 39)
**Figure 1.28.** The asymmetric three-component trifluoroalkylation reaction (p. 40)
**Figure 1.29.** Aglycons of candicanoside A and saundersioside from tigogenin (p. 41)
**Figure 1.30.** Skeletal diversity based on ring A and D rearrangement (p. 41)
**Figure 1.31.** Proposed mechanism for the formation of compounds **109**, **110** and **111** (p. 42)
**Figure 1.32**. Synthesis of eburnane family of indole alkaloids (p. 43)
**Figure 2.1.** Taxol and diterpenoids from sunflower *Helianthus annus L.* (p. 45)
**Figure 2.2.** Hydroazidation of methyl *ent*-kaurenoate (p. 46)
**Figure 2.3.** X-ray structure of methyl *ent*-17-azido-kaurenoate **135** (p. 46)
**Figure 2.4.** Radical transformations of methyl *ent*-17-azido-kaurenoate (p. 47)
**Figure 2.5.** Carboazidation and carboiodination of methyl *ent*-kaurenoate **135** (p. 50)
**Figure 2.6.** X-ray structure of compound **151** (p. 50)
**Figure 2.7.** X-ray structure of lactam **152** (p. 51)
**Figure 2.8.** Carboazidation and carboiodination of methyl 15α-hydroxy-*ent*-kaurenoate (p. 52)
**Figure 2.9.** X-ray structure of lactone **155** (p. 53)
**Figure 2.10.** Carboazidation and carboiodination of methyl 15α-hydroxy-*ent*-kaurenoate (p. 54)
**Figure 2.11.** Carbohydrogenation of methyl *ent*-kaurenoate (p. 55)
**Figure 2.12.** Carbohydrogenation of methyl 15α-hydroxy-*ent*-kaurenoate (p. 57)
**Figure 2.13.** Carbohydrogenation of methyl 15α-acetoxy-*ent*-kaurenoate (p. 58)
**Figure 3.1.** Forskolin and manoyl oxides (p. 81)
**Figure 3.2.** *Anti*-Markovnikov hydroazidation of *epi*-manoyl oxide and versatility of azido group (p. 82)
**Figure 3.3.** Carboazidation and carboiodination of manoyl oxide (p. 84)
**Figure 3.4.** Carboazidation and carboiodination of *epi*-manoyl oxide (p. 85)
**Figure 3.5.** Suggested mechanism for the triple radical translocation (p. 87)

**Figure 3.6**. Radical transformation of forskolin (p. 88)

**Figure 3.7**. Carbohydrogenation of manoyl oxide with ethyl iodoacetate (p. 89)

**Figure 3.8.** Carbohydrogenation of *epi*-manoyl oxide (p. 90)

**Figure 3.9.** Carboazidation of methyl *ent*-isocopalate **223** (p. 92)

**Figure 3.10**. NOESY correlation of compound **224** (p. 92)

**Figure 3.11.** Carboazidation of hydroxy *ent*-isocopalate (p. 93)

**Figure 4.1.** Natural verrucosins A and B (p. 114)

**Figure 4.2.** Isomerization of isocopalic diterpenes (p. 115)

**Figure 4.3.** Isomerization of diterpenic alcohol **225** (p. 116)

**Figure 4.4.** Key 2D correlations for the compounds **237** and **238** (p. 118)

**Figure 4.5.** Proposed reaction mechanism for the acid-promoted isomerization of **225** into **237** (p. 119)

**Figure 4.6.** Skeletal rearrangements of epoxide **241** under acidic conditions (p. 120)

**Figure 4.7.** Terpenes with labdanic, halimanic and clerodanic skeletons (p. 121)

**Figure 4.8.** Isomerization of homodrimane epoxide **246** (p. 121)

**Figure 4.9.** Proposed mechanism of epoxide **246** opening (p. 122)

## LIST OF ABBREVIATIONS AND SYMBOLS

| | |
|---|---|
| **Ac** | Acetate |
| **AIBN** | Azobisisobutyronitrile |
| **ATRA** | Atom transfer radical addition |
| **BHT** | Butylated hydroxytoluene |
| **bpy** | 2,2′-Bipyridine |
| **$B_2pin_2$** | Bis(pinacolato)diboron |
| **brsm** | Based on recovered starting material |
| **CatBH** | Catecholborane |
| **COSY** | Correlated spectroscopy |
| **CuTc** | Copper(I)thiophene-2-carboxylate |
| **DIPEA** | *N*,*N*-Diisopropylethylamine |
| **DBU** | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| **DEPT** | distortionless enhancement by polarization transfer |
| **DLP** | Dilauroyl peroxide |
| **DIC** | N,N′-Diisopropylcarbodiimide |
| **DMF** | Dimethylformamide |
| **DTBHN** | Di-*tert*-butyl hyponitrite |
| **DCM** | Dichloromethane |
| **DCC** | *N, N*′-Dicyclohexylcarbodiimide |
| **DMA** | *N*,*N*- Dimethylacetamide |
| **DMF** | *N*,*N*- Dimethylformamide |
| **dtbbpy** | 4,4′-Di-*tert*-butyl-2,2′-dipyridyl |
| **DTBP** | Di-*tert*-butyl peroxide |
| **dr** | Diastereomeric ratio |
| **EtOAc** | Ethyl acetate |
| **$Et_3B$** | Triethylborane |
| **e.r.** | Enantiomeric ratio |
| **ESI** | Electrospary ionization |
| **equiv.** | Equivalent |
| **GABA** | γ-aminobutyric acid |
| **FC** | Flash chromatography |
| **HFIP** | Hexafluoroisopropanol |
| **HSQC** | Heteronuclear single quantum coherence |
| **h** | hour |
| **HMBC** | Heteronuclear multiple bond correlation |
| **HRMS** | High-resolution mass spectrometry |
| **MeCN** | Acetonitrile |
| **Me** | Methyl group |
| **MeOH** | Methanol |
| **NaOCl** | Sodium hypochlorite |
| **NOESY** | Nuclear overhauser effect spectroscopy |
| **NSI** | Nanospray ionization |
| **PhIO** | Iodosylbenzene |
| **$PPh_3$** | Triphenylphosphine |
| **ppy** | 2-Phenylpyridine |
| **Ph** | Phenyl group |
| **r.t.** | Room temperature |
| **TMSCl** | Trimethyl silyl chloride |
| **TBDMSCl** | *tert*-Butyldimethylsilyl chloride |
| **$TsN_3$** | Tosyl azide |
| **TEMPO** | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| **TBC** | *tert*-Butylcatechol |
| **TFA** | Trifluoroacetic acid |
| **$TMSN_3$** | Trimethylsilyl azide |
| **TBAI** | Tetrabutylammonium iodide |
| **TBPB** | *tert*-Butyl peroxybenzoate |
| **TBAF** | Tetra-*n*-butylammonium fluoride |
| **SAR** | Structure-activity relationship |
| **SDS** | Safety data sheet |
| **s.m.** | Starting material |
| **Δ** | reflux |

# INTRODUCTION

## 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) from SDS 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 ans 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.

The presented thesis includes 4 chapters, divided into sections.

The first chapter with the title "**FUNCTIONALIZATION AND REARRANGEMENT OF NATURAL COMPOUNDS *VIA* FREE RADICAL AND CATIONIC INDUCED REACTIONS**" presents a literature review of the radical chemistry, exactly functionalization of natural compounds using radical reactions. 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. Nevertheless, due to cationic skeleton rearrangements, there were presented syntheses of natural compounds starting with commercially available terpenes.

The second chapter "**RADICAL TRANSFORMATIONS OF *ENT*-KAURANE DITERPENOIDS**" includes the results of author. In this chapter are presented the transformations of kaurenoic derivatives *via* radical reactions, such as carboazidation/carboiodination, hydroazidation and carbohydrogenation. The methyl 17-azido-16*β-ent*-kauran-19-oate that was synthesized by hydroazidation reactions was converted into amine, amides, triazoles and guanidines. There were also presented the results of some products which shown promising biological activities.

The third chapter "**RADICAL TRANSFORMATIONS OF LABDANIC AND ISOCOPALIC DITERPENOIDS**" includes carboazidation of the natural compound forskolin and the isocopalic related diterpenoids. Through carbohydrogenation reactions were obtained fluorinated products from *epi*-manoyl oxide. However, through hydroazidation and carboazidation reactions were obtained azides, which have been converted into amine and triazoles.

The fourth chapter "**SYNTHESIS OF SOME TERPENOIDS *VIA* CATIONIC REARRANGEMENTS**" includes the synthesis of the natural compound with *ent*-verrucosin, hyrtiosane and halimane skeleton using isomerization and skeletal rearrangement reactions as key strategies.

# 1. FUNCTIONALIZATION AND REARRANGEMENT OF NATURAL COMPOUNDS *VIA* FREE RADICAL AND CATIONIC INDUCED REACTIONS

Organic synthesis and radical chemistry intersected high synergy in the ‘80s, and the field of radical reactions in organic synthesis emerged. Nowadays, radical reactions are routinely considered in synthetic planning. Therefore, developing new ways for the generation and application of radicals is a highly demanding task. A variety of chemical transformations can be achieved using radical chemistry. Different steps of total synthesis include radical reactions as key steps [1] such as atom transfer radical addition methodology or C-H functionalization.

Atom transfer radical addition (ATRA) methodology represents a powerful method for building molecular architectures and it has been successfully reported for efficient modification of various substrates [2, 3]. The ATRA reactions are often used for the construction of C-C bonds, have been widely investigated over the past decade. These reactions can serve as a useful tool in organic synthesis for the step economy [1].

Synthesis of natural products and their analogues provide a fruitful field for ATRA methodology and, in our opinion, this potential is unexplored. There is still a prevalence in the scientific publications of cationic [4] processes reported for assembling C-C bonds in complex molecular frameworks, although successful examples involving ATRA are also known in natural product synthesis [5]. Sometimes radical additions represent the only solutions to overcome synthetic challenges connected to substrate reactivity and stereochemistry issues [6].

## 1.1. The radical C-H functionalization of natural compounds

The radical reactions can be used for the functionalization of C-H bonds of natural compounds [7, 8]. One can encounter some difficulties in the selective functionalization of natural compounds and complex molecules. The main difficulty is the selective functionalization of one functional group or C-H bond on the required position in the presence of other functional groups possessing similar reactivity. Another problem is the isolation of a desired pure product from the obtained mixture of products. Therefore, the reaction suitable for the selective functionalization of natural compounds should be carried out under mild conditions, in the presence of a wide range of functional groups, and should result in one product or an amenable mixture of just a few products [7].

*The C-H azidation of complex molecules*

The organic azides have been given great attention in chemistry, biology and medicine. The organic azides serve as functional groups in pharmaceuticals. For example, azidonucleotides have been reported to be markers in the treatment of AIDS [9]. Besides, they are used extensively in peptide chemistry and combinatorial chemistry due to their high stability under physiological condition and their unique reactivity, which allows them to be applied in bioconjugation *via* Staudinger ligation [10] or "click" chemistry [11]. Due to their unique physicochemical properties, organic azides have been used in numerous name reactions such as aza-Wittig reaction [12], Staudinger ligation [13], Boyer [14], Boyer-Aube [15], Sundberg [16], Curtius [17], Schmidt [18], and Hemetsberger [19] rearrangements.

Since the discovery of the first organic azide, phenyl azide by Peter Griess, in 1864 [20], numerous azidation reactions have been developed, enabling the synthesis of organic azides from a variety of functionalities [18]. These advances have significantly expanded the synthetic availability of this functional group. More recently, direct aryl C-H azidation through Friedel-Crafts reaction was performed using transition-metal catalysts (Cu, Pd or Rh) [21] or with hypervalent iodine reagents [22]. The direct aliphatic C-H azidation is scarce. Although hypervalent iodine reagent, such as $IN_3$ has been known for direct aliphatic C-H azidation. But the application of this reagent is limited to simple hydrocarbons, especially due to the harsh reaction conditions or its instability.

Deng *et al.* developed an enantioselective C-H azidation of *β*-keto esters with iron "boxmi" catalyst and azidoiodinane [23]. Later, manganese catalyzed C-H azidation was reported [24]. Manganese porphyrins and manganese-salen were used as catalysts and the aqueous sodium azide as azide source. Several bioactive molecules, such as adamantane, the terpenoid sclareolide, the estrogenic hormone, celestolide, the antimalarial artemisinin, and the ibuprofen were modified applying this method providing the corresponding azides (Figure 1.1, **1**-**6**).

The regioselectivity of C-H activation could be regulated by the proper choice of the ligand. For example, azidation of adamantane with Mn(TMP)Cl led to the ratio 1.5:1 of tertiary to secondary products **1** compared to 4:1 using manganese-salen catalyst (Figure 1.1). Sclareolide afforded C2 azidation as the major product in 57% yield and a high α/β ratio of 7:5 (Figure 1.1, **2**). In the case of estrone acetate, the major product was a diazidation product with both C9 and C6 being activated (Figure 1.1, **3**). The C10 tertiary azide was exclusively formed from the fragile molecules like artemisinin and manganese-salen catalyst (Figure 1.1, **5**).

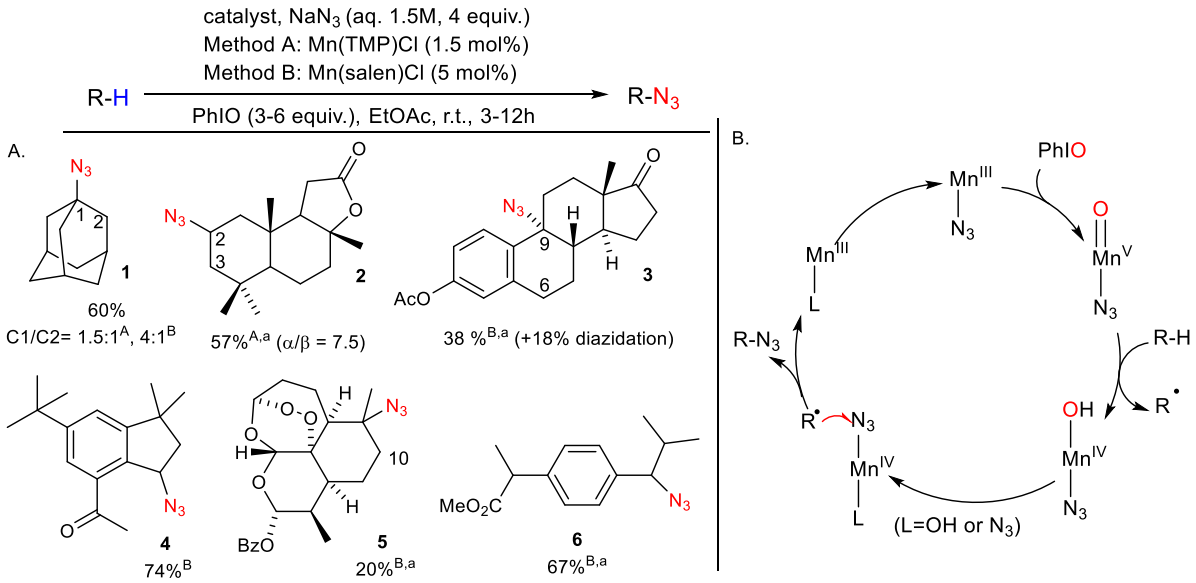



**Fig. 1.1. *A.* The C-H azidation of complex molecules *B.* Plausible mechanism [24].**

*Conditions*: ***a.*** Methyl acetate was used as solvent.

Catalytic cycle of manganese was suggested for the explanation of the reaction mechanism (Figure 1.1B). Oxidation of the Mn(III) catalyst by PhIO, led to the oxo-Mn(V), which then abstracts hydrogen forming Mn(IV)-OH species. The unique Mn(IV)-OH intermediate undergoes recombination of the hydroxy group providing Mn(IV)-$N_3$ intermediate, which was found to trap substrate radicals by efficient azide rebound process to yield the desired azidated products [25].

In their recent contribution, Sharma and Hartwig reported an elegant protocol for late-stage azidation [26] using the reactivity of azidobenziodoxolone reagent [27]. It is the first iron-catalyzed C-H azidation reaction on complex molecular scaffolds (Figure 1.2). For example, the ketone prepared from (2)-carvone underwent azidation at the tertiary C-H bond remote from the carbonyl center with high regioselectivity (Figure 1.2, **9**). $\alpha$-Dihydropinene, containing three electronically similar, but sterically distinct, tertiary C-H bonds providing 80% yield of azide **10** as a single isomer. Acetoxymenthol containing two electronically similar tertiary C-H bonds reacted preferentially at the *iso*propyl site leading to one major azide **11** in moderate yield. Biologically active molecules containing multiple C-H bonds can be selectively modified as well. For instance, podocarpic acid derivative possessing antileukemic activity, inhibition of plant cell growth and anti-inflammatory properties can undergo selective azidation at the benzylic C-H bond in high yields and good diastereoselectivity (Figure 1.2, **12**). Another example is gibberellic acid derivative. This compound is a plant hormone and pentacyclic diterpene containing four tertiary C-H bonds and multiple chiral centers. Its azidation occurs

selectively at C8 position, the most electron-rich and least sterically hindered tertiary C-H bonds, with 75% yield (Figure 1.2, **13**). Azidation of the betulinic acid derivative containing an electron- withdrawing carboalkoxy group did not provide azidation product **14**, but a structurally similar betulin derivative containing a more electron-donating acetoxymethyl group at a nearby center gave azide **15** in moderate yield (48%) [28].

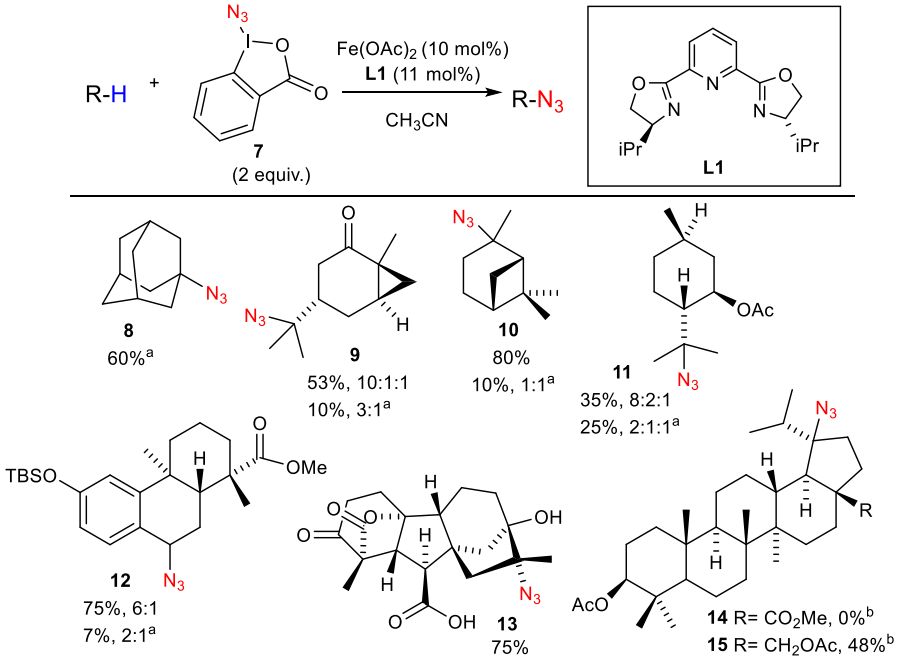



**Fig. 1.2. Iron-catalyzed C-H azidation of natural compounds [26]**.

*Conditions*: ***a.*** 10 mol% BzOOBz, 84 °C and 1,2-dichloroethane (1.0 mL) as solvent.
***b.*** Reaction was conducted in EtOAc

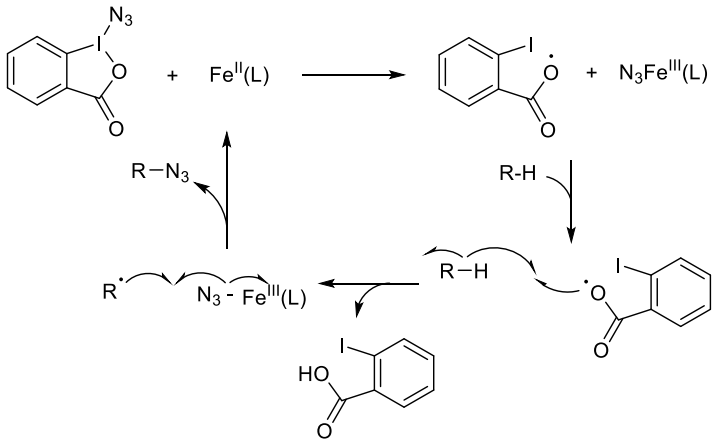



**Fig. 1.3. Plausible mechanism of C-H azidation [25].**

Functionalization of the complex molecules initiated by benzoyl peroxide demonstrated very low yields and poor selectivity, only with adamantane the desired product was observed in 68% (Figure 1.2, **8**) [28]. Selectivity in azidation using this method is lower than that in iron-

catalyzed reactions; diastereomeric ratio is very different as well. Preliminary mechanistic study of this reaction proved that the reaction proceeds through the radical pathway, as the addition of radical traps (BHT or TEMPO) completely inhibited the reaction. The iron pybox catalyst oxidizes the azidoiodinane generating 2-iodobenzoyloxy radical, which abstracts hydrogen from corresponding alkanes, generating alkyl radical. This alkyl radical reacts with azidoiron (III) intermediate providing desired azidation product, 2-iodobenzoic acid leaving as a side product (Figure 1.3) [25].

Recently, Tang *et al*. [29] reported direct C-H azidation using sulfonyl azide as the azide source without transition metal catalysis. This method requires mild conditions and can be applied for azidation of complex molecules such as artemisinin, pleuromutilin derivative or sclareolide (Figure 1.4). The azidation of sclareolide, which show antifungal and cytotoxic activities, lead to azide **18** in 29% isolated yield as the major isomer and 18% starting material. Pleuromulin derivative which has five C-H bonds reacts smoothly providing compound **19** with 24% yield and 43% of recovered starting material. Azidation at C11 methylene position occurred as the major process, because this position is more electron-rich and less sterically hindered in comparison to other positions. In the case of artemisinin (drug against *Plasmodium falciparum* malaria), which contains also five C-H bonds and a peroxide bridge, the reaction proceeded smoothly providing the azidation product **20** (33% yield and 18% starting material). The selective azidation occurred at the C6 methine position leading to the major product.

The proposed reaction mechanism is depicted in Figure 1.4B. Potassium persulfate was used as an oxidant, which generates sulfate radicals by heating. Sulfate radical oxidizes the aliphatic C-H bonds into a carbon-centered radical (**II**). Generated radical is subsequently trapped by sulfonyl azide yielding azidation product (**III**).

The vast utility of azide-containing molecules lies in the synthetic versatility of this functional group, which can be readily transformed to amines, amides, triazoles, tetrazoles, etc. The blossoming of “click” chemistry in recent decades has given organic azides an irreplaceable role in chemical biology, drug discovery and material science (Figure 1.5) [26, 30].

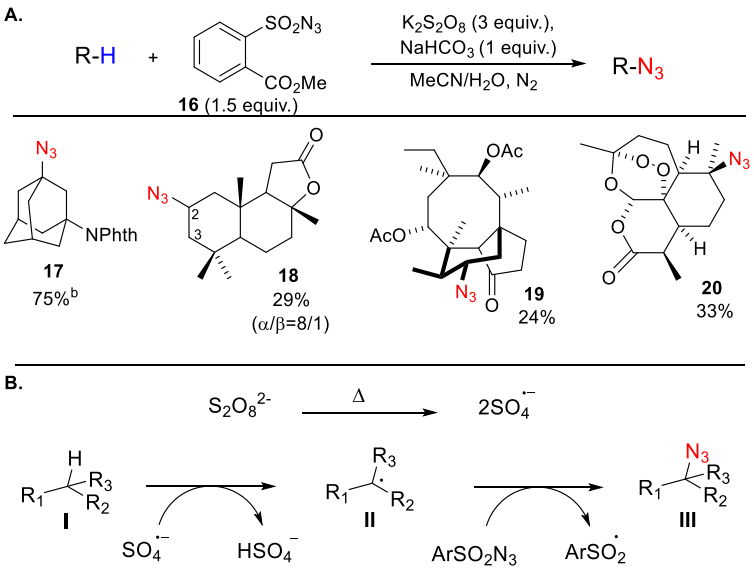



**Fig. 1.4. *A*. The transition-metal-free oxidative C-H azidation of complex molecules. *B*. The suggested mechanism [29].**

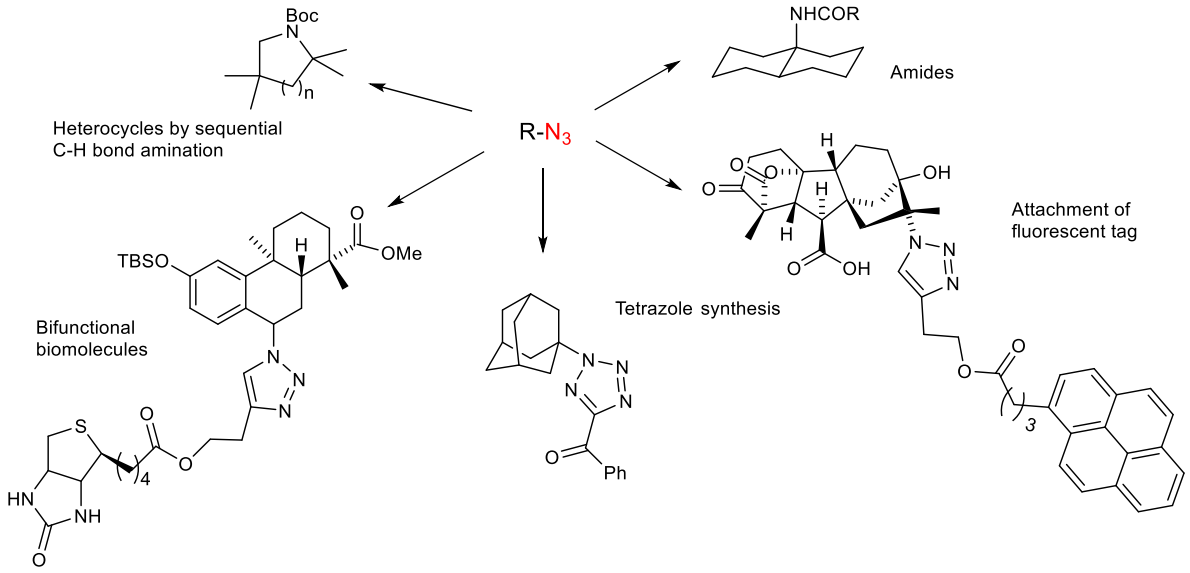



**Fig. 1.5. Late-stage diversification of azides [26].**

*Electrochemical C-H oxidation*

Electrochemical oxidation is a very attractive alternative for traditional oxidation used for the modification of natural compounds, in large part owing to the generation of less toxic waste [31]. Electrochemical reactions can be conducted either in oxidative or in reductive conditions, depending on the nature of the substrate, chosen electrodes, electrolyte and solvent. In a galvanic cell, oxidations take place at the anode and reductions at the cathode. The exceptionality of the electrochemical reactions from many ionizing reactions arises from the fact that they take place

on the surface of electrodes and produce highly reactive intermediates such as radical-cations and radical-anions diffusing into solution [32].

In recent years, electrochemical synthesis has witnessed rapid development in organic chemistry [33, 34], representing the key step in many syntheses of natural compounds [35, 36]. For example, in 2016 Baran reported allylic C-H oxidation [37] using cheap and readily available materials compared to standard conditions for electrochemical reactions: highly toxic reagents (such as salts of chromium (VI) or selenium) or expensive catalysts (such as salts of palladium or rhodium). The reaction takes place at room temperature and can be the simple set-up of two reticulated vitreous carbon (RVC) electrodes separated by a glass slide under constant current conditions (10 mA/mmol). Some examples of electrochemical allylic oxidation of terpenes (**21-24**) are shown in Figure 1.6A in comparison with the standard conditions of electrochemical reactions. Verbenone **21,** previously prepared in 13-23% [38], was prepared in 67%. The corresponding reaction with chromium (VI) provided just 49% yield [39]. Carvone **22** was obtained with better yield than when chromium (VI) was used, but the same for the rhodium-catalyzed process (42% yield).

The oxidation of steroid derivatives was made to improve properties such as solubility and pharmacokinetics. Electrochemical oxidation of unprotected dehydroepiandrosterone (DHEA) gave product **23** with 72% yield. Protected acetate-DHEA could also be oxidized to give the enone **24** in 81% yield (Figure 1.6A).

The scalability of this method was successful for all presented examples. The reaction was conducted using inexpensive graphite plate electrodes in a beaker. $LiBF_4$ was used as the supporting electrolyte. Compound **21** was prepared in 55%. Further, scale up to 100 g gave 46% yield of **21**. Product **22** was obtained from limonene on a 27 g scale in 44% yield. Sterol **23** and its acetate **24** were obtained in 48% and 62% yields respectively. Big advantages of this method are simplicity, safety, simple workup and simple isolation of the desired product.

A year later, Kuwamata reported another paper [40] where he used a simple redox mediator, quinuclidine, with cheap carbon and nickel electrodes for selective functionalization of methylene and methine fragments in complex molecules. The reaction proceeds at room temperature in a simple undivided cell under constant current conditions (25 mA/mmol). The aim of this work was to transform methylene groups into ketones. The yields and selectivity were comparable to those obtained in methyl (trifluoromethyl)dioxirane (TFDO) oxidation [41] or Barton-Gif-type (iron based) processes [42] (Figure 1.6B, **25-28**). Oxidation of complex molecules gave satisfactory results. Product **30** from *iso*-steviol ethyl ester was obtained in 48%

yield. Electrochemical oxidation of sclareolide occurred selectively at C2, but with TFDO elicited mainly C3.

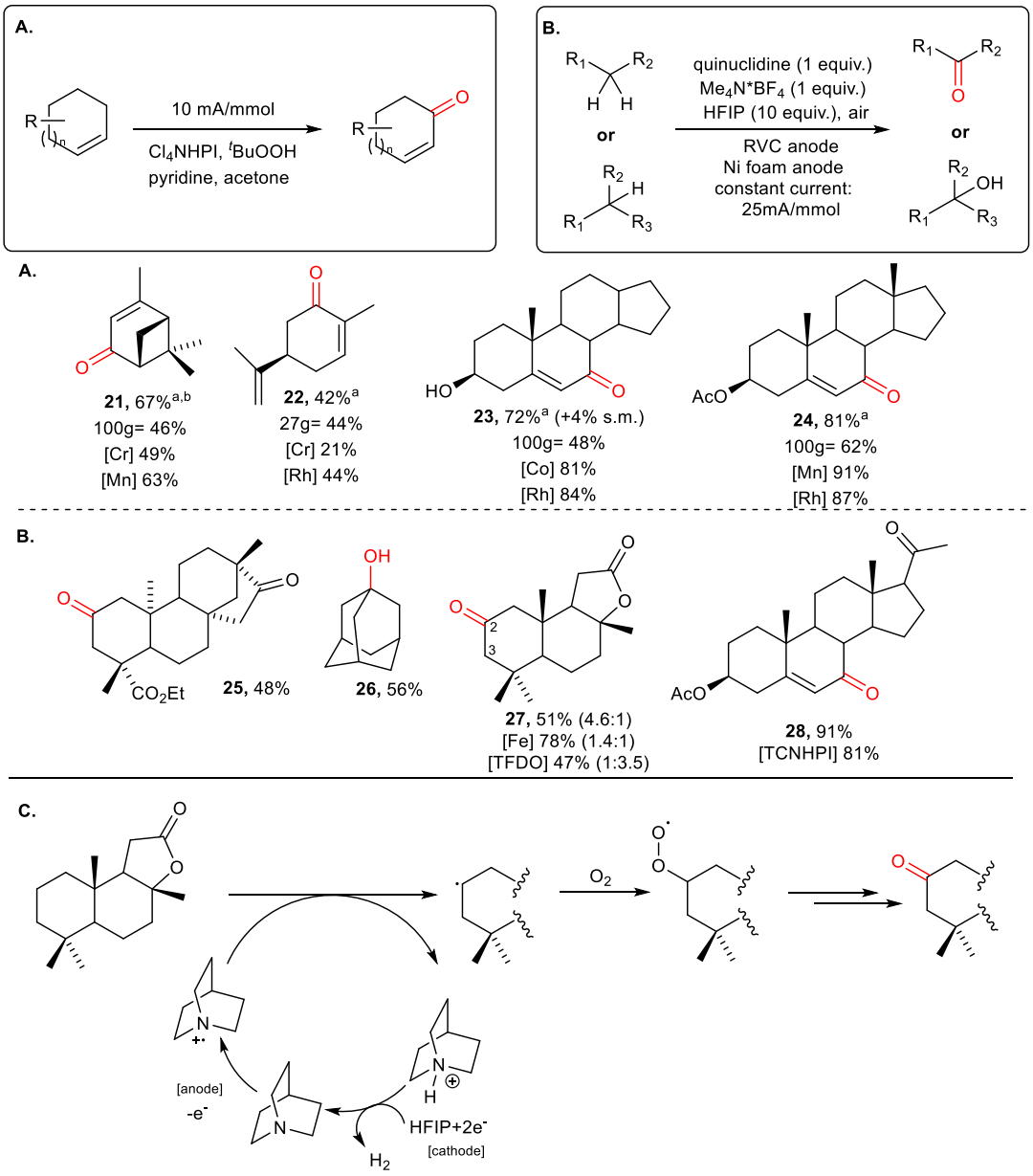



**Fig. 1.6. *A.* and *B.* The electrochemical C-H oxidation of complex molecules. *C.* The putative mechanism [37, 40].**

The mechanism of electrochemical C-H oxidation involves a quinuclidine radical cation generated after anodic oxidation. This high-energy species could homolytically cleave the C-H bond. The reaction between the ensuing carbon-centered radical and molecular oxygen then affords the oxidation product. HFIP served as the electron acceptor to generate $H_2$ in the cathodic process (Figure 1.6C) [37].

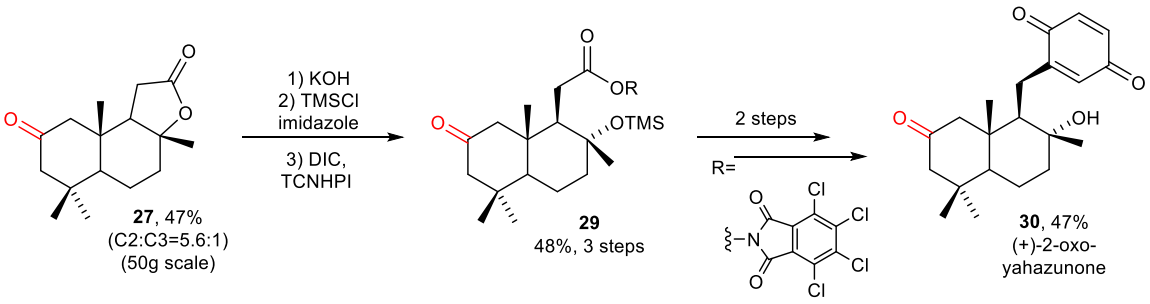



**Fig. 1.7. The synthesis of 2-oxo-yahazunone from 2-oxo-sclareolide [40].**

As it has been mentioned above, electrochemical oxidation plays an important role in the synthesis of natural compounds (Figure 1.7). Kuwamata reported a convenient method for the synthesis of meroterpenoids, using sclareolide as starting material [43]. 2-Oxo-sclareolide **27** was converted into compound **29** in three steps with 48% yield, and just in two steps was obtained the bioactive natural compound, (+)-2-oxo-yahazunone **30** in 47% yield [40].

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

Atom transfer radical addition (ATRA) of alkenes provides a useful tool to create C-C and C-X bonds [44-49] and represents a powerful method for building molecular architectures and it has been successfully reported for efficient modification of various substrates [2, 3]. ATR offers attractive routes to synthesize pharmaceutically important molecules. Reductive radical addition of alkenes represents one of the mildest procedures for the carbon-carbon bond formation. The main advantages of this process relate first of all to the atom economy and mildness of reaction conditions, making it a procedure of choice when dealing with complex substrates including multiple functional groups.

*Radical azidation of olefin and formation of new C-C bond*

The radical azidation reaction has proven to be an efficient method to install different radicals and azide moiety. Azide transfer reaction has been utilized as a point to generate organic azides of significant synthetic importance [50]. In this context, hydroazidation, carboazidation, azidocyanation and diazidation of olefins using different azide sources and conditions have been presented in this subchapter.

The hydroazidation reaction is very attractive due to the rich chemistry of organic azides [50, 51]. Carreira reported cobalt catalyzed hydroazidation of unactivated olefins to the azides with high Markovnikov selectivity using tosyl azide and a silane [52]. The reaction is mediated by a simple cobalt catalyst prepared in situ from Schiff base **32** and $Co(BF_4)_2$*$6H_2O$ [53, 54]

(Figure 1.8). *Anti*-Markovnikov hydroamination of alkenes is known [55], and also Studer reported a radical mediated *anti*-Markovnikov hydroamination of olefins [56].

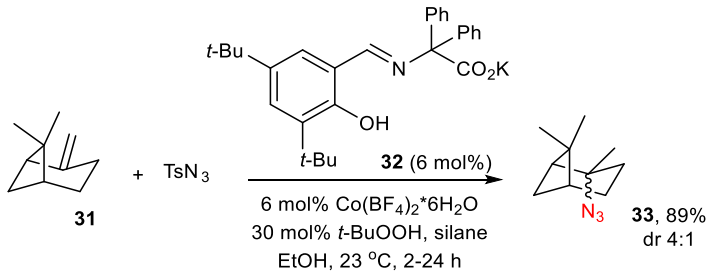



**Fig. 1.8. Cobalt-catalyzed Markovnikov hydoazidation of olefin [53].**

Later, Renaud reported one pot *anti*-Markovnikov hydroazidation of olefins. The procedure involved hydroboration with catecholborane followed by the azidation with benzene sulfonyl azide in the presence of DTBHN as radical initiator [2, 5].

(+)-$\alpha$-Pinene was hydroborated with 2 equiv. of catecholborane in $CH_2Cl_2$ using *N*,*N*-dimethylacetamide as a catalyst. After completion of the hydroboration, the excess of CatBH was treated with *t*-BuOH. Then, *in situ* generated organoborane was treated with benzene sulfonyl azide and 0.1 equiv. of DTBHN as a radical initiator in *N*,*N*-dimethylformamide. The desired azide **34** was obtained in 78%. The hydroazidation reaction of cholesterol afforded the azide **35** in 37%, but with (-)-carene afforded ring-opened azide **36** in very good yield (79%) (Figure 1.9).

Hydroazidation of natural compound, (-)-isolongifolene, took place from the less hindered face and was detected only one diastereomer **37**. The azidation of $\beta$-citronellene afforded the efficient cyclization into azide **38** in good yield and ratio 9:1.

The proposed mechanism of the *anti*-Markovnikov reaction was presented in Figure 1.9. Under the thermal condition, DTBHN was decomposed into *tert*-butoxyl radical, which reacted with $\beta$-alkylcatecholborane. Then, the resulting radical reacted with benzene sulfonyl azide gave the alkyl azide and a benzene sulfonyl radical, which propagated the chain by homolytic substitution of the starting $\beta$-alkylcatecholborane.

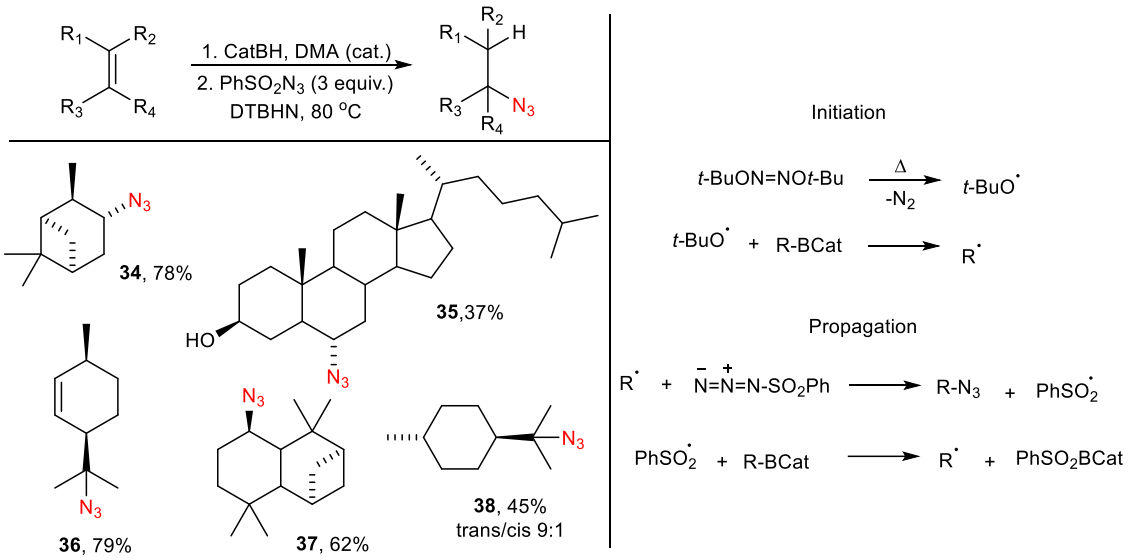



**Fig. 1.9. *Anti*-Markovnikov hydroazidation of olefins. Proposed mechanism [2, 5].**

The *anti*-Markovnikov hydroazidation reaction was shown as the key step in the different total synthesis, for example, in the synthesis of (+)-rodocaine [57] presented in Figure 1.10. Hydroazidation of **39** with monoisopinocampheylborane ($IpcBH_2$) afforded the *trans*-azide **40** in 61% yield as a single diastereomer. Rodocaine **41** was obtained over an additional five steps in 68% yield (74:26 e.r.). Recrystallization gave the enantiomerically pure product in 15% yield [58].

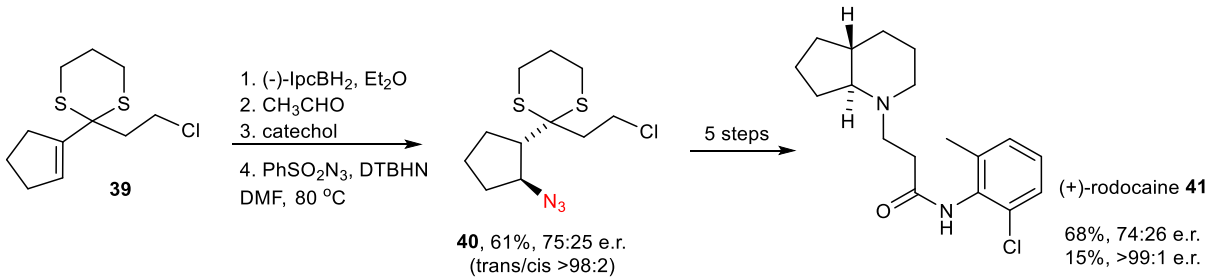



**Fig. 1.10. Synthesis of (+)-rodocaine [57].**

Another interesting paper was reported by Sun and co-workers [59]. They developed *anti*-Markovnikov hydroxyazidation using inexpensive Mn-catalyst and air as oxidant. Hydroxyazidation of complex bioactive molecules afforded the desired products in good yields (Figure 1.11) [59]. The reaction of steroid **42** led to the formation of compound **43** in 79% yield. The olefin derived from (+)-$\delta$-tocopherol **44** was suitable for the azidation reaction by changing the solvent from MeCN to ethyl acetate to enhance its solubility. The compounds **43** and **45** can be potential intermediates in medicinal chemistry.

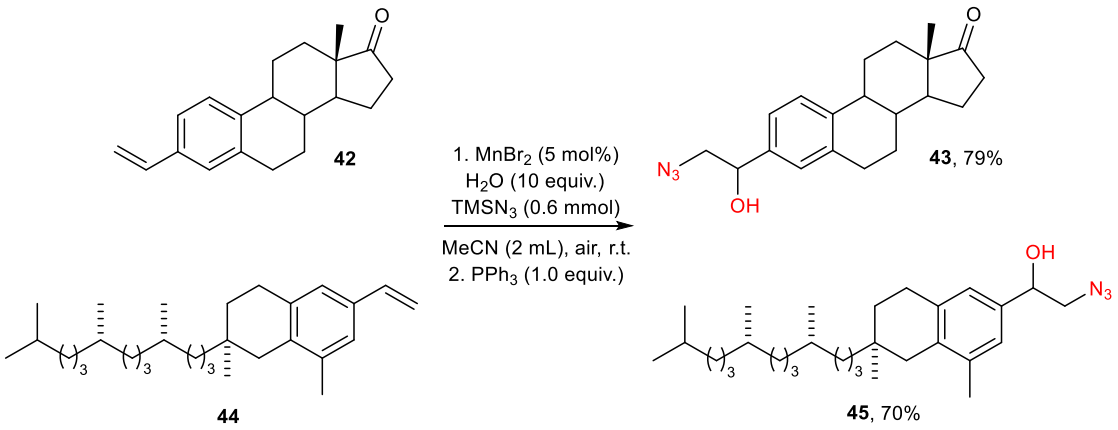



**Fig. 1.11. Radical *anti*-Markovnikov hydroxyazidation of bioactive molecules [59].**

The authors proposed the mechanism for hydroxyazidation reaction. Under the standard conditions, $MnBr_2$ catalyst is oxidized to $Mn^{III}$ or $Mn^{IV}$ by dioxygen. Subsequently, $Mn^{III}$ oxidizes $TMSN_3$ to form azido radical **A**. $Mn^{IV}$ can also participate in the oxidation of $TMSN_3$ to form azido radical **A** with the generation of $Mn^{III}$ catalyst [60]. The generated azido radical **A** then attacks alkene at the sterically less hindered position, producing carbon radical **B** which is trapped by molecular oxygen to form peroxyl radical **C**. According to the DFT calculation, it is favorable for the peroxyl radical **C** to undergo Mn-participated SET and protonation processes to afford *β*-azido peroxy alcohols **D**. In comparison, the pathway through **INT4** is disfavored. Finally, *β*-azido peroxy alcohol **D** is reduced by $PPh_3$ to form *β*-azido alcohol (Figure 1.12).

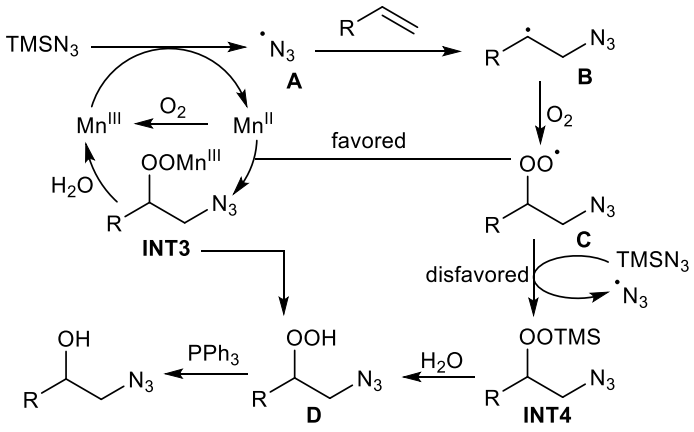



**Fig. 1.12. Proposed mechanism of *anti*-Markovnikov hydroxyazidation [59].**

Diazidation reactions are very interesting for organic and pharmaceutical chemistry because of the diverse applications of diazides. The 1,2-diazides could serve as precursors for the synthesis of valuable 1,2-diamines [61] which are prevalent in bioactive compounds and molecular ligands. Recently Lin group disclosed the metal-catalyzed electrochemical diazidation of simple olefins [62, 63], and Zhou and co-workers reported the copper-catalyzed, ligand-free

diazidation of olefins with $TMSN_3$ in organic solvent and water [64]. Zhou investigated not only simple olefins but also natural compounds such as nootkatone and drug molecules.

The drug molecules simvastatin against dyslipidemia and exemestane were converted into diazide products **46** and **47** as single isomers in 64% and 75% yields (Figure 1.13). In addition, the natural product nootkatone, a component of grapefruit was transformed to compound **48** in 56% yield and 1:1 diastereoisomeric ratio.

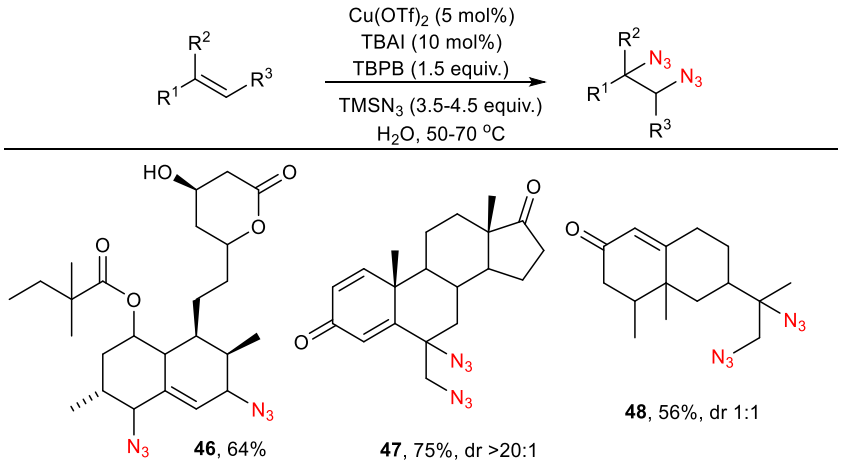



**Fig. 1.13. Diazidation of natural compounds [64].**

Renaud and co-workers [65-68] reported examples of the carboazidation. The carboazidation of olefins involves the addition of an ethyl iodoacetate **50** as an electron-poor radical and sulfonyl azide as an electrophilic radical trap. The reaction of hexabutylditin with sulfonyl radicals can sustain a chain reaction. Moreover, hexabutylditin is inert towards alkyl radicals and no competing reaction such as the direct stannation of the intermediate alkyl radical is expected.

In Figure 1.14 is presented the carboazidation reaction of oct-1-ene **49** and methylene cyclohexane **52** in different conditions. Tin-free carboazidation of oct-1-ene with triethylborane and benzene sulfonyl azide in ethanol and water led to the formation of azide **51** in 81% yield, but tin-mediated carboazidation afforded the product **51** in 79% yield. The desulfonative reaction with a sun lamp, di-*tert*-butyldiazene and sulfonyl azide afforded the azide **51** in 86% yield. In the case of methylene cyclohexane **52**, carboazidation with hexabutylditin gave the azide **53** in good yield (89%), and with triethylborane at room temperature led to the formation of the product **53** in the same yield (88%). On treatment with sulfonyl azide upon irradtion, the olefin gave the azide **53** in better yield, in 92%.

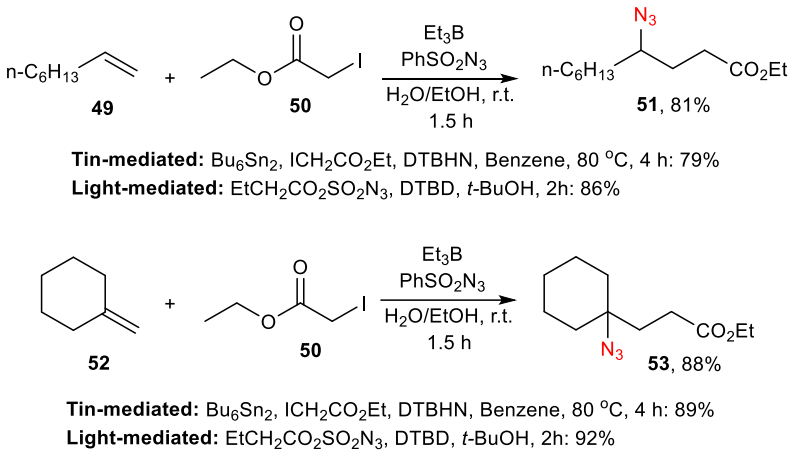



**Fig. 1.14. Carboazidation of olefins using different conditions of the reactions [65, 66, 68].**

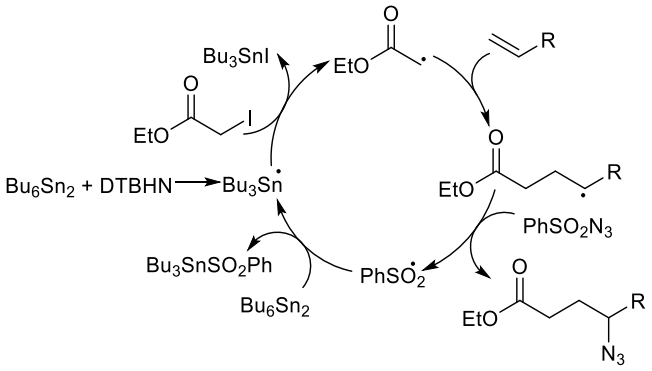



**Fig. 1.15. The proposed mechanism for the tin-mediated carboazidation reaction [65].**

Mechanistically, under thermal initiation by di-*tert*-butyl hyponitrite hexabutylditin afforded stannyl radical (Figure 1.15). The abstraction of iodide from ethyl iodoacetate by the stanny radical was followed by coupling to olefin, affording the carbon centered radical. This radical is azidated by benzene sulfonyl azide and gives the desired product. The sulfonyl radical is preserved and its addition to the ditin reagent sustains the chain process [65].

The synthetic utility of the radical carboazidation reaction has been demonstrated by the formal total synthesis of lepadiformine **56** [48] and hyacinthacine $A_1$ **59** [69, 70]. Carboazidation of allylsilane **57** showed not only good yields, but also a good level of 1,2-stereoinduction (Figure 1.16).

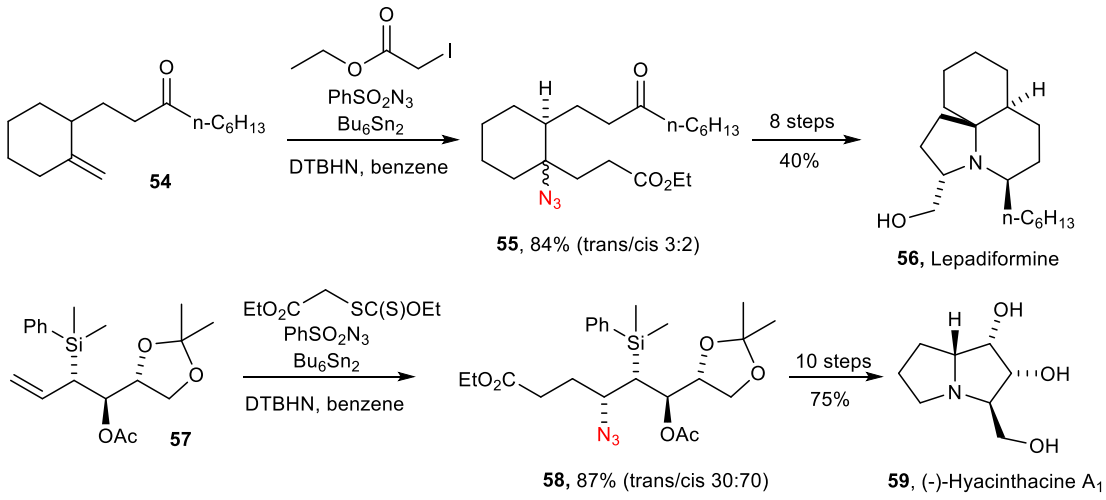



**Fig. 1.16. Application of the radical carboazidation reaction in total synthesis [48, 69].**

Other carboazidation reactions were reported by Zhang and co-workers using dimethyl sulfoxide as a methyl source and $H_2O_2$ as an oxidant [71] and Li group reported carboazidation of terminal styrenes with DTBP as oxidants and a catalytic amount of iron [72].

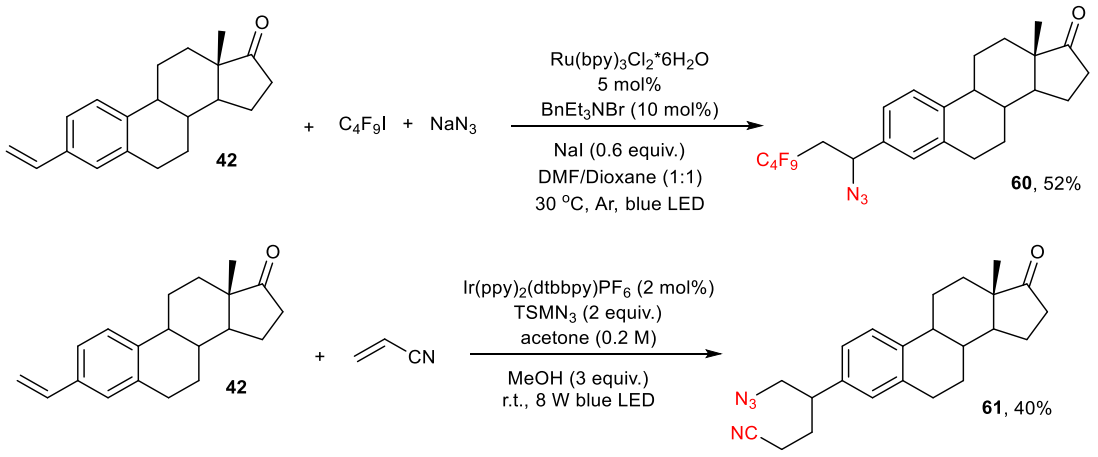



**Fig. 1.17. The carboazidation reaction of estrone derivative *via* blue LED [74, 75].**

Fluoroalkylated compounds are widely used in different fields such as materials science, agrochemistry, and medicinal chemistry owing to their unique biological properties [73]. In this regard, olefin difunctionalization represents the ideal and most straightforward way for the introduction of fluorinated functional groups.

Geng and co-workers [74] accomplished the radical azidoperfluoroalkylation of olefins using $Ru(bpy)_3Cl_2$ as photocatalyst and perfluoroalkyl iodides as a radical source in the presence of $NaN_3$. The azidoperfluoroalkylation reaction of the estrone derivative **42** with blue LED lead to the formation of the perfluoroazide **60** in 52% yield. But, Yang has used LED too for the

cyanoazidation reaction [75], with $TMSN_3$ and acrylonitrile afforded the corresponding azide **61** in only 40% yield (Figure 1.17).

The important point of the perfluoroalkylazidation reaction was that the addition of $NaN_3$ or NaI to the excited Ru catalyst resulted in a strong enhancement effect. This result indicated that reductive quenching of $Ru^{II*}$ by $NaN_3$ or NaI was involved in the mechanism. The proposed mechanism starts with excitation of the $Ru^{II}$ photocatalyst by irradiation with a blue LED, generating the excited $Ru^{II}$ catalyst, which can oxidize azide anion to form azide radical, producing $Ru^{I}$ (Figure 1.18) in the process. This reduced state of the Ru catalyst is an excellent reductant of $C_4F_9$-I, generating the $C_4F_9$ radical in the process and re-establishing the catalyst in its original oxidation state. The $C_4F_9$ radical adds to the olefin to generate radical adduct I, which is trapped by azide radical to form the product.

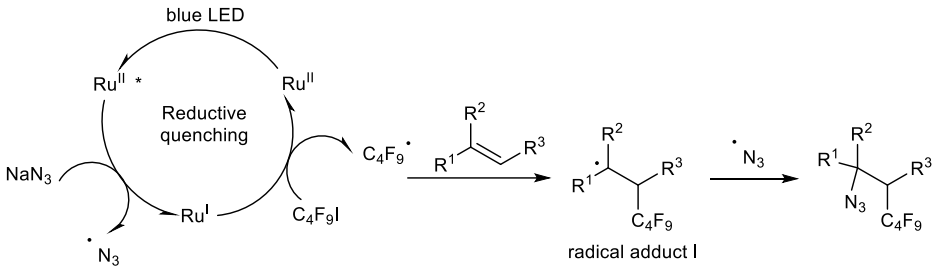



**Fig. 1.18. The plausible mechanism of azidoperfluoroalkylation reaction [74].**

Recently, Zhang described a new method for the synthesis of β-azidosulfonates using Cu(I)-mediated radical azidation of alkenes with sodium sulfonates [76]. As we know, sulfones are key synthons in many synthetic transformations and display diverse biological activities, making them one of the major components in the pharmaceutical agents [77]. The azido sulfonylation reaction with $TMSN_3$ and $NaSO_2R$ in the presence of oxidants and a cooper catalyst was reported by Zhang [76].

Various aliphatic and aromatic sodium sulfonates were proven to be suitable sulfonylation reagents, leading to diversified precursors for drug analogues (**62-66**) (Figure 1.19). Especially, compound **63** could serve as the intermediate for the synthesis of drug Apremilast **67** [78].

The plausible mechanism is shown in Figure 1.19. The *tert*-butoxyl radical reacted with $RSO_2Na$ to afford a sulfonyl radical that adds to the olefin can generate an internal radical [79]. The $Cu^{II}OBz$ species undergoes ligand exchange with azide to give $Cu^{II}N_3$. In path a, $Cu^{II}N_3$ reacted with an internal radical and led to the $Cu^{III}$ complex, which undergoes reductive

elimination to the product with the regeneration of the $Cu^{I}$ catalyst. In path b, a direct SET process possibly leads to the same products (Figure 1.19).

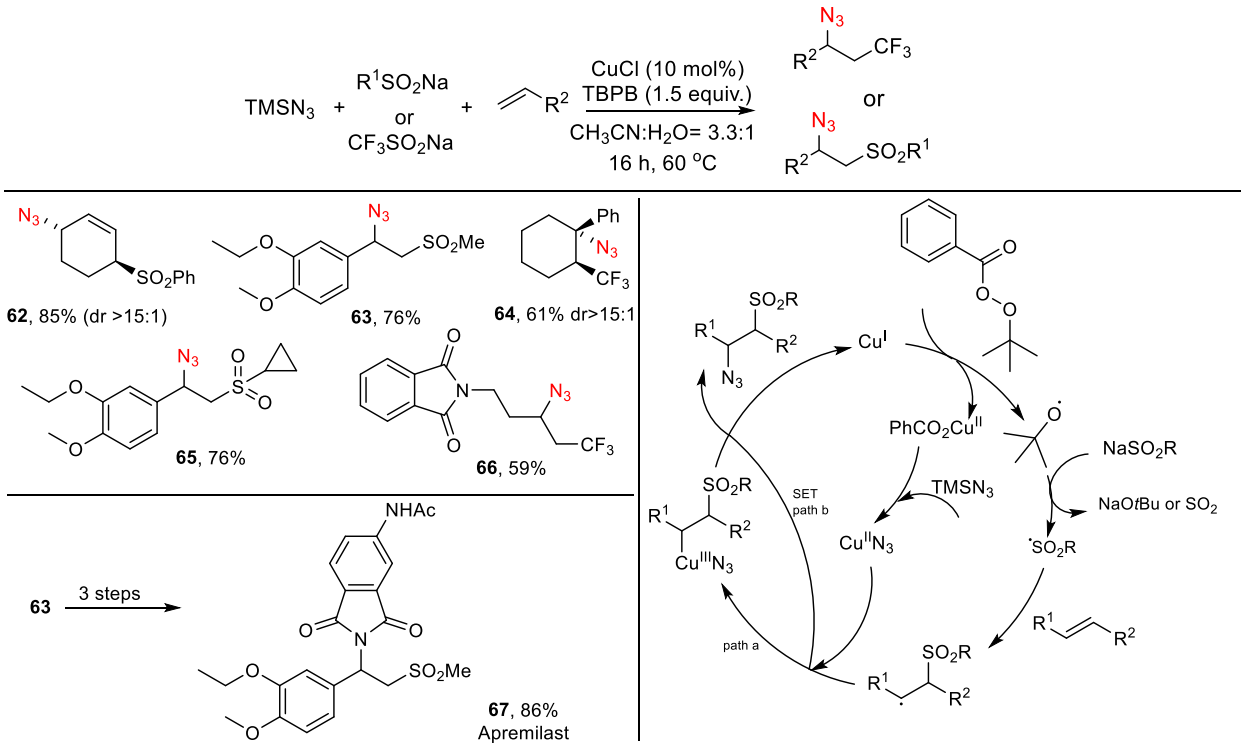



**Fig. 1.19. The azido sulfonylation reaction of alkenes and the proposed mechanism [76].**

*The other radical functionalization with the formation of the C-C and C-X bonds*

Kharasch developed the first example of atom transfer radical addition (ATRA) several decades ago [80, 81]. He reported a bromine atom transfer addition of an electrophilic carbon-centered radical onto a terminal bond in which both a carbon-carbon and carbon-bromine bond are formed. Many papers were reported after Kharasch method, such as ATRA mediated by metal, tributyl hydride, AIBN [82] or visible light [83]. Recently, Kokotos and co-workers reported the synthetic protocol for the ATRA addition of bromoacetonitrile using iridium$^{III}$ complex as the photocatalyst onto olefins with various functional groups [84]. The ATRA reaction of alkenes with non-toxic bismuth oxide as photocatalyst and organobromides under mild reaction conditions involving sunlamp have been reported by Pericas [85].

Melchiorre et. al reported the ATRA reaction using metal-free photochemical process [86]. The ATRA bromination reaction took place under mild conditions and with *p*-anisaldehyde **69** as a catalyst, 2,6-lutidine and 23W compact fluorescent light. The reaction of bromomalonate **68** with 2-norbornene led to the formation of the desired product **70** in 89% yield. The natural compounds, (*R*)-limonene and (-)-*β*-pinene participated in the ATRA process to give the

products **71** and **72** in excellent yields. The cyclobutane ring was opened and led to compound **72** in 90% yield. The reaction of a haloalkane was successfully implemented on a gram scale, and the product **73** was isolated in 99% yield and the catalyst was recovered (>90%).

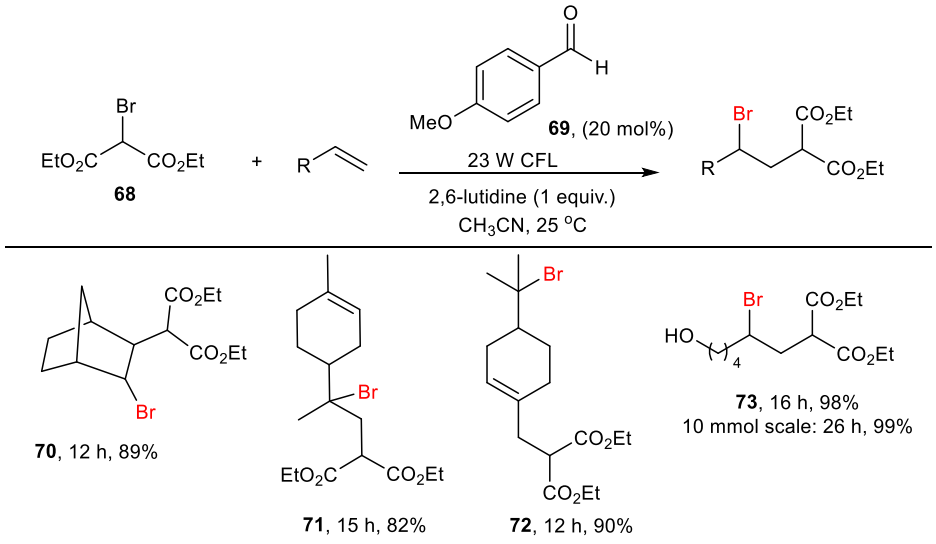



**Fig. 1.20. The ATRA bromination reaction [86].**

Recently, Kong and co-workers developed an unconventional reductive difluoroalkylation of terminal olefins [87]. They used $B_2pin_2$ as an organic reductant and two different electrophiles mediated by visible light. The substrate **74** derived from di-*iso*propylidene galactopyranose was a suitable candidate for the difluoroalkylation-thiolation and afforded the corresponding product **75** in good yield (Figure 1.21).

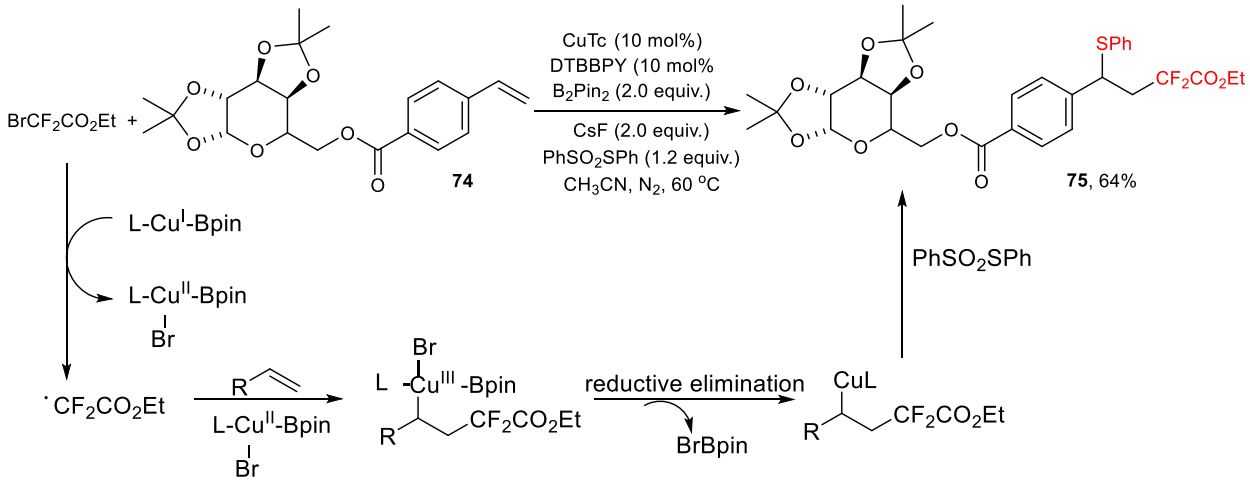



**Fig. 1.21. The reductive radical difluoroalkylation-thiolation of compound with sugar moiety [87].**

The proposed mechanism is shown in Figure 1.21. Authors speculated that a SET process between $BrCF_2CO_2Et$ and the $Cu^I$-Bpin intermediate would generate the $^{\cdot}CF_2CO_2Et$ radical and

the $Cu^{II}$ complex. Then, the radical ($^{\cdot}CF_2CO_2Et$) is added to olefin and is trapped by the Br-$Cu^{II}$-Bpin intermediate, the next $Cu^{III}$ intermediate was formed which then underwent reductive elimination to deliver the $Cu^{I}$-$CCF_2CO_2Et$-nucleophile intermediate. Thus, the intermediate with dibenzenesulfonothiolate ($PhSO_2SPh$) afforded the desired product, in that case the compound **75**.

In recent years, many radical reactions have been published using iodo- and trifluoromethyl agents [88-90]. The compounds containing fluorine atom or trifluoromethyl group are widely used in the pharmaceutical and medicinal chemistry, due to their properties such as lipophicity, permeability and metabolic stability [91]. Because of the prevalence of alkenyl moiety in biologically active compounds and synthetic intermediates, the trifluoromethylation of alkenes with the simultaneous formation of C−C or C− heteroatom bonds are an especially practical and powerful strategy for preparing trifluoromethylated building blocks for bioactive compounds [92].

Recently, Rawner published the paper using the visible light-mediated photoaddition of perfluoroalkyl iodide ($C_8F_{17}I$) with olefins and copper catalyst, pointing its unique role beyond initiating the ATRA process by a photoelectron transfer [93]. Marsuzaki and co-workers used red light irradiation with trifluoroiodomethane and various photocatalysts [94]. Beniazza and co-workers reported the trifluoromethylation of olefins using Togni reagent and benzophenone in *i*-PrOH and irradiating the reaction at 365 nm [95]. Later, Beniazza group reported the same reaction under low-intensity UVA (6 W) irradiation of alkene **76** in deoxygenated methanol solutions containing catalytic amounts of $Bu_4NCl$ leading to the formation of compound **77** in 68% yield (Figure 1.22) [96].

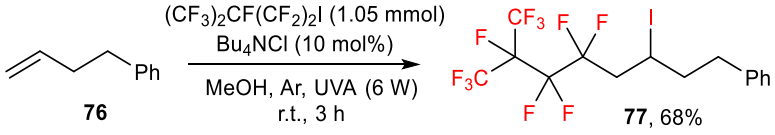



**Fig. 1.22. Iodoperfluoroalkylation of olefin 76 [96].**

Hu and co-workers reported the chlorotrifluoromethylation of terminal olefins using Cu catalyst (L2), base and visible light [97]. The chlorotrifluoromethylation of a compound with electron-withdrawing group such as phthalimide led to the formation of compound **78** in excellent yield (Figure 1.23). The reaction of $\alpha$-tocopherol afforded the product **79** in 84% yield and with substrate derived from estrone afforded 2 products, the chlorotrifluoromethyl compound **80** in 43% yield and trifluormethylsulfone **81** in 13% yield.

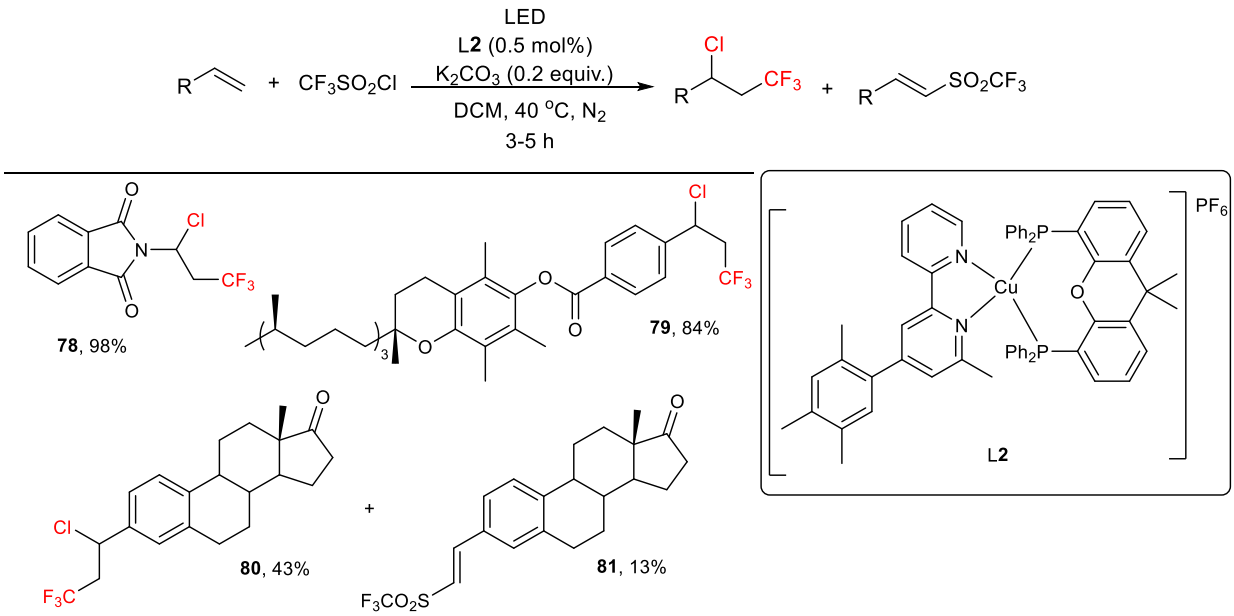



**Fig. 1.23. The chlorotrifluormethylation of terminal olefins [97].**

Chlorotrifluoromethilation reaction can take place not only under LED-irradiation conditions, but also using the electrochemical method which Lin reported in their paper [63]. Authors combined an oxidative and a reductive process to produce multiple reactive intermediates, which can subsequently be converted into the desired products. The optimal condition for the reaction is using $Mn(OAc)_2$ as the catalyst and $MnCl_2$ as chlorine source with $CF_3SO_2Na$. The electrocatalytic chlorotrifluoromethylation of cholesterol **82** led to product **83** in 70% and in only 19:1 ratio (Figure 1.24).

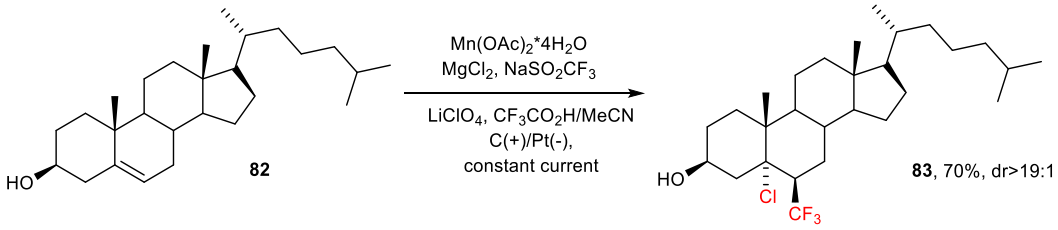



**Fig. 1.24. The chlorotrifluoromethylation of cholesterol [63].**

The authors proposed an electrolytic process built on two parallel anodic and oxidation process that generates free radical $X^1$ and $X^2$ in the form of a persistent metal complex. Many reports [98] indicate that a chloride complex of $Mn^{III}$ can react with carbon-centered radicals in a manner like TEMPO, but the catalyst can be turned over anodically after transferring the chloride in the form of the corresponding radical. The radicals $X^1$ and $X^2$ will be installed across the C=C bond, resulting in the heterodifunctionalization product.

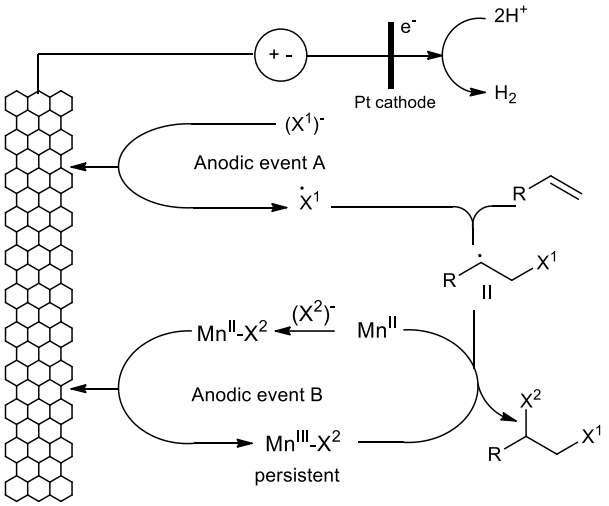



**Fig. 1.25. The electrocatalytic proposed mechanism of the chlorotrifluoromethylation reaction [63].**

Sulfones can serve as key synthetic intermediates for the construction of important building blocks in the total synthesis of natural products [99] and exhibiting a wide range of biological activities [100]. The sulfonylcyanation reaction of olefins using visible light and organo-catalysis was reported by Sun and co-workers [101]. Similar transformations have been reported as well by Fang using AIBN as an initiator [102] and by Barton et al. using the photolysis of PTOC esters [103]. These processes required an excess of olefin and are limited to electron-rich olefins in the latter case. Recently, Landais and co-workers reported sulfonylcyanation reaction using Eosin-Y (2 mol%), 1 mmol of olefins and irradiated by visible light [104]. The authors presented the utility of this process in the synthesis of metalloproteinase inhibitor **90** (Figure 1.26). The sulfonylcyanation of alkene **85** led to the desired alcohol **86** in 69% yield after the trifluoroacetate deprotection over alumina. Then, Mitsunobu reaction leading to ether **88** in 61% yield, followed by hydrolyzation under basic aqueous conditions, afforded compound **89** in 89% yield. Then, compound **89** was converted into the desired hydroxamic acid **90**.

Preparation of sulfones was reported by Renaud group, exactly radical allylation reaction with allyl sulfones as allylating agents [105]. Radical conjugate addition allylation processes are synthetically very useful procedures that are routinely achieved by tin chemistry starting from halides, activated alkenes and allylstannanes [106]. Renaud and co-workers developed a one-pot reaction involving three different alkenes and their selective coupling. The three-component coupling reaction with $\alpha$- and $\beta$-pinene, allyl sulfones and phenyl vinyl sulfone or *N*-phenylmaleimide generates reactions in very good yields (Figure 1.27).

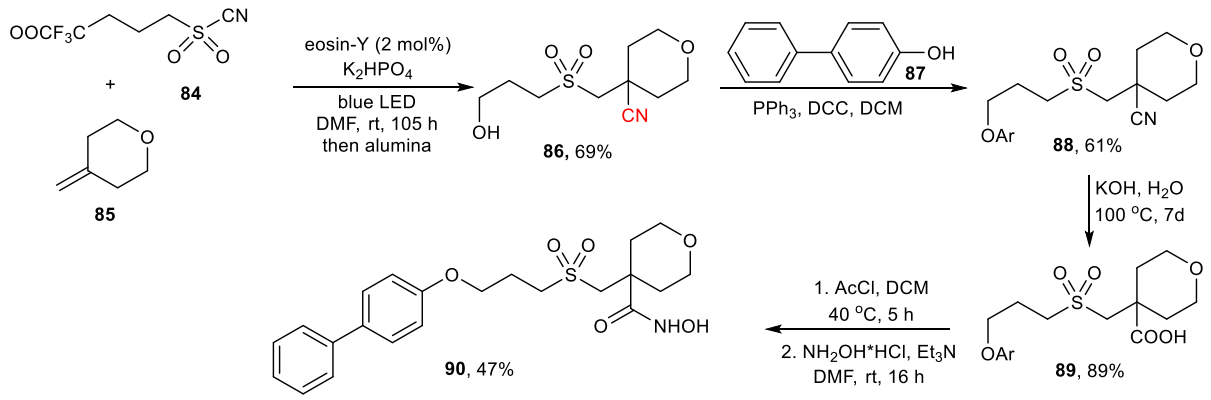



**Fig. 1.26. The synthesis of metalloproteinase inhibitor [104].**

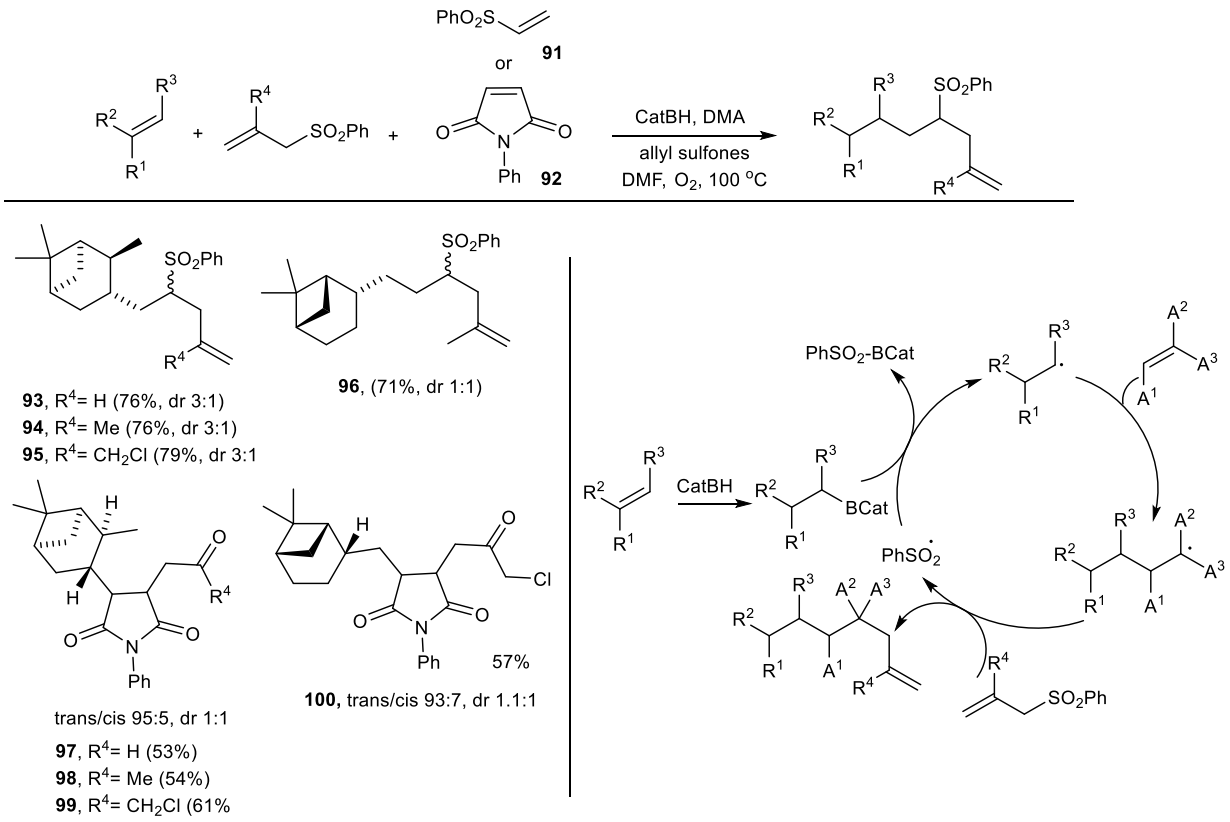



**Fig. 1.27. The three-component coupling of alkenes [105].**

The reaction between *α*-pinene, phenyl vinyl sulfone **91** and different allylsulfones led to the formation of the products **93-95** in approximately 76% yields (dr 3:1), while with *β*-pinene in 71% yield (**96**) and ratio 1:1. Preoperatively useful results were obtained with highly activated olefins such as *N*-phenylmaleimide **92**. All reactions with compound **92** were found to be *trans*-stereoselective, affording the products **97-100** in good yields.

Recently, Meggers and co-workers developed a new methodology [107] for the catalytic asymmetric conjugate addition of electron-rich radicals to alkenes under photoredox conditions

using chiral rhodium-based Lewis acid in combination with inexpensive organic photoredox mediator [108]. The asymmetric three-component fluoroalkylation reaction into a set of natural compound derivatives **101-103** was compatible with this protocol (Figure 1.28). Notably, compounds **101-103** with natural chirality were produced in high diastereoselectivities under asymmetric catalysis conditions. The fluoroalkylation reaction for various functional groups including hydroxyl and amide afforded the corresponding products **104-106** in excellent yields and good diastereoselectivities.

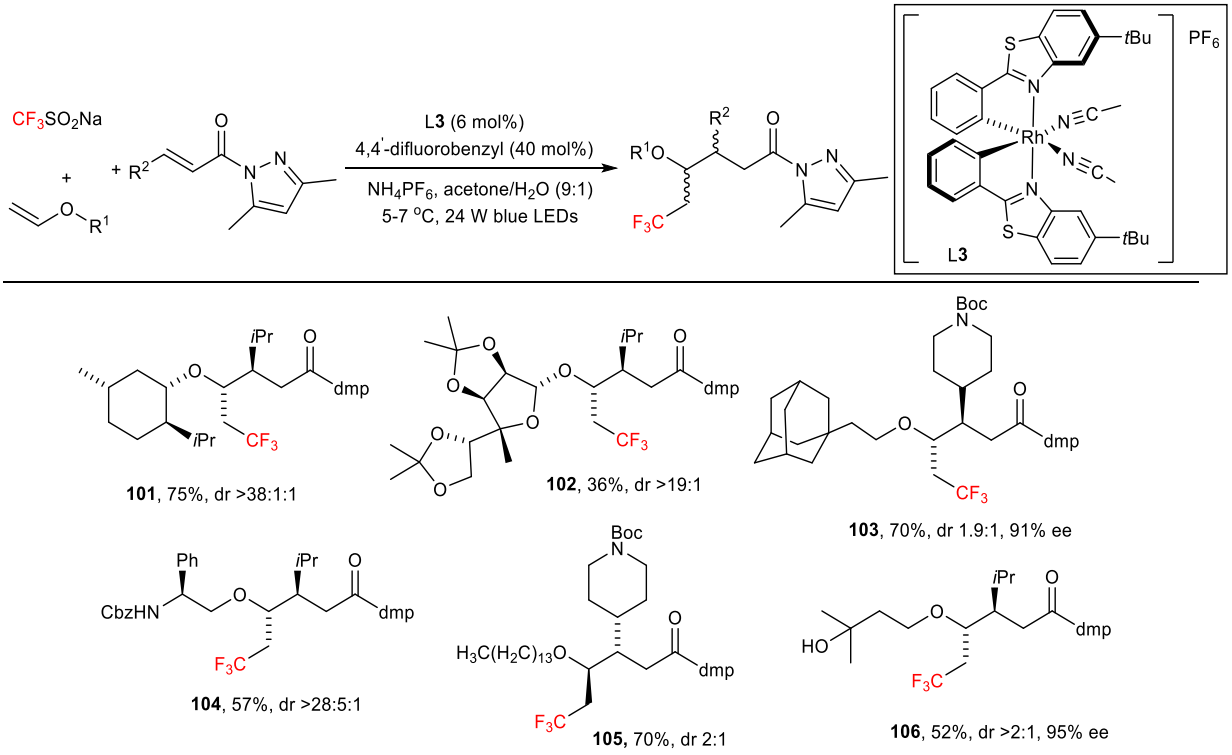



**Fig. 1.28. The asymmetric three-component trifluoroalkylation reaction [108].**

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

Functionalization of the natural compounds *via* cationic reactions is widely used in organic chemistry [109, 110]. Many of these functionalized derivatives possess significant biological properties [111], such as antifungal [112], cytotoxic anti-inflammatory and analgesic activities [113]. Therefore, obtaining them through synthetic pathways such as isomerization, skeletal rearrangements or other functionalization is very important.

Below, we introduced recent examples where the isomerization reactions and skeletal rearrangements of terpenic compounds play an important role in the total synthesis [114, 115]. For example, Shi and co-workers reported the synthesis of the natural steroidal glycosides such as saundersioside J and candicanoside A from tigogenin using Favorskii rearrangement as a key

step (Figure 1.29) [116]. Likewise, Zu used skeletal rearrangements as key strategies for the assembly of complex structures and obtaining natural alkaloids [117].

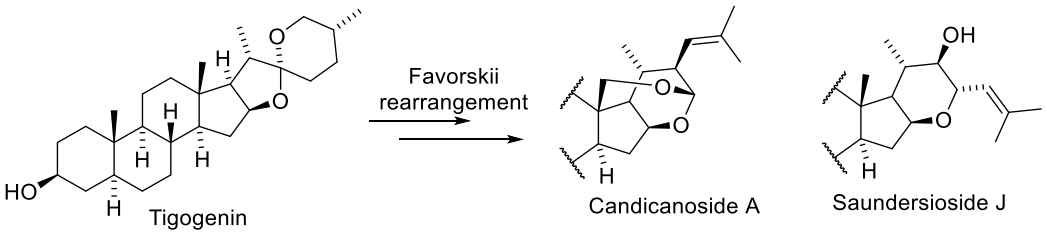



**Fig. 1.29. Aglycons of candicanoside A and saundersioside from tigogenin [109].**

Another interesting paper was reported by Ren and co-workers [118]. They used three acids promoted rearrangements, including Wagner-Meerwein, semipinacol and cyclopropylmethyl cation rearrangements, and C-H functionalization of triterpene substrate **108** (Figure 1.30). The intermediate **108** was prepared from hemslecin A, a highly oxygenated tetracyclic triterpene which includes five contiguous stereogenic centers and exhibits diverse pharmacological activities [119].

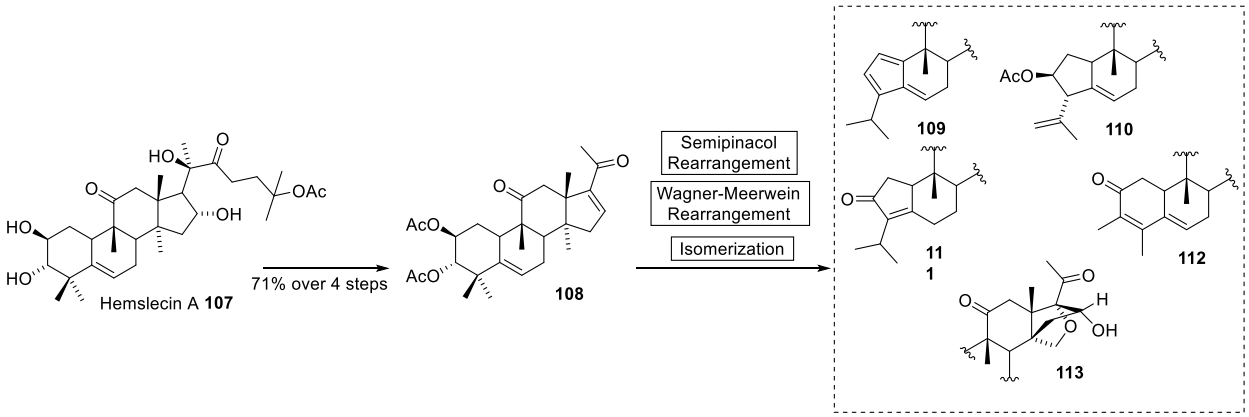



**Fig. 1.30. Skeletal diversity based on ring A and D rearrangement [118].**

The intermediate **108** was converted into different compounds **109-113** and it was remodelled in ring A and D. Compound **108** was treated with pTSA in benzene and led to the formation of the ring-contracted products **109** and **110** in 21% yields. But compound **111** was obtained in 76% yield over two steps and **112** in 78% over three steps, where isomerization was a key step (Figure 1.31).

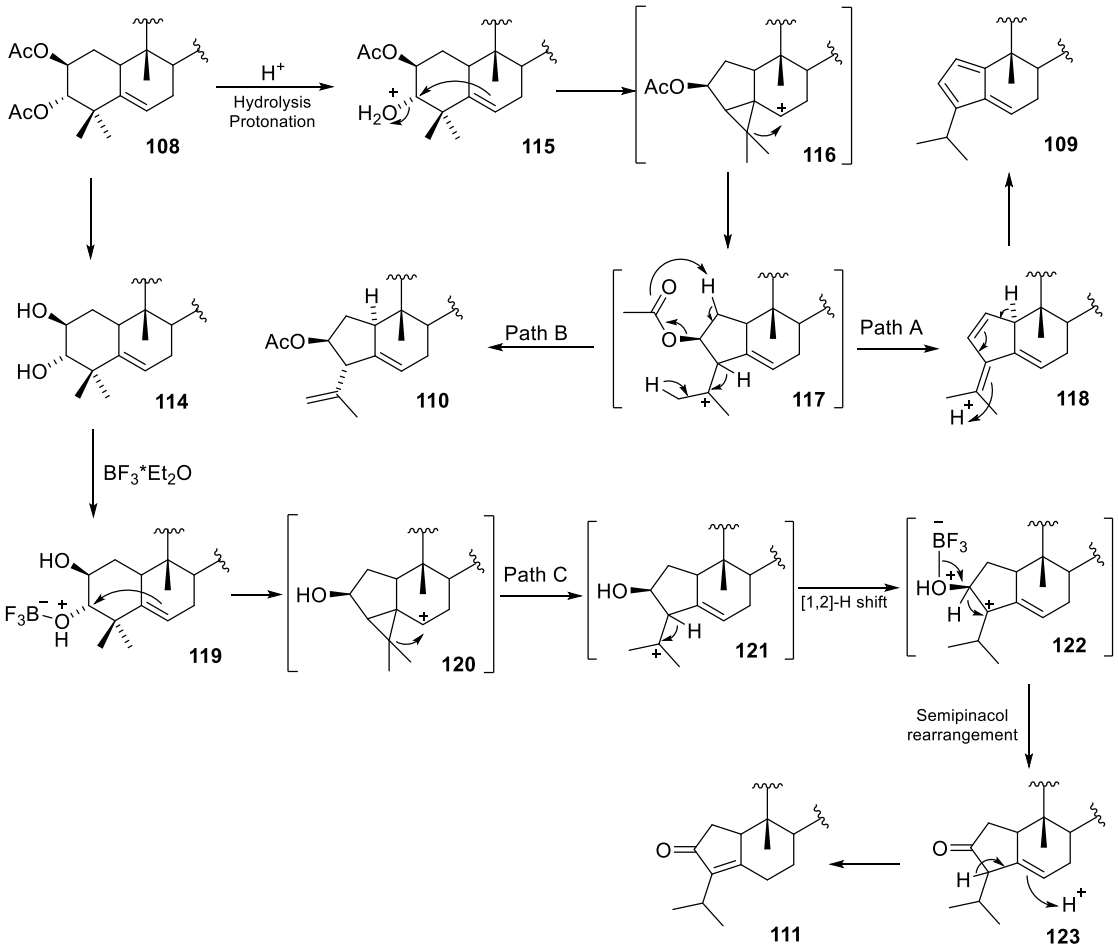



**Fig. 1.31. Proposed mechanism for the formation of compounds 109, 110 and 111 [118].**

Authors proposed that the transformation from **108** to products **109**, **110** and **111** was initiated by the formation of cyclopropyl-methyl cations **116** and **120**. The plausible pathway is shown in Figure 1.31. Hydrolysis and protonation of the intermediate **108** under acidic conditions led to the formation of the cyclopropyl methyl cation **116**. The cation **116** underwent a ring-opening reaction to give the more stable tertiary cation **117**. Deprotonation and elimination of acetic acid from cation **117** gave the intermediate **118** (Path A), whereas deprotonation of the methyl group yielded **110** (Path B). For cation **120**, the reaction pathway likely involved two [1,2]-H shifts and subsequent isomerization to give **111** (Path C).

Another group, who used skeletal rearrangements as a key step, was Guang and co-workers [120]. They developed the stereoselective total synthesis of eburnane-type indole alkaloids [121]. This eburnane class can be isolated from the plants of genus *Kopsia* and the extract of this plant has been used in traditional Chinese medicine for the treatment of rheumatoid arthritis, edema and tonsillitis [122]. More exactly, the eburnamonine has preventive effects on the cerebrovascular disorders [123] and melokhanine E, displays a potent antibacterial

activity against *P. aeruginosa* (MIC = 2 μM) [124]. Due to their promising biological activities, eburnane alkaloids have been represented targets of synthetic and medicinal chemistry [125].

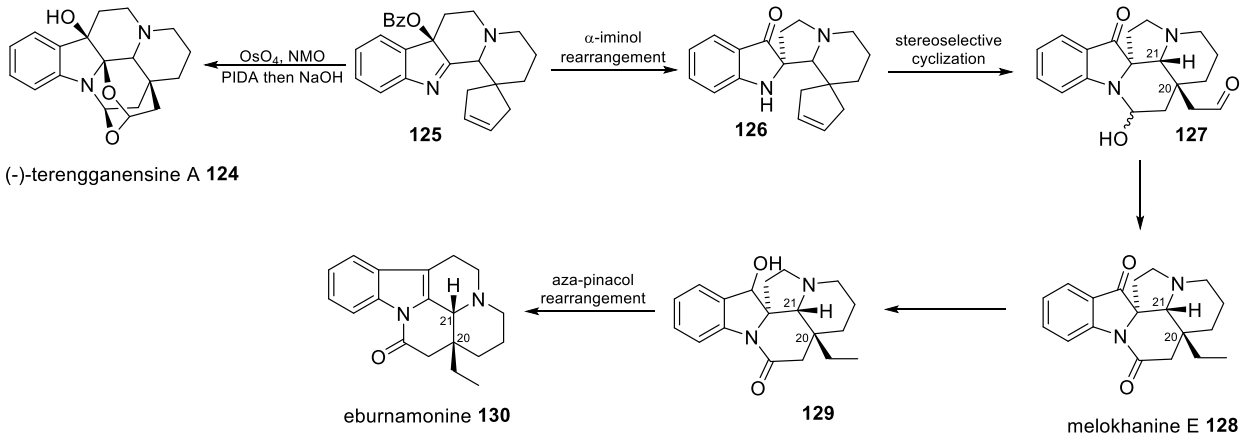



**Figure 1.32**. Synthesis of eburnane family of indole alkaloids [120].

The authors [120] recently developed a short way to the enantioselective synthesis of (-)-terengganensine A **124**, an integrated sequence involving oxidative cleavage of cyclopentene **125**, followed by a highly diastereoselective cyclization (Figure 1.32). Further, the *α*-iminol rearrangement of **125** would afford the spiroiondolinone **126**, followed by selective cyclization providing intermediate **127** with the desired C20/C21 *cis* relative stereochemistry [126]. Manipulation of the functional group of compound **127** would afford the natural compound, melokhanine E **128**. Finally, the reduction of the ketone group in **128** followed by an aza-pinnacol rearrangement of **129** would reestablish the indole system to afford eburnamonine **130** [127].

### 1.4. Conclusions to chapter 1

To conclude, all reactions and methods which were presented in this chapter, either ATRA, C-H functionalization or skeletal rearrangements are practical and convenient synthetic tools for the transformations of natural compounds [128, 129].

The radical C-H functionalization has become an efficient method for the site-selective derivatization of C-H bonds and it is broadly used in modern organic synthesis. Due to the remote C-H functionalization strategy, it allows to introduce different functional groups, for example $-N_3$, -Cl, -Br, -F, $-CF_3$, etc., obviating the necessity of pre-functionalization. The C-H functionalization or atom transfer radical addition methodology catalysed by visible light was also used in radical and organic chemistry. Importantly, photochemical methods offer unique mild entry into radical reaction manifolds, as they generally operate at ambient temperatures,

employ bench-stable reagents, and typically display high functional group tolerance than traditional methods. In contrast, classic approaches tend to require hazardous radical initiators, toxic reagent and elevated temperature.

The synthetic utility of ATRA methodology has been demonstrated by the formal total syntheses. For example, in the total synthesis of lepadiformine and hyacinthacine $A_1$ **59** the key step was radical carboazidation reaction. The azido sulfonylation reaction was used as a key step in the synthesis of the natural compounds apremilast.

Finally, skeletal rearrangements such as aza-pinacol, semipinacol, Farvorskii and Wagner-Meerwein rearrangements of natural compounds lead to the formation of different new products with amazing skeletons and relevant biological activities.

# 2. RADICAL TRANSFORMATIONS OF *ENT*-KAURANE DITERPENOIDS

Terpenoids are very abundant in natural sources and their diverse biological activities have stimulated intensive medicinal chemistry studies, culminating with sound results and relevant applications. The anticancer drug taxol is probably the most known example in this context. The relevant cytotoxic activity of this diterpenoid is due to its structural complexity, which includes many elements: developed cyclic fragments, chiral centers and a rich functionalization with heteroatomic functional groups.

Kaurane diterpenes also have diverse biological activities and have been identified from numerous medicinal plants. *Ent*-kaurenoic acid **131** has been abundantly found in *Wedelia paludosa D.C.* [130] and can be isolated from sunflower *Helianthus annuus L.* together with *ent*-trachilobanoic **132** and 15$\alpha$-angeloyl-*ent*-kaurenoic **133** acids [131]. *Ent*-kaurenoic acid has shown trypanocide [132] and cytotoxic activities [133]. 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 [134-137].

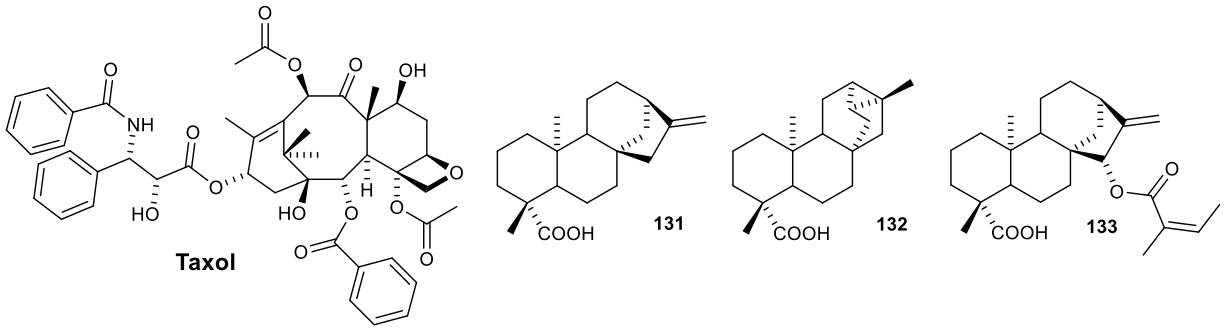



**Fig. 2.1. Taxol and diterpenoids from sunflower *Helianthus annuus L.* 131-133.**

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

Radical hydroazidation of **134** led to the formation of azide **135** in good yield and its spectral data confirmed the selectivity of addition (Figure 2.2) [138]. Position of the azide group was demonstrated based on the specific peak in the $^{13}$C NMR spectrum corresponding to the -$CH_2$-$N_3$ structural fragment resonating at 52.82 ppm and having a cross-peak in HSQC spectrum with two protons at 3.32 ppm. Unfortunately, the relative stereochemistry at adjacent C-16 could

not be unambiguously assigned. It was reasonable to expect that hydroboration step would deliver the hydrogen atom from the less sterically hindered convex face of the molecule. Long-range correlations in NMR spectra could not confirm this stereochemistry due to peak overlapping and this hypothesis was further investigated by an alternative synthesis of azide **135**. It included a classical hydroboration-oxidation sequence leading to alcohol **136**, followed by mesylation and nucleophilic substitution with sodium azide. This is a longer reaction sequence and one-step hydroazidation is a much more convenient hydroazidation tool, providing derivative **135** in higher yield.

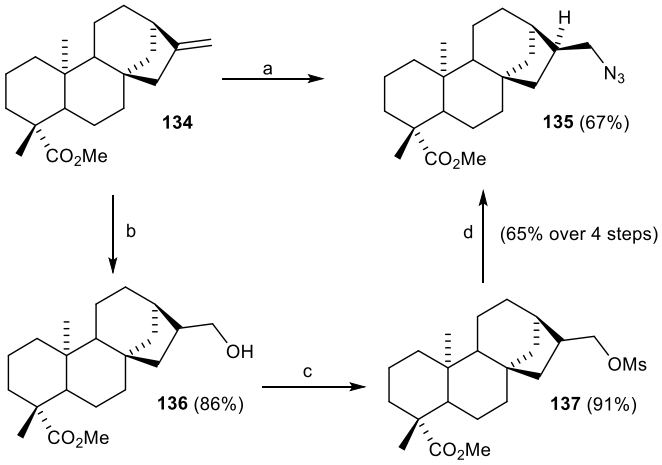



**Fig. 2.2. Hydroazidation of methyl *ent*-kaurenoate.**

*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.

In our hands, the alternative procedure gave the azide **135** identical in all aspects with the material obtained *via* radical hydroazidation. This is an additional proof of the suggested stereochemistry, which was finally demonstrated based on the X-ray crystallographic analysis of **135** (Figure 2.3).

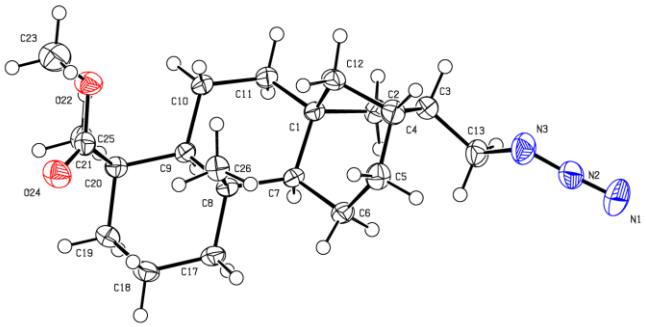



**Fig. 2.3. X-ray structure of methyl 17-azido-*ent*-kaurenoate 135.**

Following transformation of azide **135** included click reactions with a set of alkynes generated triazoles **138-141** and its reduction under mild conditions to furnish amine **143** and

amides **142,-144**. The structure of the obtained triazoles **138-141** was elucidated basing on spectral data. Thus, the $^{13}C$ NMR spectra showed the peaks characteristic to 1,2,3-triazole ring (cca.120 ppm and 140 ppm, see subchapter 2.5 for details). It is noteworthy mentioning that observation of these peaks was not possible in all cases unless a trace amount of triethylamine was added to the NMR vial [139].

The triazoles **138-141** and amine **143** have been tested for cytotoxicity and toxicity on different bacteria and fish. Surprisingly, the amine **143** 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 parallel zebrafish (*Danio rerio*) toxicity tests showed negligible *in vivo* toxicity of the title compound **143** [140].

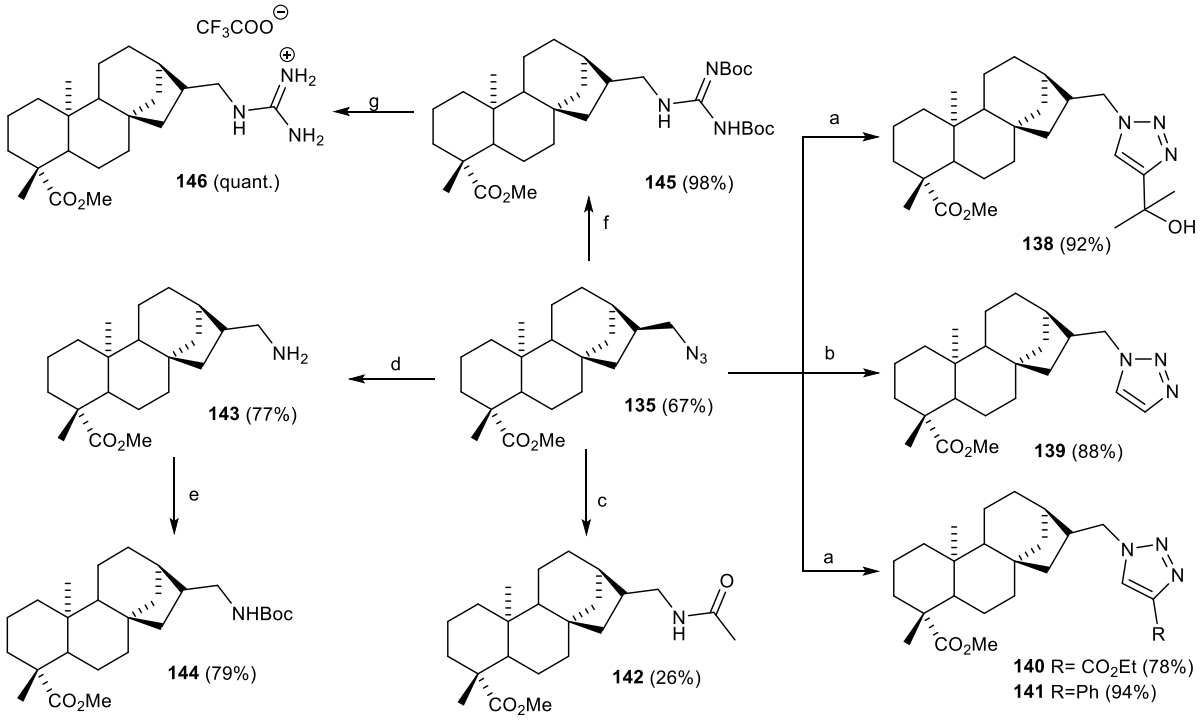



**Fig. 2.4. Transformations of methyl 17-azido-*ent*-kaurenoate.**

*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.

**Table 2.1. Cytotoxic activities of amine 143 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 |
| **143** | µM | 7.7 | 0.8 | 1.8 | 1.1 | 0.7 | 1.7 | 2.0 | 8.3 | 1.2 |

Azido-containing compounds ensure a huge synthetic versatility ranging from the simple introduction of the amino group, to the generation of nitrene to lactam, aziridine or triazole groups [7].

Treatment of azide **135** with triflyl guanidine, a small amount of DIPEA catalyzed by Pd/C under hydrogen in ethyl acetate led to the consumption of the starting material and formation of desired product **145**. The resulting di-boc-guanidine was obtained in 98% yield, followed by deprotection with trifluoroacetic acid (TFA) (Figure 2.4). Cyanobacteria, marine sponges and other marine vertebrates constitute the main group of biological sources of natural guanidines, compounds which are very often present in diverse and potent biological activities. Guanidines are very important in the chemical or pharmaceutical field due to their enhanced hydrophilic nature and a wide range of biological activities [141]. Guanidines can act as drug delivery agents [142], as ionic liquids [143] and in peptide mimetics [144].

The spectral data confirmed the conversion of azide into guanidine **146**. According to NMR data, the proton from CH-16 appeared at 2.16 ppm as multiplet, the methylene group (C-17) at 3.25 ppm as triplet and methyl group (C-20) at 3.62 ppm as a singlet. The tertiary carbon (C-16) was registered in $^{13}C$ spectrum at 38.71 ppm; the methyl groups at 29.09 ppm (C-18), at 16.07 ppm (C-21) and at 51.64 ppm (C-20); the quaternary carbons at 158.72 ppm (C-22) and at 179.64 ppm (C-19).

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

Atom transfer radical addition (ATRA) methodology represents a powerful method for building molecular architectures and it has been successfully reported for efficient modification of various substrates [3, 44]. The main advantages of this process relate, first of all, to atom economy and mildness of reaction conditions, making it a procedure of choice when dealing with complex substrates including multiple functional groups.

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 kaurene derivatives took place under two different conditions: with hexabutylditin as radical transfer reagent and di-*tert*-butyl hyponitrite (DTBHN) as radical initiator and the second- with triethylborane in the presence of air [66, 145-147].

Ditin-mediated carboazidation of methyl *ent*-kaurenoate **134** with ethyl iodoacetate led to full consumption of the starting material in only 2 h. The reaction product **147** was obtained in 83% yield. Therefore, *ent*-kaurenoic acid **131** treated with ethyl iodoacetate as a radical precursor and phenyl sulfonyl azide, afforded the azide **148** in 70% yield. Because the product

was contaminated with hexabutylditin, the resulting product was methylated with an ethereal solution of diazomethane.

The most important spectral signals of azide **147** are: in $^{1}H$ NMR, the quartet from methylene C-24 at 4.13 ppm ($J$=7.1 Hz), another methylene group from C-22 appeared as a triplet at 2.42 ppm ($J$=7.2 Hz), methyl groups from C-20 (3.62 ppm), C-18 (1.15 ppm) and C-19 (0.80 ppm) appeared as a singlet and methyl group from C-22 appeared as a triplet at 1.25 ppm; the carbon bearing the azide appeared in $^{13}C$ NMR spectrum at 73.07 ppm (C-$N_3$), ester group at 177.90 ppm (C-19) and ethyl group at 173.38 ppm (C-23).

The tin-free procedure with both substrates led to the corresponding azides in moderate yields and consumption of starting material. Carboazidation of methyl *ent*-kaurenoate **134** with 3 equiv. of triethylborane gave the desired product **147** in good yield (60%), and the reaction between *ent*-kaurenoic acid **131** and triethylborane afforded azide **148** in similar yields.

Carboiodination reaction of methyl *ent*-kaurenoate **134** took place under two different conditions. Firstly, treatment of **134** 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 **149** and **150** and approximately 40% of the starting material **134**. Unfortunately, the iodinated product has involved in a process of HI elimination, with the formation of unsaturated products after 24 h at reflux.

Carboiodination using $Bu_6Sn_2$ as a radical transfer reagent and 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 **149** and **150** were obtained in 75% total yield. The saturated product **151** was formed in 24% yield and its structure was determined by X-ray diffraction.

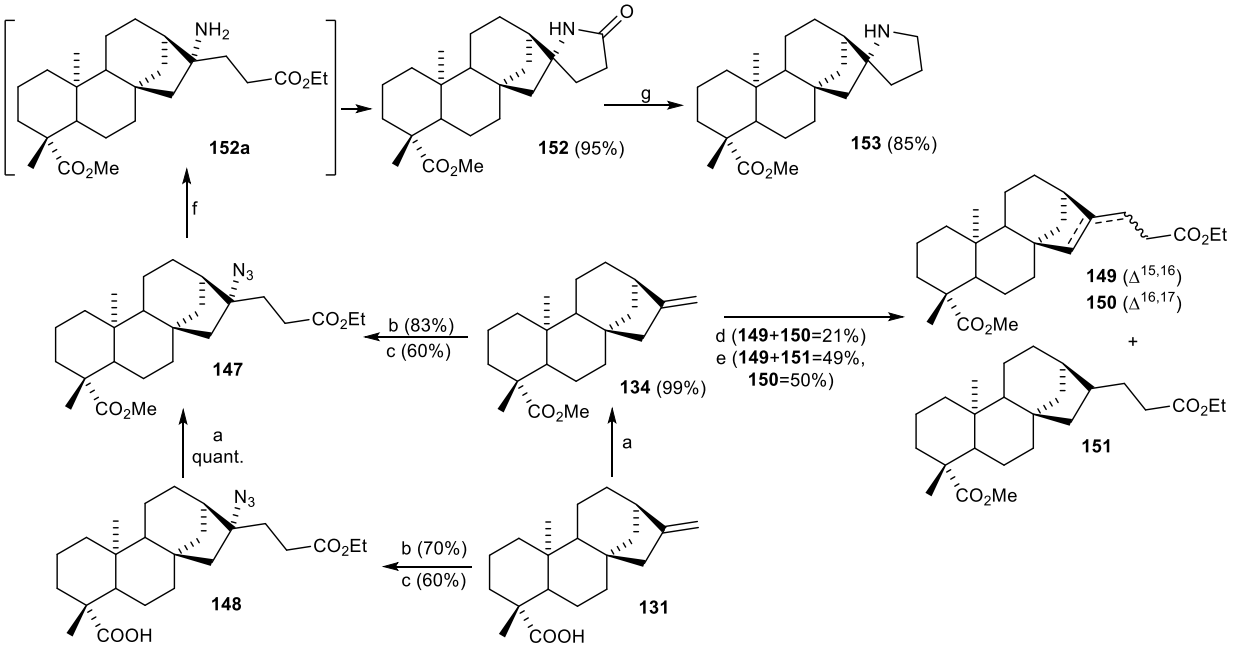



**Fig. 2.5. Carboazidation and carboiodination of methyl *ent*-kaurenoate 134.**

*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.

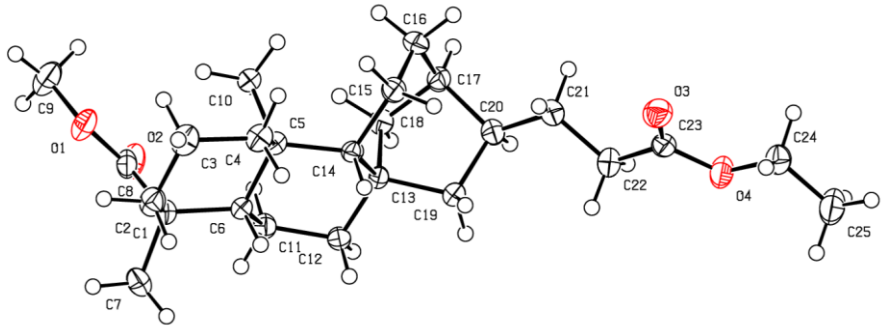



**Fig. 2.6. X-ray structure of compound 151.**

Conversion of azide **147** into lactam **152** by simple hydrogenation with 1 atmosphere of $H_2$, was catalyzed by Pd/C in ethyl acetate. We screened several solvents for reaction optimization (Table 2.2). First, the reduction of azide **147** in methanol led to the formation of amine (**152a**) in 55% and lactam (**152**) 35% in 18 h. The hydrogenation reaction in ethyl acetate of azide **147** afforded 90% of amine, 5% of lactam **152** and circa 50% conversion of the starting material in 3 h. Because partial lactamization of the amine was observed, the azide **147** was finally fully converted into lactam. The relative stereochemistry was determined by X-ray

diffraction (Figure 2.7). The lactam **152** is reduced by sodium borohydride and iodine in THF and converted into pyrrolidine **153** in 85% yield (Figure 2.5).

According to NMR data, the significant signals of pyrrolidine **153** were observed as a singlet CH-13 at 2.64 ppm, $CH_2$-23 at 3.42 ppm, NH group at 8.46 ppm, $CH_3$-18 at 1.15, $CH_3$-20 at 3.63 ppm and $CH_3$-21 at 0.81 ppm in $^1H$ spectrum; in $^{13}C$ spectrum $CH_3$-21 was registered at 15.29 ppm, $CH_3$-18 at 28.56 ppm, $CH_2$-23 at 42.65 ppm, CH-13 at 43.27 ppm, $CH_3$-20 at 51.12 ppm, C-16 at 76.85 ppm and quaternary carbon from carboxyl group C-19 at 177.87 ppm.

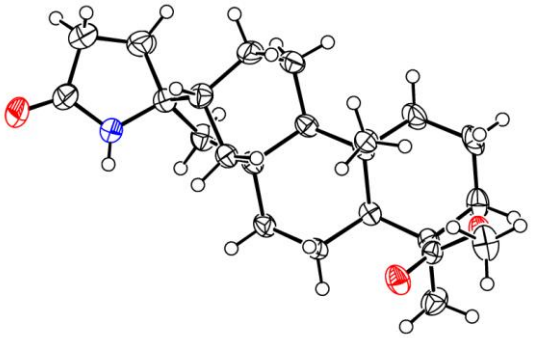


**Fig. 2.7. X-ray structure of lactam 152.**

**Table 2.2. Optimization of hydrogenation reaction of azide 147.**

| Solvent | Time (h) | Products, yields (%) | | Conversion, (%) |
|---|---|---|---|---|
| | | Amine (**152a**) | Lactam (**152**) | |
| EtOAc | 3 | 90 | 5 | 50 |
| EtOAc | 4 | 80 | 15 | 100 |
| EtOAc | 48 | - | 95 | 100 |
| MeOH | 18 | 35 | 55 | 100 |

Methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** can be prepared from natural 15$\alpha$-angeloyl-*ent*-kaurenoic acid **133** by saponification reaction [148] and methylation with an ethereal solution of diazomethane. As in the previous case of methyl *ent*-kaurenoate **134** transformations shown in Figure 2.5, methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** was used in the same carboazidation and carboiodination reactions.

Treatment of **154** with ethyl iodoacetate, DLP as a radical initiator on heating at 95 °C 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 **155** in 11% yield and unsaturated compound **156** in 24% yield. Unexpectedly, submission of **154** to

radical carboazidation conditions led to the formation of the same products as in the carboiodination reaction in 22% yield.

Carboazidation reaction of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** with ethyl iodoacetate, triehtylborane (1M in THF) at room temperature led to the formation of a mixture of *cis* **157** and *trans* **158** in a 1:1 ratio according to $^1$H spectrum (Figure 2.8). The unsaturated compounds were easily separated by flash chromatography. According to $^1$H NMR spectrum, CH-17 of *cis*-isomer appeared as triplet at 5.50 ppm, but for the *trans*-isomer at 5.80 ppm; CH-15 of *cis*-isomer - as a singlet at 3.95 ppm and for the *trans*-isomer at 3.77 ppm; methyl from ester group at 3.64 ppm (for *cis*-compound) and 3.63 ppm (for the *trans*-compound); and CH-22 as doublet at 3.26 ppm for *cis*, and at 3.09 ppm for *trans*. The carbons of *cis*- product in carbon spectrum were: C-16 at 154.79 ppm; C-17 at 115.62 ppm and C-15 at 80.39 ppm. While for the *trans*- compound, C-16 was registered at 153.52 ppm, C-17 at 116.40 ppm and C-15 at 83.16 ppm.

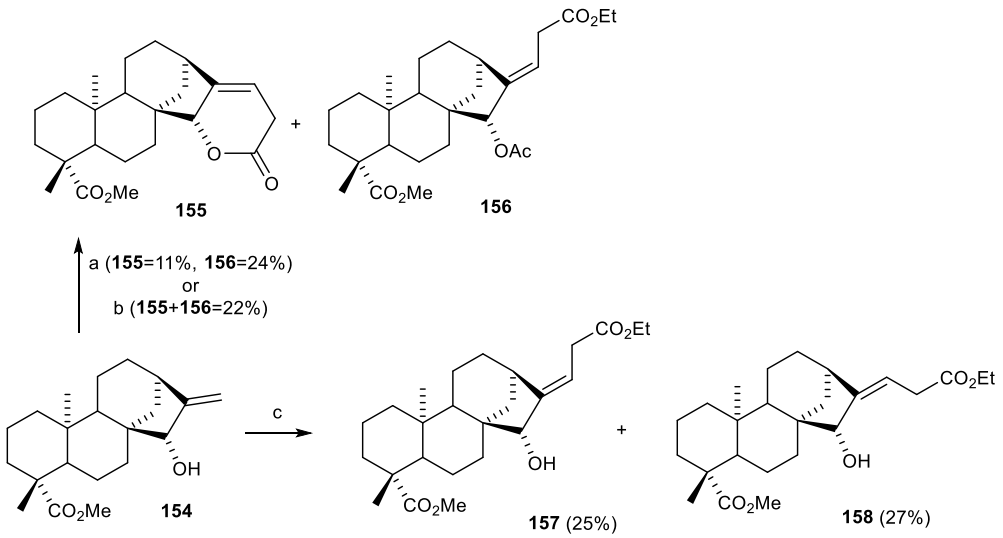



**Fig. 2.8. Carboazidation and carboiodination of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate.**
*Reagents and conditions:* **a.** $ICH_2CO_2Et$, DLP, benzene, $\Delta$, 24 h then $Ac_2O$, DMAP, Py; **b.** $ICH_2CO_2Et$ (2 equiv.), $Bu_6Sn_2$ (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, $\Delta$, 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.

Carboazidation of alcohol **154** was performed with iodoacetic acid as a radical precursor, phenyl sulphonyl azide as azide source and DTBHN as a radical initiator, in refluxing benzene. The crude reaction product was methylated with an ethereal solution of diazomethane leading to compound **159** in 42% yield and the lactone **155** in 28% after cyclization. According to NMR analysis of lactone, the significant signals were registered in $^1$H spectrum at: 4.47 ppm (CH-17), 2.82 ppm (CH-13) as broad singlets; at 3.64 ppm ($CH_3$-20), 1.19 ppm ($CH_3$-18), 0.86 ppm ($CH_3$-21) as singlets; at 5.80 ppm (CH-15) and 3.00 ppm ($CH_2$-22) as multiplets; the peaks in $^{13}$C

spectrum were: 177.85 ppm carbonyl group (C-19), 172.57 ppm carbonyl group (C-23), 148.86 and 115.31 ppm double bond (C-16 and 17) and 87.98 ppm from CH-15. The structure of lactone was demonstrated based on X-Ray diffraction (Figure 2.9).

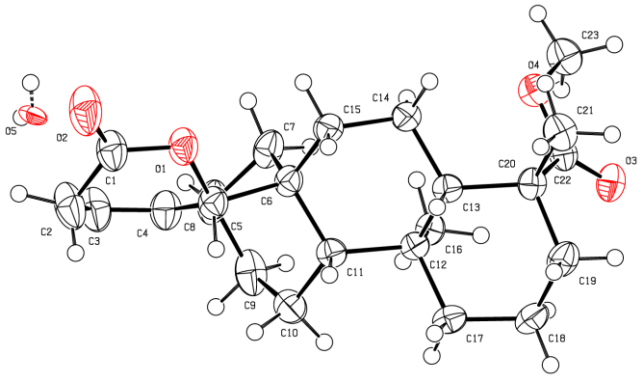



**Fig. 2.9. X-ray structure of lactone 155.**

Azide **159** was further converted into lactam by hydrogenation reaction at 1 atmosphere of $H_2$, catalyzed by Pd/C in ethyl acetate. The significant signals of lactam **160** in NMR data: in $^1$H spectrum as singlets appeared $CH_3$-20 at 3.63 ppm, $CH_3$-21 at 0.81 ppm, $CH_3$-18 at 1.16 ppm, as broad singlets CH-15 at 3.49 ppm and NH group at 6.73 ppm were registered; but in carbon spectrum the CH-15 appeared at 88.15 ppm, $CH_3$-20 at 51.13, C-10 at 178.02 ppm, C-23 at 179.08 ppm, C-16 at 70.80 ppm, CH-13 at 44.88 ppm, $CH_3$-21 at 15.53 ppm and $CH_3$-18 at 28.63 ppm.

The hydroxyl group was further protected using *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide. The corresponding ether **161** was treated with ethyl iodoacetate, 3-Py$SO_2N_3$ and DTBHN after which provided azide **162** in 73% yield. Treatment of azide **162** with TBAF in THF led to the formation of azide **163** in 51% yield. According to NMR analysis were registered peaks as quartet for the methylene group C-24 (4.15 ppm), as triplet $CH_2$-22 (2.55 ppm), as multiplet $CH_3$-25 (1.25 ppm) and as singlets $CH_3$-20 (3.64 ppm), CH-15 (3.40 ppm), $CH_3$-18 (1.16 ppm) and $CH_3$-21 (0.81 ppm); the peak in $^{13}$C spectrum at 75.50 ppm corresponds to the C-$N_3$, 85.16 ppm corresponds to the CH-15, 28.64 ppm to the $CH_3$-18, 15.34 ppm to the $CH_3$-21, 51.06 ppm to the $CH_3$-20, 14.16 ppm to the $CH_3$-25 and 60.57 ppm to the $CH_2$-24.

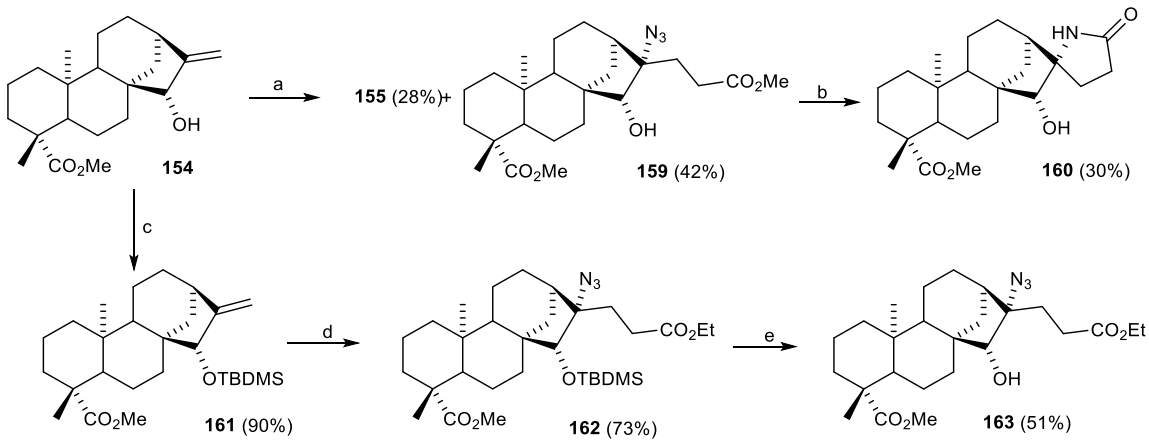



**Fig. 2.10. Carboazidation and carboiodination of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate.**
*Reagents and conditions:* **a.** $ICH_2COOH$ (2 equiv.), $Bu_6Sn_2$ (1.5 equiv.), $PhSO_2N_3$ (3 equiv.), DTBHN (0.03 equiv.), benzene, $\Delta$, 5 h then $CH_2N_2$; **b.** $H_2$, Pd/C (10% w/w), EtOAc, 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, $\Delta$, 10 h; **e.** TBAF (3 equiv.), THF, r.t., 12 h.

### 2.3. Carbohydrogenation of *ent*-kaurane derivatives

Atom transfer radical (ATRA) to alkenes provides a useful tool to create C-C and C-X bonds [44-48]. ATRA offers attractive routes to synthesize pharmaceutically important molecules. Reductive radical addition to alkenes represents one of the mildest procedures for the carbon-carbon bond formation. Curran reported a general approach for this kind of reaction in a two steps process of iodine atom transfer followed by deiodination [44]. Later, Roberts [45] and Ryu [149] have reported two different approaches of one-step carbohydrogenation reaction. We used the mildest and more convenient conditions developed by Povie [150], with 4-*tert*-butylcatechol as the source of the hydrogen atom.

Carbohydrogenation of methyl *ent*-kaurenoate **134** 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 **134** with ethyl iodoacetate led to quick consumption of the starting material and the desired product **164** was obtained in 86% yield. The structure of compound **164** was confirmed using the NMR data, HRMS and IR analysis. The reaction of olefin **134** with iodomethylphenylsulfone during 2 h gave the product **165** in 75% yield. Carbohydrogenation using isobornyl iodoacetate afforded the desired product **166** 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. The terpenic iodoacetates were prepared by iodoacetylation reaction [151].

Surprisingly, carbohydrogenation of methyl *ent*-kaurenoate **134** with perfluoroalkyl iodides ($CF_3(CF_2)_n$-I) with n=0, 3, 5 and 7 afforded the desired products in excellent yields. $^{19}F$ NMR spectra and HRMS analyses were the most useful tools for the demonstration of fluorine chain. The $^{19}F$ NMR spectrum of the compounds **168-170** is shown in Table 2.3.

Treatment of ester **134** with ethyl difluoroacetate (1.2 equiv.), triethylborane (1.3 equiv.) and TBC (2 equiv.) as a radical reductant gave the product **167** in good yield (75%). According to NMR data, fluorine atom split only 2 carbons into a triplet. In the $^{13}C$ NMR spectrum, the singlet from the carbonyl group was split into one triplet at 164.7 ppm and methylene group (C-17) at 36.13 ppm into triplet too.

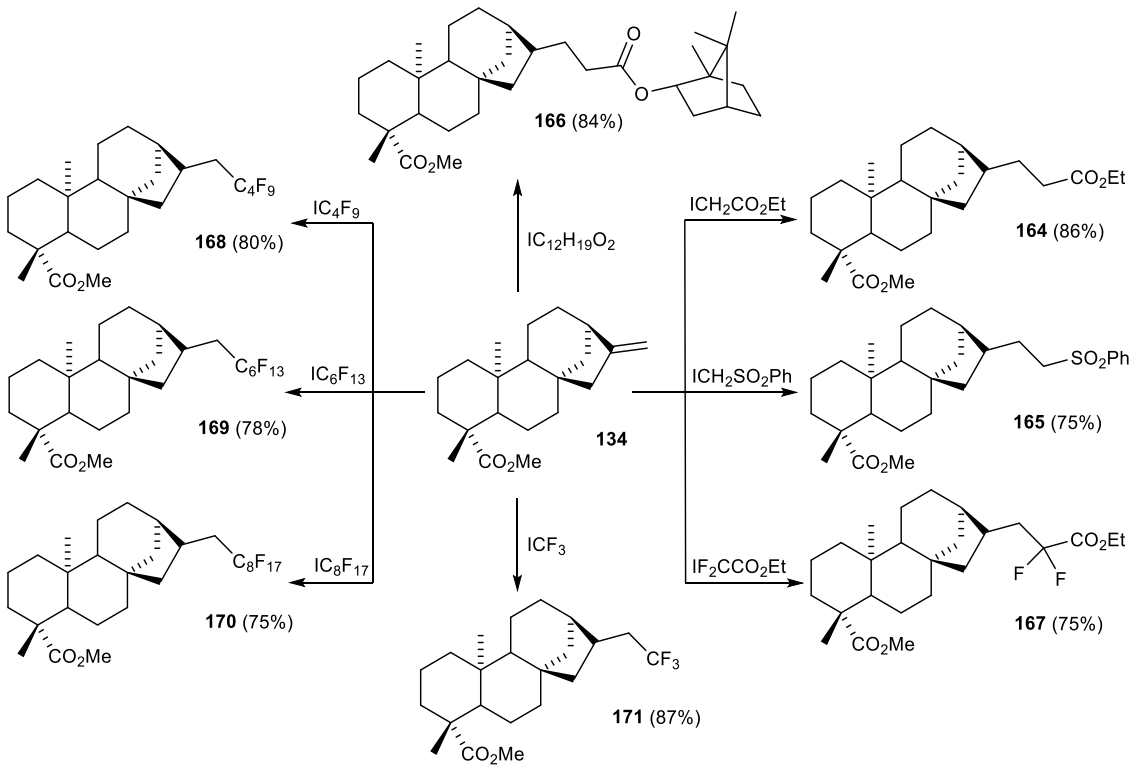



**Fig. 2.11. Carbohydrogenation of methyl *ent*-kaurenoate.**

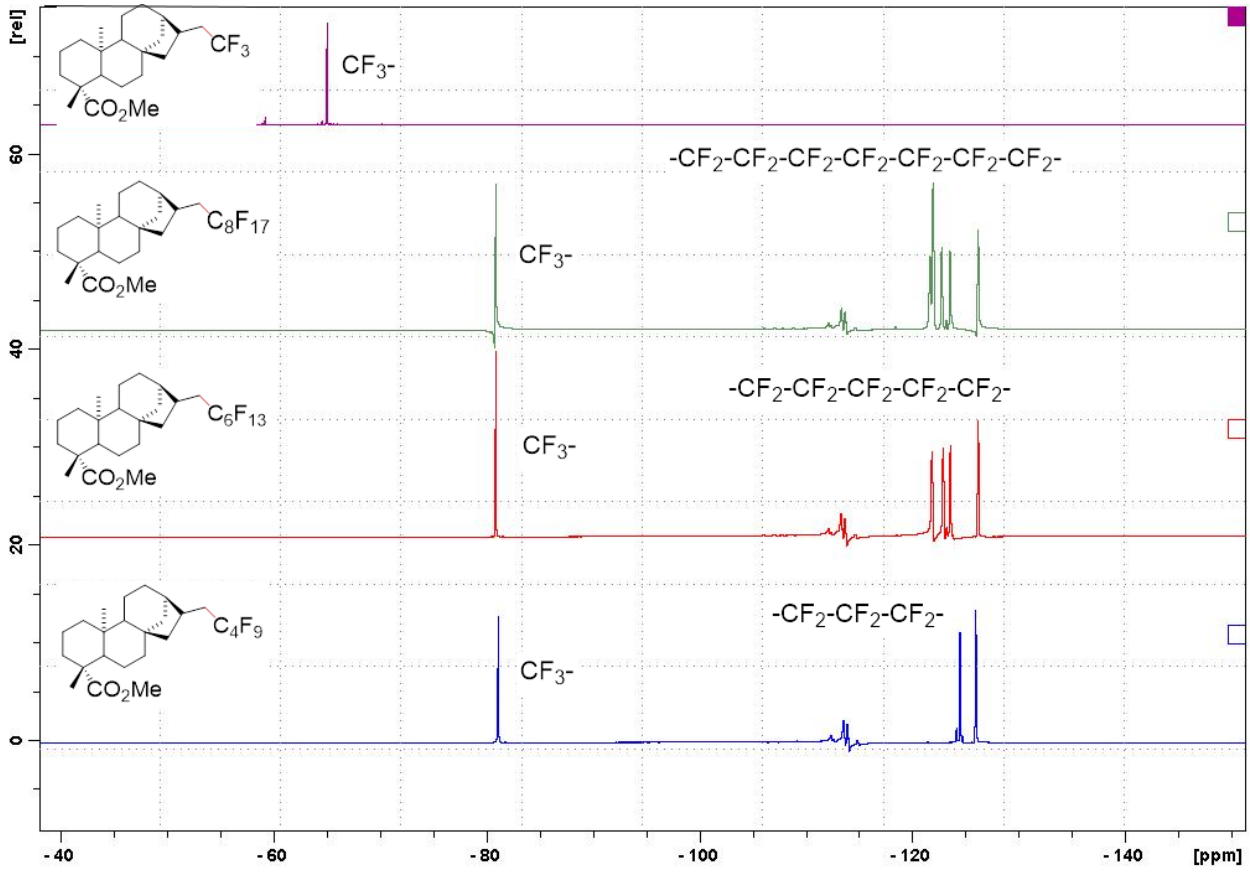
*Reagents and conditions*: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

Nonafluoro-1-iodobutane as a radical precursor delivered the desired product **168** in very good yield. In the proton spectrum there have been identified the methyl groups from C-20 (3.63 ppm), C-18 (1.16 ppm) and C-21 (0.82 ppm) as singlets. Here, we had the same problems as with *epi*-manoyl oxide, the fluorinated chain (-$CF_2$-$CF_2$-$CF_2$-$CF_3$) was not observed in the $^{13}C$ spectrum. The $CF_3$ group appeared at -81.08 ppm as a broad singlet and the $CF_2$ groups at -113.26, -124.45, 125.92 ppm as multiplets in $^{19}F$ NMR spectrum.

Carbohydrogenation of olefin **134** with perfluoro-1-iodohexane led to the formation of the product **169** in 78% yield. The structure of the resulting compound was described by $^{19}F$ NMR and HRMS analysis. Treatment of methyl *ent*-kaurenoate with perfluorooctyl iodide in dichloromethane afforded the product **170** in excellent yield (75%). In $^{19}F$ spectrum, the trifluoromethyl group appeared as a triplet at -80.82 ppm, the difluoromethylene groups as a multiplet at -113.5 ppm and as singlets at -121.65, 121.91, 122.74, 123.52, and 126.14.

In the case of trifluoroiodomethane, in the fluorine NMR was registered only one peak at -64.96 ppm ($CF_3$) as a triplet. But, in the $^{13}C$ NMR spectrum we observed that CH-16 (33.5 ppm) was split into triplet and methylene group C-17 (35.24 ppm) into a quartet. The desired product **171** was obtained in 87% yield.

**Table 2.3. $^{19}F$ NMR of compounds 168-171.**




Unexpectedly, hydroalkylation of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** led to the elimination of hydroxyl group and formation of the double bond in the cycle D. Treatment of the compound with ethyl iodoacetate as a radical precursor and 4-methoxycatechol as a reducing agent afforded the product **172** in 40% yield and decomposition of the initial olefin. According to NMR analysis, the CH-15 was registered in proton spectrum as a singlet at 5.08 ppm, the

methylene group from C-24 as a quartet at 4.12 ppm and methyl groups at 3.63 ppm ($CH_3$-20), 1.25 ppm ($CH_3$-25), 1.16 ppm ($CH_3$-18) and 0.83 ppm ($CH_3$-21). The significant signals were registered in the carbon spectrum at 178.10 ppm (C-19), 173.53 ppm (C-23), 145.16 ppm (C-16), 134.35 ppm (C-15), 51.10 ppm (C-20), 14.26 ppm (C-25) and 15.21 ppm (C-21).

The reaction of **154** with ethyl difluoroiodoacetate led to the formation of compound **173** in 43% yield, whereas *iso*-bornyl iodoacetate afforded the product **174** in 50% yield. The structure of all isolated products was confirmed by spectral data. We proposed that on carbohydrogenation of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** 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.

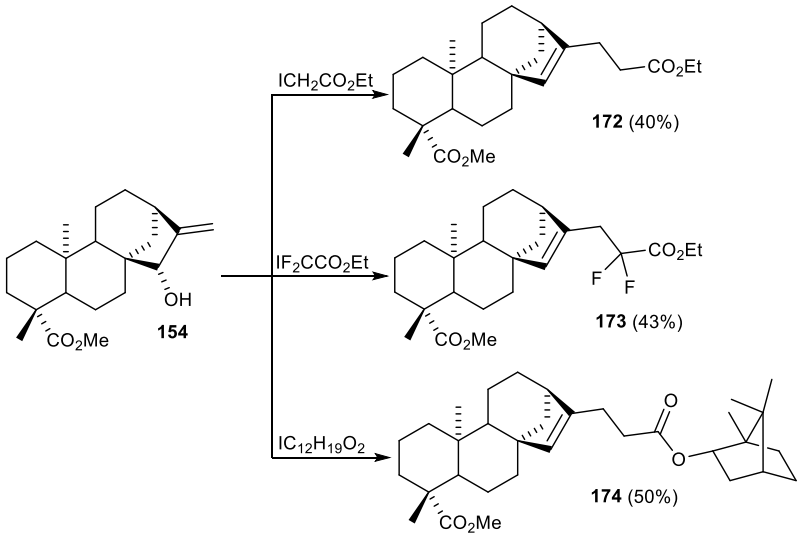



**Fig. 2.12. Carbohydrogenation of methyl 15$\alpha$-hydroxy-*ent*-kaurenoate.**
*Reagents and conditions*: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

Carbohydrogenation reactions with methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** were not so selective and the yields were lower than when methyl *ent*-kaurenoate was used.

Treatment of methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** with ethyl iodoacetate afforded the desired product **176** in only 46% yield. The significant signals in proton spectrum appeared at 4.67 ppm as doublet (CH-15); the methylene groups at 4.11 ppm as quartet (C-26) and 2.27 ppm as triplet (C-24); the methyl groups as singlet at 3.62 ppm (C-20), 2.04 ppm (C-23), 1.13 ppm (C-18) and 0.80 ppm (C-21). The quaternary carbons were identified at 178.01 ppm (C-19), 173.48 ppm (C-22), 171.03 ppm (C-25); the methyl groups at 14.26 ppm (C-27), 15.55 ppm (C-21), 21.25 ppm (C-23), 28.61 ppm (C-18) and 51.14 ppm (C-20).

Hydroalkylation of **175** with iodomethylphenylsulfone provided the compound **177** in 54% yield. The purification of the resulting product **177** from the reduced iodide

(methylphenylsulfone) was not possible. Reaction with ethyl difluoroiodoacetate as radical precursor and 4-methoxycatechol at room temperature afforded the difluoro product **178** in moderate yield (58%). The structure of products **177** and **178** was confirmed according to NMR, HRMS and IR analysis [152].

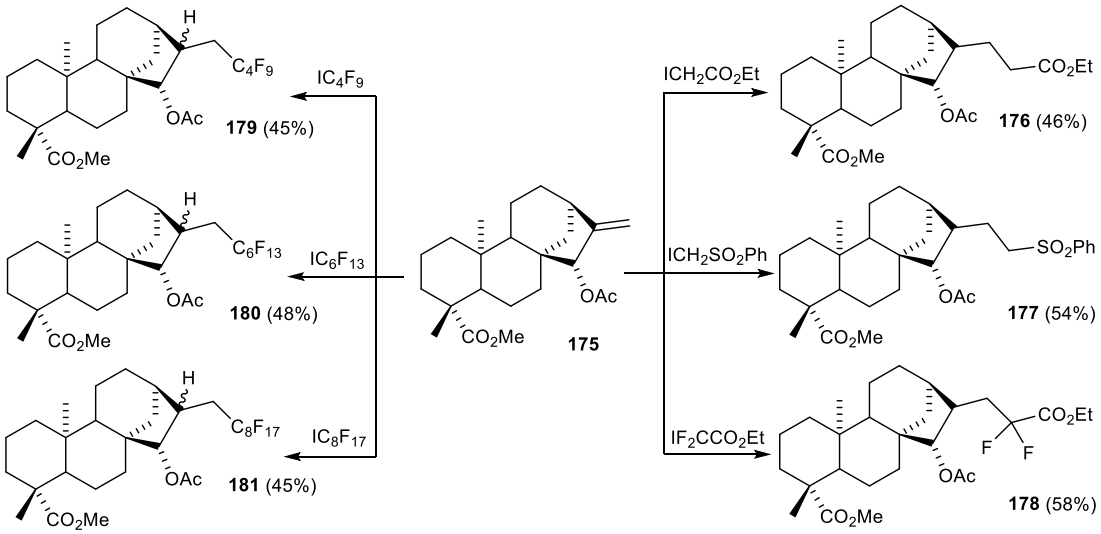



**Fig. 2.13. Carbohydrogenation of methyl 15$\alpha$-acetoxy-*ent*-kaurenoate.**
*Reagents and conditions*: iodides (1.2 equiv.), olefin (1 equiv.), 4-methoxycatechol (2 equiv.), triethylborane (1.3 equiv.), DCM, r.t., 2 h.

Coupling of olefin **175** with perfluoroalkyl iodides led to the formation of epimers at the C-16 position. Treatment of acetate **175** with nonafluoro-1-iodobutane, 4-methoxycatechol and triethylborane in dichloromethane gave the mixture **179** of two diastereomers with ratio 2:0.3 in 45% yield according to $^{1}$H spectrum. The resulting epimers were not individually separated. The significant peaks of the major epimer were registered: the CH-15 at 4.71 ppm as doublet; and the methyl groups as singlets at 3.63 ppm (C-20), 2.03 ppm (C-23), 1.15 ppm (C-18) and 0.82 ppm (C-21) in the proton spectrum. As it is known from the literature and previous results, the fluorine atom can split carbon into triplet or quartet. In that case, the methylene group (C-17) at 29.62 ppm was split into a triplet and the fluorinated chain was not observed in the $^{13}$C spectrum. The trifluoromethyl group was identified in the $^{19}$F spectrum at -81.06 ppm as a doublet, and difluoromethylene groups as multiplets at -114 ppm, -124.2 ppm and 126.0 ppm. The reaction of olefin **175** with pefluoro-1-iodohexane in dichloromethane afforded the product **180** in 48% yield and in the same ratio (2:0.3). The $F_3C$- group of the product **180** in the $^{19}$F spectrum was registered as a triplet at -80.79 ppm and as multiplets $F_2C$- groups at -113.82 ppm, -121.8 ppm, -122.9 ppm, -123.3 ppm and -126.1 ppm.

Carbohydrogenation of methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** using perfluorooctyl iodide as a radical precursor led to the formation of a mixture **181** of two diastereomers with ratio 2:0.2 in good yield according to $^{1}$H NMR (Figure 2.13). According to the proton spectrum, the major epimer gave peaks at 4.72 ppm as doublet (CH-15), as singlets at 3.63 ppm ($CH_3$-20), 2.05 ppm ($CH_3$-23), 1.15 ppm ($CH_3$-18) and 0.83 ppm ($CH_3$-21). The significant peaks in the carbon spectrum were registered at 177.94 ppm (C-19), 171.09 ppm (C-22), 86.69 ppm (C-15) and only C-17 was split into triplet at 29.70 ppm. Trifluoromethyl group in $^{19}$F spectrum was registered at -80.79 ppm as a triplet, whereas all the other signals appear as multiplets. The hydroalkylation of olefin **175** with trifluoroiodomethane failed, the only decomposition of the starting material was observed.

### 2.4. Conclusions to chapter 2

Radical chemistry based on ATRA methodology represents a convenient tool for the formation of new carbon-carbon and carbon-nitrogen bonds. We demonstrated an application of this methodology on kaurene derivatives. They have undergone radical transformations, such as carboazidation, carboiodination, hydroazidation and carbohydrogenation.

We synthesized five different azides using radical methods, which were converted into amines, triazoles, amides, lactams and guanidine in very good yields. Some of these derivatives have been submitted to a 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.

Methyl e*nt*-kaurenoate was converted into azide *via* the hydroazidation reaction, followed by "click" chemistry or guanidinylation reaction. The kaurene-guanidine was obtained in very good yield and using mild conditions of the reaction. The compounds with guanidine moiety have different biological activities and are very useful in pharmaceutical chemistry or medicine.

Carboazidation and carboiodination of methyl *ent*-kaurenoate derivatives have been presented for the first time. Carboazidation reaction with hexabutylditin refluxing in benzene led to the formation of the azide **147** and almost the same yield has been achieved in tin-free procedure with triethylborane as radical initiator under open air conditions at room temperature.

Hydroalkylation of *ent*-kaurene derivatives with perfluoroalkyl iodides as radical precursors afforded the fluorinated compounds in very good yields, which can be tested for biological activity in the following studies and implemented in medicine or radiology. All forty-

four new synthesized compounds represent promising targets for biological activity testing, including cytotoxicity, anti-inflammatory and antifungal assays.

### 2.5. Experimental Part

**General information:** All glassware was flame-dried under vacuum and allowed to cool under nitrogen. 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 drying agent. Yields refer to chromatographically or spectroscopically pure compounds. Silica gel 60 Å (63-200 μm) from SDS was used for flash chromatography and column chromatography. All commercial reagents have been used as received from supplier. The starting material was isolated from sunflowers according to known procedure [131].

**Instrumentation:** Unless otherwise stated, $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AVANCE-300 spectrometer operating at 300 MHz for $^1H$ and 75 MHz for $^{13}C$ at 22 °C. Some $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AVANCE II-400 ($^1H$: 400 MHz; $^{13}C$: 100 MHz). Chemical shift data is reported in units of δ (ppm) using as the internal standard residual $CHCl_3$ ($\delta = 7.26$ for $^1H$ NMR spectra and $\delta = 77.0$ for $^{13}C$ NMR spectra), $CH_3OH$ ($\delta = 3.35; 4.78$ for $^1H$ NMR spectra and $\delta = 49.3$ for $^{13}C$ NMR spectra) and $C_6H_6$ ($\delta = 7.26$ for $^1H$ NMR spectra and $\delta = 128.0$ for $^{13}C$ NMR spectra). Multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet) for $^1H$ spectra. Coupling constants, *J*, are reported in Hz. 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.

**General Procedure 1**: To a mixture of CuI (0.02 mmol), DIPEA (0.04 mmol) and AcOH (0.04 mmol) in $CH_2Cl_2$ (2 mL) was added a mixture of alkynes (1 mmol) and methyl *ent*-17-azido-kaurenoate (1 mmol) at room temperature. The resulting mixture was stirred for 2 h. After this time the reaction mixture was purified by column chromatography (pentane/EtOAc).

**General procedure 2:** To a solution of azide (1 mmol) in dry EtOAc were added 1,3-di-boc-2-(trifluoromethylsulfoyl)-guanidine (2 mmol), 10% Pd/C (0.1 mmol) and DIPEA (1.5 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (pentane/EtOAc).

A solution of guanidine product (1 mmol) in a mixture of TFA/$CH_2Cl_2$ (1:10) was stirred at room temperature (8-12 h). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography ($CH_2Cl_2$/MeOH).

**General Procedure 3:** DTBHN (0.03 mmol) was added every 2 h to a solution of iodoester (1.5 mmol), olefin (1 mmol), $PhSO_2N_3$ or 3-$PySO_2N_3$ (3 mmol) and $Bu_6Sn_2$ (1.5 mmol), in dry $C_6H_6$ (5.0 mL) at reflux under $N_2$. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (pentane/EtOAc).

**General Procedure 4:** DLP (0.05 mmol) was added every 2 h to a solution of iodine (1.5 mmol) and olefin (1 mmol) in dry $C_6H_6$ (5.0 mL) at reflux under $N_2$. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (pentane/EtOAc).

**General Procedure 5:** A solution of $Et_3B$ (1 M in THF) in dry EtOH (2.0 mL) was added at room temperature over 2 h by using a syringe pump to an open-air vigorously stirred mixture of ethyl iodoacetate (2 mmol), alkene (1 mmol), and $PhSO_2N_3$ or 3-$PySO_2N_3$ (3 mmol) in solvent (*important*: the needle should be immersed into the reaction mixture to avoid direct contact of $Et_3B$ drops with air). The reaction was monitored by TLC. The reaction was extracted with $Et_2O$ and organic phase were washed with brine and dried over $Na_2SO_4$. The crude product was purified by column chromatography (hexane/EtOAc).

**General Procedure 6:** To a solution of alkene (1 equiv.) and iodide (1.2 equiv.) in $CH_2Cl_2$ (10 mL/0.5 mmol of iodide) was added 4-*tert*-butylcatechol or 4-methoxycatechol (2 equiv.) followed by $Et_3B$ (1.3 equiv., 1M solution in hexane). The resulting solution was stirred at room temperature in the presence of air and protected from moisture by a $CaCl_2$ guard tube. After 2 h, the reaction mixture was filtered over short pad of neutral $Al_2O_3$ using $Et_2O$ to trap the catechol derivative and boron containing side products. The resulting crude filtrate was concentrated under reduce pressure and purified by FC (pentane/EtOAc).

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-(azidomethyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (135)*

To a solution of the ester **134** (350 mg, 1.1 mmol) and *N*,*N*-dimethylacetamide (0.01 mL, 0.11 mmol) in DCM (2 mL) was added dropwise catecholborane (0.35 mL, 3.3 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was heated under reflux for 5 h, then *t*-BuOH (0.2 mmol) was added at 0°C to solvolyze the excess of cathecolborane. After the evaporation of solvent under vacuum, DMF (2 mL), 3-$PySO_2N_3$ (607 mg, 3.3 mmol), DTBHN (19 mg, 0.11 mmol) were added and the solution was stirred at 80°C. After 2 h the solution turned black and was filtered through a pad of $Al_2O_3$ to remove polar boron containing residues using $Et_2O$ as eluent. The filtrate was washed with water, dried over $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography (hexane/EtOAc 98:2) and afforded the azide **135** (265 mg, 67%). $[a]_D^{20}$ = -46° (*c*= 0.54, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2926, 2095, 1718, 1264, 1113, 727. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 3.28-3.38 (*m*, $CH_2$-17), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.0 (*s*, C-19), 56.9 (*d*, C-5), 56.2 (*d*, C-9), 52.8 (*t*, C-17), 51.1 (*q*, C-20), 44.5 (*t*, C-15), 44.4 (*s*, C-4), 43.7 (*s*, C-8), 41.9 (*t*, C-7), 40.7 (*t*, C-11), 40.2 (*t*, C-14), 40.0 (*d*, C-13), 39.4 (*s*, C-10), 38.0 (*t*, C-3), 37.6 (*d*, C-16), 28.7 (*q*, C-18), 25.9 (*t*, C-12), 22.1 (*t*, C-6), 19.09 (*t*, C-2), 19.04 (*t*, C-11), 15.3 (*q*, C-21).

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-(hydroxymethyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (136)*

To a solution of the ester **134** (100 mg, 0.31 mmol) in THF (1.5 mL) was added $BH_3$*$Me_2S$ (0.15 mL, 1.5 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at r.t. for 3 h. After this time NaOH 15% (4 mL) and $H_2O_2$ 35% (4 mL) very carefully added and the solution was stirred overnight at r.t. Solution of $H_2SO_4$ 10% was added dropwise to the reaction mixture and extracted with $Et_2O$. The organic layer was washed with $NaHCO_3$, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc 95:5) and afforded the alcohol **136** (89 mg, 86%) as a colorless oil. $[a]_D^{20}$ =-37.2° (c= 0.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3357, 2918, 2849, 1725, 1462, 1235, 1154, 1033, 755. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.69-3.72 (*m*, $CH_2$-17), 3.63 (*s*, $CH_3$-20), 1.15 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.11, 64.28, 56.96, 56.41, 51.10, 44.23, 43.79, 43.59, 43.25, 42.07, 40.74, 40.34, 39.41, 38.08, 36.91, 28.72, 26.01, 22.21, 19.15, 19.11, 15.34. **GCMS** m/z calculated for $[C_{21}H_{34}O_3]^+$: 334.25; found 334.2.

The alcohol **136** (50 mg, 0.15 mmol) was dissolved in DCM (1.4 mL) and cooled at 0°C. $Et_3N$ (0.12 mL, 0.9 mmol) and MsCl (0.05 mL, 0.75 mmol) were added and the reaction was

stirred for 2 h at 0°C. The resulting mixture was extracted with $Et_2O$, washed with brine, dried over $Na_2SO_4$ and concentrated. The compound **137** was used without further purification to the next step. The crude (59 mg, 0.14 mmol) was dissolved in DMF (1.5 mL) and $NaN_3$ (35 mg, 0.54 mmol) was added. The reaction mixture was stirred at 80°C overnight. After this time it was extracted with EtOAc, washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by column chromatography (hexane/EtOAc 98:2) and afforded the azide **135** (46 mg, 86%).

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-((4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-methyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (138)*

According to general procedure 1 from azide **135** (250 mg, 0.69 mmol) and 2-methyl-3-butyn-2-ol (62 µL, 0.65 mmol). The crude mixture was purified by column chromatography (hexane/EtOAc 80:20) and afforded triazole **138** (282 mg, 92%) as a white powder. M.p. 125-128 °C. $[\alpha]_D^{20}$ = -37º (*c*= 1.9, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3381, 2927, 2854, 1723, 1462, 1374, 1150, 1047, 729. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.44 (*bs*, CH-5´); 4.26-4.38 (*m*, $CH_2$-17); 3.55 (*s*, $CH_3$-20); 1.55 (*s*, $2CH_3$-7´); 1.08 (*s*, $CH_3$-18); 0.7 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ (ppm) 177.58, 56.67, 55.89, 51.52, 50.93, 44.30, 44.17, 43.55, 41.59, 40.74, 40.50, 40.04, 39.19, 37.81, 37.41, 31.24, 28.49, 25.67, 21.88, 18.86, 18.80, 15.16. **$^1$H NMR with $Et_3N$** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.43 (*s*, CH-5´); 4.25-4.42 (*m*, $CH_2$-17); 3.59 (*s*, $CH_3$-20); 2.52 (*q*, *J*=7 Hz, $Et_3N$); 1.59 (*s*, $2CH_3$-7´); 1.12 (*s*, $CH_3$-18); 1.00 (*t*, *J*=7 Hz, $Et_3N$); 0.78 (*s*, $CH_3$-21). **$^{13}$C NMR with $Et_3N$** (100 MHz, $CDCl_3$) $\delta$ (ppm) 177.98 (*s*, C-19), 155.57 (*s*, C-4´), 118.77 (*d*, C-5´), 68.42 (*s*, C-6´), 56.87 (*d*, C-5), 56.09 (*d*, C-9), 51.72 (*t*, C-17), 51.10 (*q*, C-20), 46.01 ($Et_3N$), 44.50 (*s*, C-4), 44.39 (*t*, C-15), 43.74 (*s*, C-8), 41.77 (*t*, C-7), 40.95 (*d*, C-13), 40.70 (*t*, C-1), 40.22 (*t*, C-14), 39.38 (*s*, C-10), 38.00 (*t*, C-3), 37.62 (*d*, C-16), 30.48 (*2q*, C-7´), 28.67 (*q*, C-18), 25.85 (*t*, C-12), 22.06 (*t*, C-6), 19.05 (*t*, C-2), 19.00 (*t*, C-11), 15.34 (*q*, C-21), 11.00 ($Et_3N$). **HRMS** (ESI) calculated for $[C_{26}H_{41}N_3O_3]^+$: 444.3206; found 444.3221.

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-((1H-1,2,3-triazol-1-yl)-methyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (139)*

To a solution of azide **135** (200 mg, 0.56 mmol), propiolic acid (52 µL, 0.48mmol) in DMF (2 mL), were added CuI (22 mg, 0.11 mmol), Na ascorbate (44 mg, 0.22 mmol) and DBU (42 µL, 0.28 mmol). The reaction mixture was stirred at 60ºC for 3 h under $N_2$. The mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc 80:20) and afforded triazole **139** (235 mg, 88%) as a colorless

oil. $[a]_D^{20}$ = -39º (*c*= 1.2, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3397, 2926, 2853, 1721, 1462, 1150, 774, 731. **$^1$H NMR with Et$_3$N** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.67 (*s*, CH-4´); 7.54 (*s*, CH-5´); 4.34-4.51 (*m*, $CH_2$-17); 3.62 (*s*, $CH_3$-20); 2.60 (*q*, *J*=7 Hz, $Et_3N$); 1.14 (*s*, $CH_3$-18); 1.07 (*t*, *J*=7 Hz, $Et_3N$); 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR with Et$_3$N** (100 MHz, $CDCl_3$) δ (ppm) 178.00 (*s*, C-19), 133.71 (*d*, C-5´), 122.97 (*d*, C-4´), 56.89 (*d*, C-5), 56.12 (*d*, C-9), 51.64 (*t*, C-17), 51.12 (*q*, C-20), 46.00 ($Et_3N$), 44.51 (*s*, C-4), 44.35 (*t*, C-15), 43.77 (*s*, C-8), 41.79 (*t*, C-7), 41.08 (*d*, C-13), 40.72 (*t*, C-1), 40.24 (*t*, C-14), 39.40 (*s*, C-10), 38.02 (*t*, C-3), 37.62 (*d*, C-16), 28.69 (*q*, C-18), 25.88 (*t*, C-12), 22.07 (*t*, C-6), 19.07 (*t*, C-2), 19.01 (*t*, C-11), 15.36 (*s*, C-21), 10.94 ($Et_3N$). **HRMS** (ESI) calculated for $[C_{25}H_{35}N_3O_2]^+$: 386.2790; found 386.2802.

*Ethyl 1-(((4R,6aS,8R,9R,11aR,11bS)-4-(methoxycarbonyl)-4,11b-dimethyltetra-decahydro-6a,9-methanocyclohepta[a]naphthalen-8-yl)-methyl)-1H-1,2,3-triazole-4-carboxylate (140)*

According to general procedure 1 from azide **135** (250 mg, 0.69 mmol) and ethyl propiolate (66 µL, 0.65 mmol). The crude mixture was purified by column chromatography (hexane/EtOAc 85:15) and afforded triazole **140** (300 mg, 78%) as a white powder. M.p. 114-116 ºC. $[a]_D^{20}$ =-24º (*c*= 0.6, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3143, 2932, 2250, 1720, 1542, 1462, 1375, 1193, 1043, 911, 775, 728. **$^1$H NMR with Et$_3$N** (400 MHz, $CDCl_3$) $\delta$ (ppm) 8.06 (*s*, CH-5´); 4.38-4.51 (*m*, $CH_2$-17); 4.34-4.39 (*m*, $CH_2$-7´); 3.58 (*s*, $CH_3$-20); 2.52 (*q*, *J*=7 Hz, $Et_3N$); 1.36 (*t*, *J*= 7.1 Hz, $CH_3$-8´); 1.11 (*s*, $CH_3$-18); 1.00 (*t*, *J*=7 Hz, $Et_3N$); 0.77 (*s*, $CH_3$-21). **$^{13}$C NMR with Et$_3$N** (100 MHz, $CDCl_3$) $\delta$ (ppm) 177.91, 160.84, 140.18, 127.05, 61.19, 56.82, 56.02, 52.10, 51.09, 46.01 ($Et_3N$), 44.54, 44.17, 43.73, 41.70, 40.92, 40.68, 40.16, 39.37, 37.97, 37.52, 28.65, 25.81, 22.03, 19.03, 18.96, 15.33, 14.28, 10.99 ($Et_3N$). **HRMS** (ESI) calculated for $[C_{26}H_{39}N_3O_4]^+$: 458.3002; found 458.3013.

*Methyl (4R,6aS,8R,9R,11aR,11bS)-4,11b-dimethyl-8-((4-phenyl-1H-1,2,3-triazol-1-yl)-methyl)-tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (141)*

According to general procedure 1 from azide **135** (250 mg, 0.69 mmol) and phenyl acetylene (71 µL, 0.65 mmol). The crude product was purified by column chromatography (hexane/EtOAc 85:15) and afforded **141** (243 mg, 94%) as a white powder. M.p. 130-132 ºC. $[a]_D^{20}$ = -40º (*c*= 0.6, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3143, 2929, 2250, 1718, 1462, 1149, 909, 763, 729, 694. **$^1$H NMR with Et$_3$N** (400 MHz, $CDCl_3$) $\delta$ (ppm) 7.80-7.82 (*m*, CH-7´); 7.76 (*s*, CH-5´); 7.39 (*t*, *J*= 7.5, CH-8´); 7.28-7.32 (*m*, CH-9´); 4.39-4.51 (*m*, $CH_2$-17); 3.61 (*s*, $CH_3$-20); 2.61 (*q*, *J*=7 Hz, $Et_3N$); 1.14 (*s*, $CH_3$-18); 1.07 (*t*, *J*=7 Hz, $Et_3N$); 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR with Et$_3$N** (100 MHz, $CDCl_3$) $\delta$ (ppm) 177.99, 147.65, 130.76, 128.79 (2C), 128.02 (2C), 125.64, 119.28, 56.88, 56.11,

51.87, 51.12, 46.01 ($Et_3N$), 44.54, 44.36, 43.77, 41.79, 41.07, 40.72, 40.26, 39.41, 38.02, 37.64, 28.70, 25.90, 22.08, 19.08, 19.03, 15.37, 11.03 ($Et_3N$). **HRMS** (ESI) calculated for $[C_{29}H_{39}N_3O_2]^+$: 462.3105; found 462.3115.

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-(acetamidomethyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (142)*

To a solution of azide **135** (30 mg, 0.08 mmol) in benzene was added acetyl chloride (11 µL, 0.16 mmol) and $Ph_3P$ (27 mg, 0.1 mmol). The reaction was stirred for 48 h at room temperature. The reaction mixture was extracted with $CH_2Cl_2$, washed with brine, dried and concentrated under reduced pressure. The crude product was purified by column chromatography ($CH_2Cl_2$/MeOH 95:5) and afforded amide **142** (8 mg, 26%) **IR** (ν, $cm^{-1}$): 3266, 2918, 2849, 1721, 1666, 1437, 1193, 1119, 721, 695. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 1.92 (*s*, $CH_3$-23), 1.14 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.08, 170.45, 56.95, 56.23, 51.10, 44.57, 44.37, 43.79, 42.00, 41.25, 40.70, 40.26, 39.98, 39.39, 38.06, 37.42, 28.72, 25.96, 23.04, 22.15, 19.09, 19.03, 15.35.

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-(aminomethyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (143)*

To a solution of azide **135** (50 mg, 0.14 mmol) in THF (1 mL) was added $Ph_3P$ (55 mg, 0.21 mmol) and water (50 mg, 2.8 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and purified by column chromatography ($CH_2Cl_2$ /MeOH 98:2) affording amine **143** (36 mg, 77%). $[a]_D^{20}$= -22º (*c*= 0.6, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2928, 2851, 1720, 1548, 1404, 1230, 1149, 1016, 735. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.28 (*bs*, $NH_2$), 3.63 (*s*, $CH_3$-20); 3.05 (*bs*, $CH_2$-17); 1.15 (*s*, $CH_3$-18); 0.79 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.97, 56.89, 55.88, 51.13, 44.68, 44.17, 43.76, 41.70, 41.27, 40.68, 40.14, 39.38, 38.65, 38.02, 37.25, 28.73, 25.74, 22.12, 19.07, 18.84, 15.29. Elemental analysis for $C_{21}H_{35}NO_2$ (333.22): C, 75.63; H, 10.58; N, 4.20; O, 9.59.

*Methyl (4R,6aS,8R,9R,11aR,11bS)-8-(((tert-butoxycarbonyl)-amino)-methyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (144)*

To a solution of amine **143** (40 mg, 0.1 mmol) in THF (1 mL) were added $Boc_2O$ (35 µL, 0.15 mmol) and $Et_3N$ (8 µL, 0.06 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and purified by column chromatography ($CH_2Cl_2$/MeOH 95:5) giving the amide **144** (55 mg, 79%). $[a]_D^{20}$ =-46° (*c*= 1.7, $CHCl_3$). **IR** (*ν*, $cm^{-1}$): 3379, 2927, 2548, 1713, 1515, 1365, 1236, 1166, 775. **$^1$H NMR** (400

MHz, $CDCl_3$) δ (ppm) 3.62 (*s*, $CH_3$-20); 3.11-3.29 (*m*, $CH_2$-17); 1.43 (*s*, $CH_3$-24); 1.15 (*s*, $CH_3$-18); 0.79 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.98, 155.97, 78.98, 57.02, 56.35, 50.99, 44.53, 44.36, 43.81, 42.07, 41.9, 40.75, 40.67, 40.30, 39.42, 38.10, 37.39, 28.69, 28.41(3C), 25.9, 22.16, 19.11, 19.06, 15.35.

*Methyl (4R,6aS,8R,9R,11bS)-8-(((E)-2,3-bis(tert-butoxycarbonyl)-guanidino)methyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (145)*

According to general procedure 2 from azide **135** (50 mg, 0.14 mmol) in EtOAc (2mL) were added 1,3-di-boc-2-(trifluoromethylsulfoyl)-guanidine (109 mg, 0.28 mmol), 10% Pd/C (15 mg, 0.014 mmol) and DIPEA (36 µL, 0.21 mmol). The reaction mixture was stirred for 96 h at room temperature. The crude product was purified by column chromatography (pentane/EtOAc 95:5) and gave the di-boc-guanidine **145** (79 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ = - 44.97° (c= 3.96, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3327, 3294, 3345, 2980, 2934, 2856, 1790, 1720, 1637, 1615, 1575 (w). **$^1$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 11.45 (*s*, -NH), 8.30 (*s*, -NH), 3.62 (*s*, $CH_3$-20), 3.36-3.55 (*m*, $CH_2$-17), 1.49 (*s*, 3$CH_3$-25), 1.47 (*s*, 3$CH_3$-28), 1.14 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 178.05 (*s*, C-19), 163.04 (*s*, C-26), 156.04 (*s*, C-22), 153.30 (*s*, C-23), 83.92 (*s*, C-24), 79.17 (*s*, C-27), 56.96 (*d*, C-5), 56.29 (*d*, C-9), 51.08 (*q*, C-20), 44.44 (*s*, C-8), 44.31 (*t*, C-15), 43.78 (*s*, C-4), 42.33 (*t*, C-17), 41.94 (*t*, C-7), 40.72 (*t*, C-12), 40.23 (*t*, C-1), 39.64 (*d*, C-13), 39.40 (*s*, C-10), 38.07 (*t*, C-3), 37.32 (*d*, C-16), 28.73 (*q*, C-18), 28.29 (*q*, 3C-25), 28.06 (*q*, 3C-28), 25.86 (*t*, C-14), 22.16 (*t*, C-6), 19.08 (*t*, C-2), 19.03 (*t*, C-11), 15.33 (*q*, C-20).

*Amino((((4R,6aS,8R,9R,11bS)-4-(methoxycarbonyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalen-8-yl)methyl)amino)methaniminium 2,2,2-trifluoroacetate (146)*

A solution of di-boc-guanidine **145** (10 mg, 0.019 mmol) in 10% TFA/$CH_2Cl_2$ (1 mL) was stirred for 8 h at room temperature. The crude product was purified by column chromatography ($CH_2Cl_2$/MeOH) to give the product **146** (9 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ = - 45.13° (c= 4.03, MeOH). **IR** (ν, $cm^{-1}$): 3352 (w), 3185 (w), 2929, 2857, 1666, 1545 (w). **$^1$H RMN** (400 MHz, $D_3COD$) δ (ppm) 5.51 (*s*, -NH), 3.65 (*s*, $CH_3$-20), 3.27 (*d*, *J*= 7.7 Hz, $CH_2$-17), 1.18 *(s*, $CH_3$-18), 0.87 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $D_3COD$) δ (ppm) 178.23, 157.39, 56.82, 56.31, 50.23, 44.23, 44.18, 43.62, 42.63, 41.72, 40.53, 39.82, 39.40, 39.25, 37.71, 37.30, 27.68, 25.40, 21.19, 18.80, 18.65, 14.66.

*Methyl (4R,6aS,8R,9R,11bS)-8-azido-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (147)*

According to general procedure 3 from methyl *ent*-kaurenoate **134** (100 mg, 0.36 mmol), ethyl iodoacetate (64 µL, 0.54 mmol), $PhSO_2N_3$ (200 mg, 1.08 mmol), $Bu_6Sn_2$ (272 µL, 0.54 mmol) and DTBHN (2 mg, 0.01 mmol). The reaction mixture was refluxed for 2 h. The crude product was purified by column chromatography (pentane/EtOAc 98:2) and gave the azide **147** (133 mg, 83%). $[a]_D^{20}$= - 79.50° (*c*= 0.84, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2944, 2873, 2096, 1727, 1502. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.12 (*q*, *J* = 7.2 Hz, $CH_2$-24), 3.62 (*s*, $CH_3$-20), 2.42 (*t*, *J* = 7.9 Hz, $CH_2$-22), 1.25 (*t*, *J* = 7.2 Hz, $CH_3$-25), 1.14 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.90 (*s*, C-19), 173.38 (*s*, C-23), 73.07 (*s*, C-16), 60.54 (*t*, C-24), 56.72 (*d*, C-5), 55.80 (*d*, C-9), 51.51 (*t*, C-15), 51.13 (*q*, C-20), 44.67 (*s*, C-4), 44.31 (*d*, C-13), 43.74 (*s*, C-8), 41.44 (*t*, C-7), 40.59 (*t*, C-1), 39.41 (*s*, C-10), 37.99 (*t*, C-14), 37.70 (*t*, C-3), 30.30 (*t*, C-17), 29.73 (*t*, C-22), 28.66 (*q*, C-18), 26.13 (*t*, C-12), 21.96 (*t*, C-6), 19.00 (*t*, C-2), 18.47 (*t*, C-11), 15.26 (*q*, C-21), 14.19 (*q*, C-25). **GCMS** m/z calculated for [$C_{25}H_{39}N_3O_4$]: 445.28; found: 402.3 (M-$HN_3$).

According to general procedure 5 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), ethyl iodoacetate (39 µL, 0.33 mmol), $PhSO_2N_3$ (87 mg, 0.47 mmol) and $Et_3B$ (0.47 mL). The reaction mixture was stirred for 2 h at room temperature. The crude product was purified by column chromatography (pentane/EtOAc 98:2) and gave the azide **147** (43 mg, 60%) as a colorless oil.

According to general procedure 3 from *ent*-kaurenoic acid **131** (87 mg, 0.29 mmol), ethyl iodoacetate (51.5 µL, 0.44 mmol), $PhSO_2N_3$ (159 mg, 0.87 mmol), $Bu_6Sn_2$ (222 µL, 0.44 mmol) and DTBHN (1.5 mg, 0.087 mmol). The reaction was refluxed for 2 h and after this time the crude product was purified by column chromatography (pentane/EtOAc 90:10) giving the compound **148** (70%) with small amount of hexabutylditin. This impurified product was methylated with an ethereal solution of diazomethane, concentrated and purified by column chromatography (pentane/EtOAc 98:2) afforded azide **147** (90 mg, 70%).

*(4R,6aS,8R,9R,11bS)-8-azido-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylic acid (148)*

According to general procedure 5 from methyl *ent*-kaurenoate (50 mg, 0.17 mmol), ethyl iodoacetate (39 µL, 0.33 mmol), $PhSO_2N_3$ (91 mg, 0.50 mmol) and $Et_3B$ (0.67 mL). The reaction mixture was stirred for 2 h at room temperature. The crude product was purified by column

chromatography (pentane/EtOAc 85:15) and gave the azide **148** (44 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ = -69.22° (*c*= 1.9, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2935, 2900, 2872, 2848, 2626, 2098, 1734, 1693. **$^1$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 4.14 (*q*, *J*= 7.1 Hz, $CH_2$-23), 2.43 (*t*, *J*= 8.1 Hz, $CH_2$-21), 1.26 (*t*, *J*= 7.1 Hz, $CH_3$-24), 1.22 (*s*, $CH_3$-18), 0.93 (*s*, $CH_3$-20). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 184.28, 173.44, 73.06, 60.57, 56.69, 55.81, 51.52, 44.68, 44.31, 43.70, 41.42, 40.53, 39.63, 37.73, 37.67, 30.31, 29.72, 28.87, 26.13, 21.85 18.93, 18.49, 15.43, 14.19.

According to general procedure 4 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), ethyl iodoacetate (28 µL, 0.24 mmol) and DLP (3 mg, 0.008 mmol). The reaction mixture was heated under reflux for 24 h. The mixture was purified by column chromatography (pentane/EtOAc 98:2) and gave a mixture of compound **149** and **150** (21% of the mixture).

*Methyl (4R,6aS,9R,11bS)-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyl-1,2,3,4,4a,5,6,9,10,11,11a, 11b-dodecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (149)*

**IR** (ν, $cm^{-1}$): 3804, 3736, 3674, 3608, 2927, 1728, 1445, 1231, 1156. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.07 (*s*, CH-15), 4.13 (*q*, *J* = 7.1 Hz, $CH_2$-24), 3.63 (*s*, $CH_3$-20), 2.44-2.49 (*m*, $CH_2$-22), 1.25 (*t*, *J*= 7.1 Hz, $CH_3$-25), 1.16 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.0 (*s*, C-19), 173.4 (*s*, C-23), 145.1 (*s*, C-16), 134.4 (*d*, C-15), 60.2 (*t*, C-24), 56.8 (*d*, C-5), 51.0 (*d*, C-20), 49.0 (*s*, C-8), 47.8 (*d*, C-9), 43.87 (*s*, C-4), 43.8 (*t*, C-7), 43.6 (*d*, C-13), 40.8 (*t*, C-1), 39.6 (*s*, C-10), 39.5 (*t*, C-14), 38.1 (*t*, C-3), 32.4 (*t*, C-17), 29.6 (*t*, C-22), 28.7 (*q*, C-18), 25.3 (*t*, C-12), 20.8 (*t*, C-6), 19.1 (*t*, C-2), 18.9 (*t*, C-11), 15.2 (*q*, C-21), 14.0 (*q*, C-25). **GCMS** m/z calculated for $[C_{25}H_{38}O_4]^+$: 402.28; found: 402.3.

*Methyl (4R,6aS,9R,11bS)-8-(3-ethoxy-3-oxopropylidene)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (150)*

**IR** (ν, $cm^{-1}$): 3674, 2931, 1728, 1449, 1234, 1171, 1150. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.09-4.16 (*m*, $CH_2$-24), 3.63-3.64 (*s*, $CH_3$-20), 1.25 (*m*, $CH_3$-25), 1.17 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.0, 172.4, 148.9, 149.9, 109.9, 110.3, 60.3, 57.0, 57.1, 55.0, 55.1, 51.0, 49.3, 43.8, 43.5, 43.4, 41.4, 40.7, 39.4, 39.6, 39.2, 38.1, 34.6, 34.8, 33.0, 28.7, 21.9, 19.1, 18.4, 18.7, 15.2, 15.4, 14.1, 14.2. **GCMS** m/z calculated for $C_{25}H_{38}O_4$: 402.28; found: 402.3.

*Methyl (4R,6aS,8R,9R,11bS)-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (151)*

According to general procedure 3 from methyl *ent*-kaurenoate **134** (100 mg, 0.36 mmol), ethyl iodoacetate (64 µL, 0.54 mmol), $Bu_6Sn_2$ (272 µL, 0.54 mmol) and DTBHN (2 mg, 0.01 mmol).

The reaction mixture was refluxed for 2 h. The crude product was purified by column chromatography (pentane/EtOAc 98:2) and gave the mixture of 3 compounds: the compound **149** - 45 %, **150** - 22% and compound **151** with a 21% yield. **IR** (ν, $cm^{-1}$): 3750, 2921, 1729, 1506, 1448, 1370, 1191, 1042. **$^{1}$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 4.12 (*q*, $CH_2$-24), 3.63 (*s*, $CH_3$-20), 2.29 (*m*, $CH_2$-17), 1.25 (*t*, *J*= 7.1 Hz, $CH_3$-25), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 178.10, 174.03, 60.17, 57.15, 56.61, 51.05, 46.74, 44.41, 43.89, 42.22, 40.87, 40.51, 40.13, 38.49, 38.21, 34.09, 28.77, 26.66, 25.88, 22.24, 19.19, 15.42, 14.28. **GCMS** m/z calculated for $C_{25}H_{40}O_4$: 404.29; found: 404.3.

*Methyl (4'R,6a'S,9'R,11b'S)-4',11b'-dimethyl-5-oxododecahydro-7'H-spiro[pyrrolidine-2,8'-[6a,9]methanocyclohepta[a]naphthalene]-4'-carboxylate (152)*

A solution of azide **147** (53 mg, 0.12 mmol) and 10% Pd/C (10% w/w) in dry EtOAc (2 mL) was stirred for 48 h at room temperature under $H_2$ (1 atm). The catalyst was filtered off, the solvent was removed under reduced pressure and the crude purified by column chromatography ($CH_2Cl_2$/MeOH 90:10) giving the lactam **152** (42 mg, 95%) as a white powder. M.p. 150-152 °C, $[a]_D^{20}$= -77.37° (*c*= 4.50, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3676, 3209, 2937, 2298, 1712, 1683. **$^{1}$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 6.68 (*s*, -NH), 3.63 (*s*, $CH_3$-20), 2.30 (*m*, $CH_2$-17), 2.05 (*d*, *J* = 11.9 Hz, $CH_2$-22), 1.15 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 177.91, 176.79, 67.23, 57.62, 56.90, 55.64, 51.09, 46.56, 44.89, 43.80, 41.85, 40.72, 39.43, 38.88, 38.09, 31.15, 29.99, 28.68, 27.09, 22.05, 19.08, 18.84, 15.45.

*Methyl (4'R,6a'S,9'R,11b'S)-4',11b'-dimethyldodecahydro-7'H-spiro[pyrrolidine-2,8'-[6a,9] methanocyclohepta[a]naphthalene]-4'-carboxylate (153)*

To a solution of lactam **152** (50 mg, 0.13 mmol) in THF (4 mL) were added $NaBH_4$ (20 mg, 0.53 mmol) and $I_2$ (102 mg, 0.4 mmol). The reaction mixture was refluxed for 8 h and after this time it was purified by column chromatography ($CH_2Cl_2$/MeOH 90:10) giving the compound **153** (40 mg, 85%) as a colorless oil. $[\alpha]_D^{25}$ = - 73.56° (*c*= 2.74, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3424, 2940, 2871, 2744, 2483, 1722, 1599. **$^{1}$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 8.46 (*s*, NH) 3.63 (*s*, $CH_3$-20), 3.43 (*bs*, $CH_2$-23), 2.65 (*s*, CH-13), 1.15 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 177.87, 76.85, 56.72, 55.68, 52.42, 51.11, 45.70, 43.81, 43.33, 42.73, 40.70, 40.26, 39.49, 38.54, 38.07, 32.96, 28.60, 26.88, 22.69, 22.07, 19.05, 18.64, 15.33.

According to general procedure 4 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (60 mg, 0.18 mmol), ethyl iodoacetate (32 µL, 0.27 mmol) and DLP (3.6 mg, 0.009 mmol). The reaction was refluxed for 23 h and after this time the crude product was purified by column

chromatography (pentane/EtOAc 95:5) giving the mixture of 2 compounds. After, this mixture was acetylated with acetic anhydride (0.2 mL, 2.6 mmol) and DMAP (0.5 mol%) in pyridine (5 mL) at room temperature for 48 h. The crude mixture was extracted with $Et_2O$, neutralized with 10% aqueous $H_2SO_4$ and washed with brine. The organic layer was dried, and the solvent was removed under reduced pressure. The crude was purified by column chromatography (pentane/EtOAc 97:3) to afford lactone **155** (7 mg, 11%) and acetate **156** (20 mg, 24%).

*Methyl (3R,7aR,7bR,10R,13aS,13bS)-10,13a-dimethyl-6-oxo-1,2,3,5,7a,8,9,9a,10,11,12,13,13a, 13b-tetradecahydro-6H-3,7b methanonaphtho [1',2':6,7]cyclohepta[1,2-b]pyran-10-carboxylate (155)*

M.p. 180-182 °C, $[a]_D^{20}$= + 11.40° (*c*= 2.83, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3054, 2986, 2933, 2865, 1740, 1722. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.81 (*dt*, *J* = 5.4, 2.3 Hz, CH-17), 4.48 (*d*, *J*= 1.66 Hz, CH-15), 3.64 (*s*, $CH_3$-20), 3.03 (*m*, $CH_2$-22), 2.82 (*bs*, CH-13), 1.19 (*s*, $CH_3$-18), 0.86 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.86 (*s*, C-19), 172.57 (*s*, C-23), 148.87 (*s*, C-16), 115.31 (*d*, C-17), 87.99 (*d*, C-15), 56.82 (*d*, C-5), 54.61 (*d*, C-9), 51.11 (*q*, C-20), 46.09 (*s*, C-8), 43.78 (*s*, C-4), 40.82 (*d*, C-13), 40.71 (*t*, C-1), 39.56 (*s*, C-10), 38.41 (*t*, C-7), 38.00 (*t*, C-3), 34.32 (*t*, C-12), 33.13 (*t*, C-22), 29.96 (*t*, C-14), 28.66 (*q*, C-18), 20.74 (*t*, C-6), 19.03 (*t*, C-2), 18.94 (*t*, C-11), 15.68 (*q*, C-21). **GCMS** m/z calculated for $C_{23}H_{32}O_4$: 359.28; found 328.2 ($M^+$-$CO_2$).

*Methyl (4R,6aR,7R,9R,11aS,11bS,E)-7-acetoxy-8-(3-ethoxy-3-oxopropylidene)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (156)*

$[a]_D^{20}$= - 69.81° (*c*= 2.36, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2984, 2930, 2859, 1727. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.62 (*t*, *J*= 7.4 Hz, CH-17), 5.44 (*s*, CH-15), 4.12 (*q*, *J* = 7.8, 7.3 Hz, 2H), 3.63 (*s*, $CH_3$-20), 2.97 (*d*, *J*= 7.1 Hz, $CH_2$-22), 2.79 (*bs*, CH-13), 2.07 (*s*, $CH_3$-27), 1.25 (*t*, *J*= 7.9 Hz, $CH_3$-25), 1.15 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.93, 171.51, 170.71, 148.75, 117.35, 80.74, 60.57, 56.60, 52.52, 51.09, 47.85, 43.77, 42.31, 40.58, 39.66, 37.94, 36.97, 34.69, 34.34, 33.10, 28.62, 20.87, 20.86, 19.09, 18.39, 15.55, 14.17.

According to general procedure 3 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (50 mg, 0.15 mmol), ethyl iodoacetate (36 µL, 0.3 mmol), $PhSO_2N_3$ (83 mg, 0.45 mmol), $Bu_6Sn_2$ (115 µL, 0.23 mmol) and DTBHN (0.9 mg, 0.005 mmol). The reaction mixture was refluxed for 4 h. The crude product was purified by column chromatography (pentane/EtOAc 95:5) and gave the mixture of the compound **155** and **156** (22% total yield).

According to general procedure 5 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (50 mg, 0.15 mmol), ethyl iodoacetate (36 μL, 0.3 mmol), $PhSO_2N_3$ (83 mg, 0.45 mmol) and $Et_3B$ (0.45 mL, 0.45 mmol). The crude product was purified by column chromatography (pentane/EtOAc 95:5) and afforded the compound **157** in 25% yield and **158** in 27%.

*Methyl (4R,6aR,7R,9R,11bS,E)-8-(3-ethoxy-3-oxopropylidene)-7-hydroxy-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (157)*

**IR** (ν, $cm^{-1}$): 3483, 2932, 2871, 1725, 1463. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.50 (*t, J*=7.3 Hz, CH-17), 4.14 (*q, J*=7.1 Hz, $CH_2$-24), 3.95 (*s*, CH-15), 3.65 (*s*, $CH_3$-20), 3.26 (*d, J*= 7.6 Hz), 1.25 (*t, J*=7.1 Hz, $CH_3$-25), 1.18 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.08, 172.84, 154.84, 115.67, 80.44, 61.01, 57.11, 53.16, 51.10, 47.84, 43.89, 42.18, 40.84, 39.66, 38.11, 36.05, 35.17, 35.14, 33.23, 28.74, 21.11, 19.19, 18.32, 15.62, 14.17.

*Methyl (4R,6aR,7R,9R,11bS,Z)-8-(3-ethoxy-3-oxopropylidene)-7-hydroxy-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (158)*

$[\alpha]_D^{20}$= -89.83° (*c*= 4.80, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3484, 2933, 2871, 1724, 1462. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.80 (*t, J*=7.3 Hz, CH-17), 4.13 (*q, J*=7.1 Hz, $CH_2$-24), 3.77 (*s*, CH-15), 3.64 (*s*, $CH_3$-20), 3.09 (*d, J*= 7.5 Hz), 1.25 (*t, J*=7.1 Hz, $CH_3$-25), 1.17 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.11, 171.90, 153.54, 116.42, 83.18, 60.69, 56.96, 52.89, 51.16, 47.33, 43.82, 40.75, 39.60, 38.02, 36.09, 35.14, 34.65, 30.56, 28.72, 21.03, 19.13, 18.66, 15.64, 14.19.

*Methyl (4R,6aR,7R,8R,9R,11bS)-8-azido-7-hydroxy-8-(3-methoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (159)*

According to general procedure 3 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (50 mg, 0.15 mmol), iodoacetic acid (56 mg, 0.3 mmol), $PhSO_2N_3$ (83 mg, 0.45 mmol), $Bu_6Sn_2$ (115 μL, 0.23 mmol) and DTBHN (0.9 mg, 0.005 mmol). The reaction mixture was refluxed for 6 h. After this time the crude was purified by column chromatography (pentane/EtOAc 90:10) giving lactone **155** (16 mg, 28%) and azide **159** (27 mg, with impurities of reagents), which was methylated with an ethereal solution of diazomethane and purified by column chromatography (pentane/EtOAc 97:3) affording methylated azide **159** (42%). $[\alpha]_D^{20}$= - 55.81° (*c*= 2.13, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3737, 3526 (w), 2940, 2872, 2853, 2299, 2107, 1725, 1445. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.69 (*s*, $CH_3$-24), 3.63 (*s*, $CH_3$-20), 3.40 (*s*, CH-15), 2.56 (*t, J*= 7.9 Hz, $CH_2$-22), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.84 (*s*, C-19), 173.61 (*s*, C-23), 85.22 (*d*, C-15), 75.44 (*d*, C-16), 56.71 (*d*, C-5), 54.72 (*d*, C-9), 51.71 (*q*, C-

20), 51.06 (*q*, C-24), 47.55 (*s*, C-8), 43.78 (*s*, C-4), 41.87 (*d*, C-13), 40.59 (*t*, C-1), 39.59 (*s*, C-10), 37.98 (*t*, C-12), 36.05 (*t*, C-7), 35.66 (*t*, C-3), 29.41 (*t*, C-17), 28.63 (*q*, C-18), 28.41 (*t*, C-22), 25.78 (*t*, C-14), 21.03 (*t*, C-6), 18.99 (*t*, C-2), 18.19 (*t*, C-11), 15.34 (*q*, C-21). **GCMS** m/z calculated for $C_{25}H_{39}N_3O_4$: 445.28; found: 402.3 ($M^+$-$HN_3$).

*Methyl (4'R,6a'R,7'R,9'R,11b'S)-7'-hydroxy-4',11b'-dimethyl-5-oxododecahydro-7'H-spiro[pyrrolidine-2,8'-[6a,9]methanocyclohepta[a]naphthalene]-4'-carboxylate (160)*

A solution of azide **159** (53 mg, 0.12 mmol) and 10% Pd/C (10% w/w) in dry EtOAc (2 mL) was stirred for 64 h at room temperature under $H_2$ (1 atm). The catalyst was filtered off, the solvent was removed under reduced pressure and the crude purified by column chromatography ($CH_2Cl_2$/MeOH 85:15) giving the lactam **160** (14 mg, 30%) as a yellowish oil. $[\alpha]_D^{25}$ = - 90.85° (c= 3.0, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3351, 2933, 2871, 2322, 1722, 1685, 1552. **$^1$H RMN** (400 MHz, $CDCl_3$) δ (ppm) 6.73 (*s*, NH), 3.63 (*s*, $CH_3$-20), 3.49 (*s*, CH-15), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C RMN** (100 MHz, $CDCl_3$) δ (ppm) 179.09 (*s*, C-23), 178.04 (*s*, C-19), 88.17 (*d*, C-15), 70.82 (*s*, C-16), 56.80 (*d*, C-5), 54.39 (*d*, C-9), 51.14 (*q*, C-20), 47.42 (*s*, C-8), 44.91 (*d*, C-13), 43.75 (*s*, C-4), 40.67 (*t*, C-1), 38.01 (*t*, C-3), 39.61 (*s*, C-10), 36.63 (*t*, C-7), 35.44 (*t*, C-12), 30.57 (*t*, C-17), 29.32 (*t*, C-22), 28.64 (*q*, C-18), 26.34 (*t*, C-14), 21.16 (*t*, C-6), 19.04 (*t*, C-2), 19.02 (*t*, C-11), 15.55 (*q*, C-21).

*Methyl (4R,6aR,7S,9R,11bS)-7-((tert-butyldimethylsilyl)oxy)-4,11b-dimethyl-8-methylenetetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (161)*

To a solution of alcohol **154** (100 mg, 0.3 mmol) and imidazole (82 mg, 1.2 mmol) in DMF (3 mL) at 0°C was added *tert*-butyldimethylsilyl chloride (TBDMSCl) (90 mg, 0.6 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was extracted with EtOAc, and the organic layer was washed with brine and water, dried, concentrated. The crude was purified by column chromatography (pentane/EtOAC 98:2) to give the ether **161** (120 mg, 90%). $[\alpha]_D^{20}$= -66º (*c*= 0.98, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2926, 2095, 1718, 1264, 1113, 727. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.02 (*s*, $CH_2$-17), 4.99 (*s*, $CH_2$-17), 3.82 (*s*, CH-15), 3.64 (*s*, $CH_3$-20), 1.19 (*s*, $CH_3$-21), 0.89 (*s*, $3CH_3$-23), 0.82 (*s*, $CH_3$-18), 0.10 (*d*, *J*= 2.0 Hz, $2CH_3$-24, 25). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 178.19, 159.49, 107.84, 83.08, 57.20, 53.26, 51.09, 48.60, 43.85, 42.24, 40.86, 39.75, 38.08, 36.41, 36.13, 33.08, 28.74, 26.06 ($3CH_3$), 21.27, 19.17, 18.42, 18.23, 15.65, -3.49, -3.87.

*Methyl (4R,6aR,7R,8S,9R,11bS)-8-azido-7-((tert-butyldimethylsilyl)oxy)-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (162)*

According to general procedure 3 from ether **161** (100 mg, 0.22 mmol), ethyl iodoacetate (39 µL, 0.33 mmol), 3-$PySO_2N_3$ (121 mg, 0.66 mmol), $Bu_6Sn_2$ (167 µL, 0.33 mmol) and DTBHN (1 mg, 0.0066 mmol). The reaction mixture was refluxed for 10 h. The crude mixture was purified by column chromatography (pentane/EtOAc 96:4) and afforded the azide **162** (92 mg, 73%) as a colorless oil. **IR** (ν, $cm^{-1}$): **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.14 (*q*, *J* = 7.8, 7.3 Hz, $CH_2$-24), 3.63 (*s*, $CH_3$-20), 3.59 (*s*, CH-15), 2.18 (*m*, $CH_2$-22), 1.26 (*t*, *J* = 7.1 Hz, $CH_3$-25), 1.18 (*s*, $CH_3$-18), 0.97 (*s*, $CH_3$-28), 0.80 (*s*, $CH_3$-21), 0.13 (*d*, *J* = 7.3 Hz, $CH_3$-26). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.97, 173.19, 88.92, 74.56, 60.56, 57.04, 54.58, 51.14, 47.86, 43.78, 41.59, 40.79, 39.61, 37.96, 36.52, 36.27, 30.02, 28.70, 27.84, 26.28 (3C-Me), 25.66, 21.14, 19.06, 18.98, 18.22, 15.33, 14.18, -3.44, -3.65.

*Methyl (4R,6aR,7R,8S,9R,11bS)-8-azido-8-(3-ethoxy-3-oxopropyl)-7-hydroxy-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (163)*

To a solution of azide **162** (92 mg, 0.16 mmol) in THF (4 mL) was added TBAF (125 mg, 0.48 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc and dried over $Na_2SO_4$. The solvent was removed under reduced pressure. The crude was purified by column chromatography (pentane/EtOAc 90:10) and afforded the azide **163** (38 mg, 51%) as a white powder. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.15 (*q*, *J*= 7.1 Hz, $CH_2$-24), 3.64 (*s*, $CH_3$-20), 3.40 (*s*, CH-15), 2.55 (*t*, *J*= 8.0 Hz, $CH_2$-22), 1.30-1.24 (*m*, $CH_3$-25), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.85, 173.19, 85.22, 75.50, 60.57, 56.72, 54.72, 51.06, 47.55, 43.78, 41.86, 40.59, 39.59, 37.98, 36.06, 35.68, 29.66, 28.63, 28.38, 25.79, 21.04, 19.00, 18.19, 15.34, 14.16.

*Methyl (4R,6aS,8R,9R,11bS)-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (164)*

According to general procedure 1 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), ethyl iodoacetate (23 µL, 0.19 mmol), *tert*-butylcatechol (53 mg, 0.32 mmol), $Et_3B$ (0.21 mL, 0.21 mmol). The crude mixture was purified by FC (pentane/EtOAc 95:5) gave the corresponding product **164** (55 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ = -62.5° (*c*= 1.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2931, 2359, 2341, 1727, 1374, 1149, 669. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.10 (*q*, *J* = 7.1 Hz, $CH_2$-24), 3.57 (*s*, $CH_3$-20), 2.28 (*m*, $CH_2$-22), 1.24 (*t*, *J* = 7.1 Hz, $CH_3$-25), 1.14 (*s*, $CH_3$-18),

0.80 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.14, 174.07, 60.19, 57.04, 56.49, 51.09, 46.64, 44.35, 43.81, 42.15, 40.78, 40.44, 40.03, 39.41, 38.40, 38.13, 34.04, 28.74, 26.60, 25.84, 22.20, 19.14, 19.10, 15.37, 14.27. **HRMS (ESI)** calculated for $[C_{25}H_{40}O_4]^+$: 405.2995; found 405.2999.

*Methyl (4R,6aS,8S,9R,11bS)-4,11b-dimethyl-8-(2-(phenylsulfonyl)ethyl)tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (165)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (35 mg, 0.11 mmol), iodomethylphenylsulphone (37 mg, 0.13 mmol), *tert*-butylcatechol (36 mg, 0.22 mmol), $Et_3B$ (0.14 mL, 0.14 mmol). The crude mixture was purified by FC (pentane/EtOAc 90:10) and gave the corresponding product **165** (39 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ = -48.7º (*c*= 3.3, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2927, 1721, 1446, 1305, 1145, 740. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.89-7.92 (*m*, CH-24), 7.62-7.77 (*m*, CH-26), 7.53-7.58 (*m*, CH-25), 3.61 (s, $CH_3$-20), 3.06 (*dd*, *J* = 9.7, 6.3 Hz, $CH_2$-22), 1.13 (*s*, $CH_3$-18), 0.77 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.04, 139.27, 133.60, 129.25 (2C), 128.03 (2C), 56.95, 56.26, 56.01, 51.10, 46.34, 44.39, 43.79, 41.97, 40.73, 40.27, 39.38, 39.14, 38.19, 38.07, 28.73, 25.65, 24.02, 22.11, 19.10, 18.98, 15.34. **HRMS (ESI)** calculated for $[C_{28}H_{40}O_4S]^+$: 473.2712; found 473.2729.

*Methyl (4R,6aS,8R,9R,11bS)-4,11b-dimethyl-8-(3-oxo-3-(((2S,4R)-1,7,7-trimethylbicyclo [2.2.1] heptan-2-yl)oxy) propyl) tetradecahydro-6a,9-methanocyclohepta [a]naphthalene-4-carboxylate (166)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), isobornyl iodoacetate (58 mg, 0.19 mmol), *tert*-butylcatechol (50 mg, 0.3 mmol), $Et_3B$ (0.2 mL, 0.2 mmol). The crude mixture wad purified by FC (pentane/EtOAc 93:7) and gave the corresponding product **166** (69 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ = -36.7º (*c*= 4.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2929, 1725, 1451, 1151, 975, 771. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.65 (*dd*, *J* = 7.7, 3.2 Hz, CH-24), 3.63 (*s*, $CH_3$-20), 2.23-2.28 (*m*, $CH_2$-22), 1.15 (*s*, $CH_3$-18), 0.97 (*s*, $CH_3$-32), 0.83 (*s*, $2CH_3$-31), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.10, 173.54, 80.72, 57.05, 56.49, 51.09, 48.63, 46.93, 46.67, 45.05, 44.35, 43.82, 42.16, 40.80, 40.44, 39.93, 39.43, 38.89, 38.31, 38.14, 34.42, 33.77, 28.75, 27.05, 26.74, 25.83, 22.20, 20.14, 19.91, 19.14, 19.09, 15.38, 11.47. **HRMS (ESI)** calculated for $[C_{33}H_{52}O_4]^+$: 513.3927; found 513.3938.

*Methyl (4R,6aS,8S,9R,11bS)-8-(3-ethoxy-2,2-difluoro-3-oxopropyl)-4,11b-dimethyltetra decahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (167)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (40 mg, 0.12 mmol), ethyl difluoroiodoacetate (22 µl, 0.15 mmol), *tert*-butylcatechol (40 mg, 0.24 mmol), $Et_3B$ (0.15 mL, 0.15 mmol). The crude was purified by FC (pentane/EtOAc 95:5) and gave the corresponding product **167** (40 mg, 75%) as a colorless oil. $[a]_D^{20}$ = -45.3º (*c*= 3.0, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2931, 1766, 1724, 1464, 1233, 1191, 1072, 773. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.31 (*q*, *J* = 7.1 Hz, $CH_2$-24), 3.62 (*s*, $CH_3$-20), 1.34 (*t*, *J* = 7.2 Hz, $CH_3$-25), 1.15 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.08, 164.7(t), 120.1, 62.73, 56.98, 56.28, 51.11, 46.90, 44.53, 43.79, 41.83, 40.76, 40.16, 39.48, 39.38, 38.09, 36.13(t), 33.25(t), 28.73, 25.94, 22.14, 19.11, 18.95, 15.36, 13.98. **HRMS (ESI)** calculated for $[C_{25}H_{38}F_2O_4]^+$: 441.2799; found 441.2811.

*Methyl (4R,6aS,8S,9R,11bS)-4,11b-dimethyl-8-(2,2,3,3,4,4,5,5,5-nonafluoropentyl) tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (168)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), nonafluoro-1-iodobutane (42 µL, 0.24 mmol), *tert*-butylcatechol (50 mg, 0.3 mmol), $Et_3B$ (0.2 mL, 0.2 mmol). The crude mixture was purified by FC (pentane/EtOAc 97:3) and gave the corresponding product **168** (68 mg, 80%) as a colorless oil. $[a]_D^{20}$ = -41.5º (*c*= 4.0, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2930, 2359, 2342, 1725, 1228, 1131, 880, 687. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 1.25 (*s*, $CH_2$-17), 1.16 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.06, 56.98, 56.23, 51.10, 47.15, 44.49, 43.80, 41.79, 40.75, 40.14, 39.48, 39.39, 38.08, 32.12, 31.84, 29.70, 28.72, 25.88, 22.13, 19.11, 18.99, 15.36. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -81.08 (*bs*, 3F), -113.26 – -114.08 (*m*, 2F), -124.41 – -124.53 (*m*, 2F), -125.92 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{25}H_{33}F_9O_2]^+$: 537.2406; found 537.2410.

*Methyl (4R,6aS,8S,9R,11bS)-4,11b-dimethyl-8-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl) tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (169)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), perfluoro-1-iodohexane (52 µL, 0.24 mmol), *tert*-butylcatechol (50 mg, 0.3 mmol), $Et_3B$ (0.2 mL, 0.2 mmol). The crude mixture was purified by FC (pentane/EtAOc 97:3) and gave the corresponding product **169** (79 mg, 78%) as a colorless oil. $[a]_D^{20}$ = -34.1º (*c*= 4.5, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2932, 2360, 2341, 1725, 1142, 707. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 1.25 (*s*, $CH_2$-17), 1.16 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.06, 56.98, 56.23, 51.09, 47.15, 44.49, 43.80, 41.79, 40.75, 40.13, 39.49, 39.39, 38.08,

32.15, 31.93, 29.70, 28.71, 25.88, 22.13, 19.11, 18.99, 15.35. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -80.84 (*d*, *J* = 13.7 Hz, 3F), -113.50 (*m*, 2F), -121.85 (*m*, 2F), -122.88 (*m*, 2F), -123.56 (*m*, 2F), -126.17 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{27}H_{33}F_{13}O_2]^+$: 637.2342; found 637.2346.

*Methyl (4R,6aS,8S,9R,11bS)-8-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (170)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), perfluorooctyl iodide (62 µL, 0.24 mmol), *tert*-butylcatechol (50 mg, 0.3 mmol), $Et_3B$ (0.2 mL, 0.2 mmol). The crude mixture was purified by FC (pentane/EtOAc 97:3) gave the corresponding product **170** (85 mg, 75%) as a colorless oil. $[a]_D^{20}$ = -26.4º (*c*= 4.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2359, 2341, 1717, 1240, 1111, 906, 728, 647. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 1.25 (*s*, $CH_2$-17), 1.16 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.06, 56.98, 56.23, 51.09, 47.15, 44.49, 43.80, 41.79, 40.75, 40.14, 39.48, 39.39, 38.08, 32.16, 31.93, 29.70, 28.71, 25.88, 22.13, 19.11, 18.99, 15.35. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -80.82 (*t*, *J* = 9.8 Hz, 3F), -113.02 – -113.82 (*m*, 2F), -121.65 (*s*, 2F), -121.91 (*s*, 4F), -122.74 (*s*, 2F), -123.52 (*s*, 2F), -126.14 (*s*, 2F). **HRMS (ESI)** calculated for $[C_{27}H_{33}F_{13}O_2]^+$: 737.2260; found 737.2282.

*Methyl (4R,6aS,8S,9R,11bS)-4,11b-dimethyl-8-(2,2,2-trifluoroethyl)tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (171)*

According to general procedure 6 from methyl *ent*-kaurenoate **134** (50 mg, 0.16 mmol), trifluoroiodomethane (47 mg, 0.24 mmol), *tert*-butylcatechol (50 mg, 0.3 mmol), $Et_3B$ (0.2 mL, 0.2 mmol). The crude mixture was purified by FC (pentane/EtOAc 97:3) and gave the corresponding product **171** (54 mg, 75%) as a colorless oil. $[a]_D^{20}$ = -55.3º (*c*= 2.4, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2932, 1724, 1253, 1142, 1116, 982, 834, 643. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.63 (*s*, $CH_3$-20), 1.16 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.06, 139.10-125.75 ($CF_3$), 56.98, 56.24, 51.11, 46.57, 44.46, 43.80, 41.81, 40.76, 40.15, 39.39, 39.04, 38.09, 35.79-34.70 ($CH_2$-$CF_3$), 33.57-33.54 (CH-$CH_2$-$CF_3$), 28.73, 25.87, 22.14, 19.11, 18.91, 15.36. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -64.96 (*t*, *J*= 10.7 Hz). **HRMS (ESI)** calculated for $[C_{22}H_{33}F_3O_2]^+$: 387.2493; found 387.2505.

*Methyl (4R,6aS,9R,11bS)-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyl-1,2,3,4,4a,5,6,9,10,11,11a,11b-dodecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (172)*

According to general procedure 6 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (50 mg, 0.15 mmol), ethyl iodocetate (21 µL, 0.18 mmol), 4-methoxycatechol (42 mg, 0.3 mmol), $Et_3B$ (0.19 mL, 0.19 mmol). The crude mixture was purified by FC (pentane/EtOAc 95:5) to give the product **172** (24 mg, 40%) as a colorless oil. $[a]_D^{20}$ = -22.6º (*c*= 1.5, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2923, 2851, 2359, 2342, 1730, 1456, 1188, 1157, 668. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.08 (*s*, CH-15), 4.12 (*q*, *J*= 7.1 Hz, $CH_2$-24), 3.63 (*s*, $CH_3$-20), 1.25 (*t*, *J*=7.1 Hz, $CH_3$-25), 1.16 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.10, 173.53, 145.16, 134.35, 60.30, 56.83, 51.10, 49.00, 47.83, 43.86, 43.80, 43.59, 40.80, 39.63, 39.49, 38.16, 32.38, 29.71, 28.75, 25.39, 25.30, 20.86, 19.16, 18.95, 15.21, 14.26. **HRMS (ESI)** calculated for $[C_{25}H_{38}O_4]Na^+$: 425.2659; found 425.2663.

*Methyl (4R,6aS,9R,11bS)-8-(3-ethoxy-2,2-difluoro-3-oxopropyl)-4,11b-dimethyl-1,2,3,4,4a,5,6,9,10,11,11a,11b-dodecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (173)*

According to general procedure 6 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (50 mg, 0.15 mmol), ethyl difluoroiodocetate (23 µL, 0.18 mmol), 4-methoxycatechol (42 mg, 0.3 mmol), $Et_3B$ (0.19 mL, 0.19 mmol). The crude mixture was purified by FC (pentane/EtOAc 95:5) to give the product **173** (34 mg, 43%) as a colorless oil. $[a]_D^{20}$ = -42.0º (*c*= 2.0, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2926, 2359, 2341, 1770, 1723, 1446, 1230, 1186, 1158, 1065, 774. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.34 (*s*, CH-15), 4.29 (*q*, *J*= 7.1 Hz, $CH_2$-24), 3.63 (*s*, $CH_3$-20), 1.33 (*t*, *J*=7.1 Hz, $CH_3$-25), 1.15 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.01, 141.02, 135.93, 62.71, 56.74, 51.13, 49.30, 47.20, 43.84, 43.71, 43.69, 40.73, 39.61, 39.11, 38.11, 35.49 (t), 29.71, 28.74, 24.78, 20.69, 19.12, 18.75, 15.21, 14.00. **HRMS (ESI)** calculated for $[C_{25}H_{38}F_2O_4]Na^+$: 461.2466; found 461.2474.

*Methyl (4R,6aS,9R,11bS)-4,11b-dimethyl-8-(3-oxo-3-(((2S,4R)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)oxy)propyl)-1,2,3,4,4a,5,6,9,10,11,11a,11b-dodecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (174)*

According to general procedure 6 from methyl 15$\alpha$-hydroxy-*ent*-kaurenoate **154** (30 mg, 0.12 mmol), isobornyl iodoacetate (46 mg, 0.14 mmol), 4-methoxycatechol (34 mg, 0.24 mmol), $Et_3B$ (0.15 mL, 0.15 mmol). The crude mixture was purified by FC (pentane/EtOAc 95:5) to give the

product **174** (31 mg, 50%) as a colorless oil. $[a]_D^{20}$ = -17.8º (*c*= 1.7, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2952, 2928, 2365, 2341, 1725, 1455, 1262, 1242, 1085, 669. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.08 (*s*, CH-15), 3.63 (*s*, $CH_3$-20), 1.15 (*s*, $CH_3$-18), 0.99 (*s*, $CH_3$-32), 0.84 (*s*, $CH_3$-21), 0.83 (*s*, $2CH_3$-31). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.09, 173.06, 145.21, 134.28, 82.86, 56.84, 51.09, 49.00, 48.62, 47.83, 46.93, 44.97, 43.79, 43.61, 43.79, 40.81, 39.63, 39.50, 38.77, 38.26, 33.78, 32.69, 28.75, 25.36, 21.33, 20.86, 20.13, 19.95, 19.86, 19.16, 18.97, 15.22, 11.33. **HRMS (ESI)** calculated for $[C_{33}H_{50}O_4]Na^+$: 533.3603; found 533.3601.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-8-(3-ethoxy-3-oxopropyl)-4,11b-dimethyl tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (176)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (45 mg, 0.12 mmol), ethyl iodoacetate (17 µL, 0.14 mmol), 4-methoxycatechol (34 mg, 0.24 mmol), $Et_3B$ (0.15 mL, 0.15 mmol). The crude mixture was purified by FC (pentane/EtOAc 92:8) and gave the corresponding product **176** (30 mg, 46%) as a colorless oil. $[a]_D^{20}$ = -68.7º (*c*= 1.5, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2929, 1725, 1238, 1024, 915, 729. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.67 (*d*, *J* = 3.7 Hz, CH-15), 4.11 (*q*, *J*= 7.1 Hz, $CH_2$-26), 3.62 (*s*, $CH_3$-20), 2.27 (*t*, *J*= 7.1 Hz, $CH_2$-24), 2.04 (*s*, $CH_3$-23), 1.23 (*t*, *J*= 7.2 Hz, $CH_3$-27), 1.13 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 178.01, 173.48, 171.03, 86.74, 60.29, 56.48, 53.47, 51.14, 48.73, 47.50, 43.73, 40.35, 39.57, 38.51, 37.94, 36.96, 34.87, 33.29, 28.62, 24.86, 24.14, 21.25, 21.13, 19.03, 18.74, 15.55, 14.26. **HRMS (ESI)** calculated for $[C_{27}H_{42}O_6]$ $Na^+$: 485.2877; found 485.2874.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-4,11b-dimethyl-8-(2-(phenylsulfonyl)ethyl) tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (177)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (40 mg, 0.11 mmol), iodomethylphenylsulphone (37 mg, 0.13 mmol), 4-methoxycatechol (31 mg, 0.22 mmol), $Et_3B$ (0.14 mL, 0.14 mmol). The crude mixture was purified by FC (pentane/EtOAc 85:15) giving the corresponding product **177** (32 mg, 54%) as a yellowish oil. **IR** (ν, $cm^{-1}$): 2924, 1722, 1446, 1306, 1240, 1147, 743, 688. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.88-7.96 (*m*, CH-26), 7.63-7.68 (*m*, CH-27), 7.54-7.59 (*m*, CH-28), 4.60 (*d*, *J* = 3.3 Hz, CH-15), 3.61 (*s*, $CH_3$-20), 2.02 (*s*, $CH_3$-23), 1.12 (*s*, $CH_3$-18), 0.77 (*s*, $CH_3$-21). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 177.93, 170.94, 133.72, 129.31, 128.07, 86.24, 56.43, 55.16, 53.32, 51.16, 48.08, 47.55, 44.51, 43.71, 40.32, 39.54, 38.28, 37.88, 36.71, 34.80, 28.61, 24.66, 21.99, 21.19, 21.06, 18.99, 18.65, 15.52. **HRMS (ESI)** calculated for $[C_{30}H_{42}O_6S]$ $Na^+$: 553.2599; found 553.2594.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-8-(3-ethoxy-2,2-difluoro-3-oxopropyl)-4,11b-dimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (178)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (40 mg, 0.11 mmol), ethyl difluoroiodoacetate (19 µL, 0.13 mmol), 4-methoxycatechol (31 mg, 0.22 mmol), $Et_3B$ (0.14 mL, 0.14 mmol). The crude mixture was purified by FC (pentane/EtOAc 93:7) and gave the corresponding product **178** (32 mg, 58%) as a colorless oil. $[a]_D^{20}$ = -48.7º (*c*= 2.3, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2938, 1722, 1236, 1024, 850. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.62 (*d*, *J* = 4.3 Hz, CH-15), 4.30 (*q*, *J*= 7.1 Hz, $CH_2$-26), 3.62 (*s*, $CH_3$-20), 2.04 (*s*, $CH_3$-23), 1.33-1.37 (*m*, $CH_2$-17), 1.24 (*t*, *J* = 7.0 Hz, $CH_3$-27), 1.13 (*s*, $CH_3$-18), 0.81 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] (75 MHz, $CDCl_3$) δ (ppm) 178.02, 171.15, 163.80, 86.75, 63.79, 62.86, 56.43, 53.35, 51.18, 47.22, 43.72, 42.66, 40.36, 39.55, 38.41, 37.91, 37.74, 34.76, 28.60, 24.90, 21.11, 21.07, 19.01, 18.61, 17.92, 15.55, 15.35, 13.96. **HRMS (ESI)** calculated for $[C_{27}H_{40}F_2O_6]$ $Na^+$: 521.2691; found 521.2585.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-4,11b-dimethyl-8-(2,2,3,3,4,4,5,5,5-nonafluoropentyl) tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (179)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (50 mg, 0.13 mmol), nonafluoro-1-iodobutane (45 µL, 0.24 mmol), 4-methoxycatechol 49 (38 mg, 0.27 mmol), $Et_3B$ (0.17 mL, 0.17 mmol). The crude mixture was purified by FC (pentane/EtOAc 93:7) and gave the corresponding product **179** (35 mg, 45%, dr 2:0.3) as a yellowish oil. **IR** (ν, $cm^{-1}$): 2933, 1725, 1228, 1131, 1026, 729. **$^1$H NMR** of the minor epimer (15%) (300 MHz, $CDCl_3$) δ (ppm) 3.64 (*s*, $CH_3$-20), 2.05 (*s*, $CH_3$-23), 1.16 (*s*, $CH_3$-18), 0.84 (*s*, $CH_3$-21). **$^1$H NMR** of the major epimer (85%) (300 MHz, $CDCl_3$) δ (ppm) 4.71 (*d*, *J* = 3.5 Hz, CH-15), 3.63 (*s*, Me-20), 2.03 (*s*, Me-23), 1.15 (*s*, Me-18), 0.82 (*s*, Me-21). **$^{13}$C NMR** [$^{19}$F] major epimer (75 MHz, $CDCl_3$) δ (ppm) 177.95, 171.10, 86.69, 56.44, 53.37, 51.18, 47.17, 43.72, 41.75, 40.37, 39.57, 38.39, 37.90, 37.77, 34.80, 29.62, 28.60, 24.85, 21.10, 20.98, 19.01, 18.64, 15.55. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -81.06 (*d*, *J* = 13.9 Hz, 3F), -113.85 – -114.23 (*m*, 2F), -124.12 – -124.50 (*m*, 2F), -125.79 – -126.04 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{27}H_{35}F_9O_6]$ $Na^+$: 617.2284; found 617.2284.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-4,11b-dimethyl-8-(2,2,3,3,4,4,5,5,5,5,7,7,7-tridecafluoroheptyl)-tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (180)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (50 mg, 0.13 mmol), perfluoro-1-iodohexane (55 µL, 0.24 mmol), 4-methoxycatechol (38 mg, 0.27 mmol), $Et_3B$ (0.17 mL, 0.17 mmol). The crude mixture was purified by FC (pentane/EtOAc 93:7) gave the corresponding product **180** (43 mg, 48%, dr 2:0.3) as a yellowish oil. **IR** (ν, $cm^{-1}$): 2931, 1725, 1230, 1190, 1143, 1027, 707. **$^1$H NMR** of the minor epimer (13%) (300 MHz, $CDCl_3$) δ (ppm) 3.64 (*s*, $CH_3$-20), 2.06 (*s*, $CH_3$-23), 1.16 (*s*, $CH_3$-18), 0.84 (*s*, $CH_3$-21). **$^1$H NMR** major epimer (87%) (300 MHz, $CDCl_3$) δ (ppm) 4.72 (*d*, *J* = 3.6 Hz, CH-15), 3.63 (*s*, $CH_3$-20), 2.05 (*s*, $CH_3$-23), 1.14 (*s*, $CH_3$-18), 0.82 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] major epimer (75 MHz, $CDCl_3$) δ (ppm) 177.94, 86.69, 56.44, 53.37, 51.17, 47.18, 43.72, 41.76, 40.37, 39.57, 38.39, 37.90, 37.79, 34.80, 29.71, 28.60, 24.85, 21.10, 20.98, 19.01, 18.64, 15.55. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -80.79 (*t*, *J* = 9.8 Hz, 3F), -113.82 (*m*, 2F), -121.48 – -121.96 *(m*, 2F), -122.75 – -122.93 (*m*, 2F), -123.21 – -123.39 (*m*, 2F), -126.14 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{27}H_{35}F_9O_6]Na^+$: 717.2135; found 717.2137.

*Methyl (4R,6aR,7S,8S,9R,11bS)-7-acetoxy-8-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononyl)-4,11b-dimethyl tetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (181)*

According to general procedure 6 from methyl 15$\alpha$-acetoxy-*ent*-kaurenoate **175** (50 mg, 0.13 mmol), perfluorooctyl iodide (65 µL, 0.24 mmol), 4-methoxycatechol (38 mg, 0.27 mmol), $Et_3B$ (0.17 mL, 0.17 mmol). The crude mixture was purified by FC (pentane/EtOAc 97:3) and gave the corresponding product **181** (58 mg, 56%, dr 2:0.2) as a yellowish oil. **IR** (ν, $cm^{-1}$): 2933, 1726, 1232, 1199, 1144, 1028, 704. **$^1$H NMR** of the minor epimer (10%) (300 MHz, $CDCl_3$) δ (ppm) 3.64 (*s*, $CH_3$-20), 2.07 (*s*, $CH_3$-23), 1.16 (*s*, $CH_3$-18), 0.84 (*s*, $CH_3$-21). **$^1$H NMR** of the major epimer (90%) (300 MHz, $CDCl_3$) δ (ppm) 4.72 (*d*, *J*= 3.7 Hz, CH-15), 3.63 (*s*, $CH_3$-20), 2.05 (*s*, $CH_3$-23), 1.15 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-21). **$^{13}$C NMR** [$^{19}$F] major epimer (75 MHz, $CDCl_3$) δ (ppm) 177.94, 171.09, 86.69, 56.44, 53.37, 51.16, 47.17, 43.72, 41.76, 40.36, 39.57, 38.38, 37.89, 37.79, 34.80, 29.70, 28.59, 24.84, 21.10, 20.96, 19.00, 18.64, 15.54. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -80.79 (*t*, *J* = 9.8 Hz, 3F), -113.37 – -114.33 (*m*, 2F), -121.58 (*s*, 2F), -121.92 (*s*, 4F), -122.70 (*s*, 2F), -123.30 (*s*, 2F), -126.11 (*s*, 2F).

# 3. RADICAL TRANSFORMATIONS OF LABDANIC AND ISOCOPALIC DITERPENOIDS

Manoyl oxide **182** represents the carbon skeleton of forskolin **183,** but lacks the rich „decoration" with oxygenated functional groups. Their selective direct introduction by organic synthesis methods still represents a challenging task. It can be successfully addressed, based on the modern remote functionalization procedures, which rely upon mild free radical processes, compatible with the relatively fragile structure of **182** and **184**. Both substrates can be easily obtained from sclareol in a single step [153]. Manoyl oxide **182** and *epi*-manoyl oxide **184** have undergone some transformations through radical reactions, such as hydroazidation, carboazidation or carboiodination and carbohydrogenation [154-156].

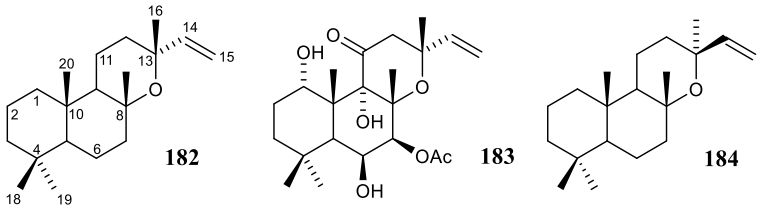



**Fig. 3.1. Forskolin and manoyl oxides.**

### 3.1. Hydroazidation of *epi*-manoyl oxide

Free radical transformations are intensively explored nowadays as efficient synthetic tools provided the broad range of potential transformations, mild reaction conditions and high functional group tolerance. In particular, a very efficient methodology for *anti*-Markovnikov hydroazidation of olefins has been recently reported, and it showed promising results with diverse substrates, including natural isoprenoids [2]. Further exploitation of this simple, two steps – one-pot procedure was envisaged as a molecular editing tool for olefinic fragments, which are ubiquitous in natural product scaffolds. This strategy is based on the versatile chemical reactivity of the azide group, which once present in a molecular framework can follow a myriad of chemical transformations. "Click"-chemistry procedures represent a relevant but not the only one example.

*Anti*-Markovnikov hydroazidation of **184** was performed according to the procedure reported by Renaud [2]. Azide **185** was obtained in 40% yield and the spectral data confirmed the selectivity of addition. According to NMR spectral data, the position of azide group was registered at 47.67 ppm in $^{13}C$ spectrum and having a cross-peak in HSQC spectrum with

multiplet at 3.37 ppm. The methylene group from C-14 at 39.51 ppm in carbon spectrum and 2.03 ppm as a multiplet in the proton spectrum was registered as well (Figure 3.2).

Following transformation of azide **185** included its reduction under mild conditions to furnish amine **190** and click reaction with a set of alkynes. The structure of the obtained triazoles **186-189** was elucidated basing on spectral data. Thus, the $^{13}C$ NMR spectra showed the peaks characteristic to 1,2,3-triazole ring (cca. 120 ppm and 140 ppm, see the experimental part for details). It is noteworthy mentioning, that observation of these peaks was not possible for triazole **186** unless a trace amount of triethylamine was added to the NMR vial [139]. For triazoles **187-189** the characteristic peaks were registered in deuterated chloroform without the need to add a small amount of triethylamine, as was for triazole **186** (Figure 3.2).

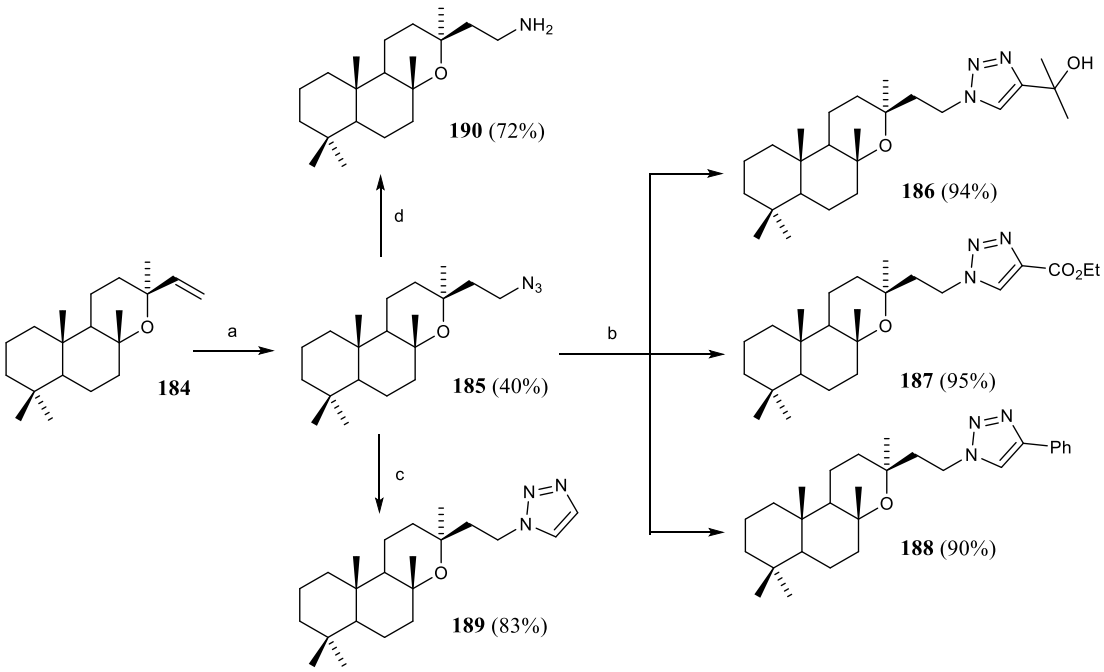



**Fig. 3.2. *Anti*-Markovnikov hydroazidation of *epi*-manoyl oxide and versatility of azido group**

*Reagents and conditions:* **a.** CatBH, DMA, DCM; 3-$PySO_2N_3$, DTBHN, DMF; **b.** alkynes (1. $HC{\equiv}CC(CH_3)_2OH$, 2. $HC{\equiv}CCO_2C_2H_5$, 3. $HC{\equiv}CC_6H_5$), 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 [6]. Sometimes radical additions represent the only solutions to overcome synthetic challenges connected to substrate reactivity and stereochemistry issues [6].

The field of medicinal chemistry could also benefit from the application of ATRA, even though current SAR studies on relevant biomolecules are mostly targeting functional group transformations of natural scaffolds, leaving the carbon backbone intact. In our opinion, assembling of new C-C bonds in natural products of known biological activity can provide opportunities for broadening molecular diversity leading to new chemical space, in addition to trivial functional group transformations.

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 **182** and **184**.

Treatment of **182** 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 **191** 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 **192**, which could be possibly formed after a 1,5-radical migration, followed by elimination (Figure 3.3). The structure of the other component of the isolated fraction was tentatively assigned as **195**, which can derive from a reductive hydrogen radical abstraction.

The complex nature of reaction products suggested parallel substrate reactivity, due to acid-catalyzed transformations induced by free iodoacetic acid. To diminish this effect, the reaction of **182** 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 **194**. A minor fraction was also isolated, and the NMR data showed a mixture of esters **195** and **196**, like esters **192** and **193** derived from the reaction of **182** with iodoacetic acid. All attempts to separate individual **196** and **196** failed.

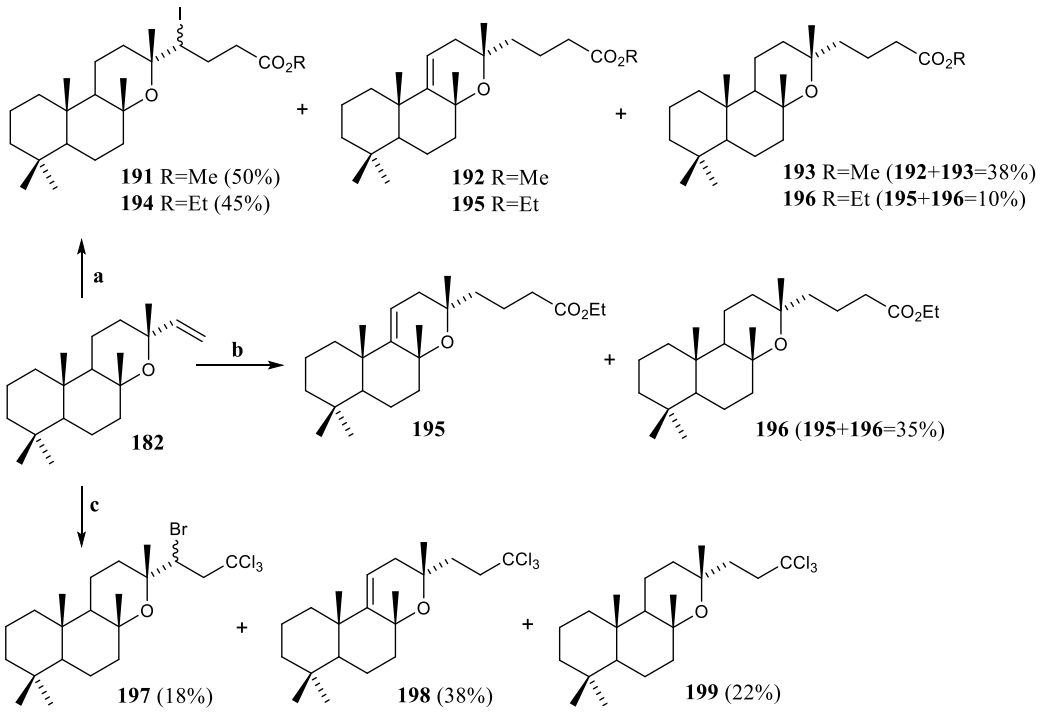



**Fig. 3.3. Carboazidation and carboiodination of manoyl oxide.**

*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.

Surprisingly, the interaction of oxide **182** with bromotrichloromethane occurred with a totally opposite selectivity. Bromide **197**, resulting from 1,2-addition, was minor in this case and the predominating products **198** and **199** have been isolated in individual form. Their structure was assigned univocally based on 2D-NMR spectra. The difference in the reaction selectivity of the same substrate with different alkylating agents can be explained by both the steric effects of the bulkier trichloromethyl radical and by the lower transfer rate of bromine radical vs. iodine. In line with this conclusion, using the massive iodomethylphenylsulfone as alkylating agent resulted in a very sluggish reaction and complex reaction product profile. No individual reaction product was isolated. On the other hand, the reaction of the same substrate under carboazidation conditions with ethyl iodoacetate and phenyl sulfonyl azide as azide source led to the same mixture of esters **195** and **196**. No azide radical transfer was observed.

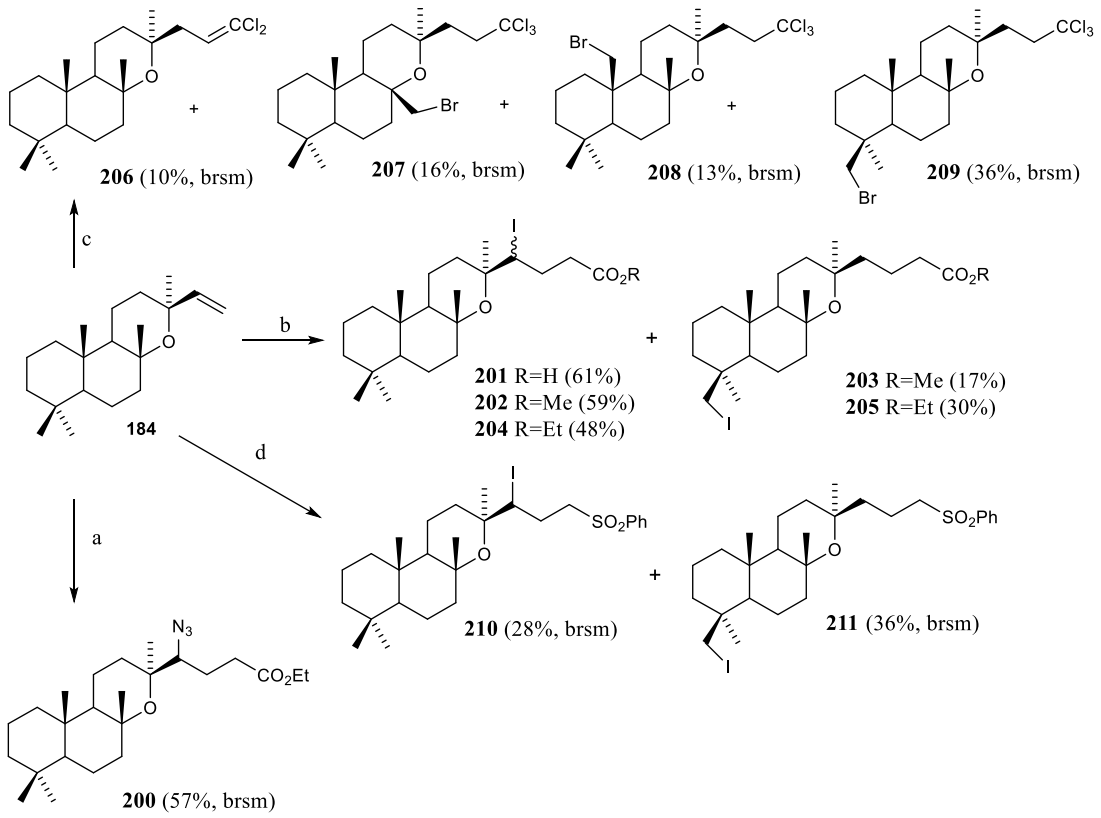



**Fig. 3.4. Carboazidation and carboiodination of *epi*-manoyl oxide.**

*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.

The most interesting aspect of these transformations is represented by manoyl oxide derivatives with the unsaturation in the cycle C. Formation of compounds **192**, **195** and **198** can be accounted for a radical translocation mechanism leading to a formal remote functionalization. 1,5-Translocations are known phenomena in radical chemistry [157-159] and include generation of a carbon or heteroatom centered radical, followed by a 1,5-hydrogen atom transfer (HAT) and quenching of the translocated radical by either intramolecular [160] or intermolecular [161] processes. This pathway represents a very important approach for remote functionalization of unactivated C-H bonds and the reported procedures based on this strategy relies upon different methods of initial radical generation. These are based mostly on oxygen, nitrogen centered initial radicals [162], and relevant examples are the well-known Hofmann–Löffler–Freytag reaction of *N*-haloamines or Barton's nitrite ester photolysis.

**Table 3.1. NMR data for compounds 201 and 202 (assigned basing on $^{1}H$, $^{13}C$, DEPT, HSQC, HMBC, COSY-45, NOESY NMR experiments).**

| No C | **201** (major) | | **201** (minor) | | **202** (major) | | **202** (minor) | |
|---|---|---|---|---|---|---|---|---|
| | δ $^{1}H$; m/J, Hz | δ $^{13}C$; m | δ $^{1}H$; m/J, Hz | δ $^{13}C$; m | δ $^{1}H$; m/J, Hz | δ $^{13}C$; m | δ $^{1}H$; m/J, Hz | δ $^{13}C$; m |
| 1 | 1.56; m<br>0.85; m | 38.92; t | 1.56; m<br>0.88; m | 39.04; t | 1.55; m<br>0.84; m | 38.89; t | 1.56; m<br>0.85; m | 39.03; t |
| 2 | 1.59; m<br>1.42; m | 18.46; t | 1.59; m<br>1.49; m | 18.48; t | 1.55; m<br>1.32; m | 18.43; t | 1.57; m<br>1.42; m | 18.47; t |
| 3 | 1.37; m<br>1.15; m | 42.08; t | 1.37; m<br>1.15; m | 42.07; t | 1.36; m<br>1.14; m | 42.04; t | 1.37; m<br>1.15; m | 42.06; t |
| 4 | - | 33.18; s | - | 33.19; s | - | 33.14; s | - | 33.18; s |
| 5 | 0.93;<br>d/12 | 56.52; d | 0.94;<br>dd/12.4<br>; 2.4 | 56.49; d | 0.92;<br>dd/12.1<br>; 2.2 | 56.45; d | 0.93;<br>dd/12.2<br>; 2.4 | 56.46; d |
| 6 | 1.63; m<br>1.24; m | 20.00; t | 1.64; m<br>1.24; m | 20.00; t | 1.62; m<br>1.21; m | 19.15; t | 1.63; m<br>1.23; m | 19.96; t |
| 7 | 1.76; m<br>1.33; m | 43.28; t | 1.82; m<br>1.40; m | 43.50; t | 1.75; m<br>1.32; m | 43.42; t | 1.81; m<br>1.38; m | 43.47; t |
| 8 | - | 75.89; s | - | 76.27; s | - | 75.80; s | - | 75.18; s |
| 9 | 1.34; m | 55.01; d | 1.43; m | 55.08; d | 1.30; m | 55.20; d | 1.41; m | 55.34; d |
| 10 | - | 36.93; s | - | 36.93; s | - | 36.93; s | - | 37.03; s |
| 11 | 1.56; m<br>1.34; m | 14.85; t | 1.57; m<br>1.43; m | 15.14; t | 1.55; m<br>1.32; m | 14.80; t | 1.55; m<br>1.41; m | 15.19; t |
| 12 | 2.25; m<br>1.76; m | 36.00; t | 2.17; m<br>1.76; m | 36.26; t | 2.26; m<br>1.73; m | 36.12; t | 2.15; m<br>1.74; m | 30.42; t |
| 13 | - | 74.74; s | - | 74.54; s | - | 74.72; s | - | 74.49; s |
| 14 | 4.18;<br>d/ 11.1 | 48.31; d | 4.27;<br>dd/11.5<br>; 1.8 | 53.56; d | 4.17;<br>dd/11.3<br>; 1.5 | 48.31; d | 4.28;<br>dd/11.5<br>; 1.8 | 54.12; d |
| 15 | 2.56; m<br>2.01; m | 30.22; t | 2.17; m<br>1.76; m | 31.26; t | 2.53; m<br>2.32; m | 30.22; t | 2.12; m<br>1.91; m | 31.49; t |
| 16 | 1.34; s | 25.28; q | 1.32; s | 28.73; q | 1.32; s | 25.43; q | 1.30; s | 28.75; q |
| 17 | 1.17; s | 24.94; q | 1.36; s | 24.34; q | 1.16; s | 24.85; q | 1.34; s | 24.20; q |
| 18 | 0.76; s | 21.32; q | 0.76; s | 21.32; q | 0.76; s | 33.29; q | 0.85; s | 33.32; q |
| 19 | 0.85; s | 33.29; q | 0.85; s | 33.33; q | 0.84; s | 21.28; q | 0.78; s | 21.22; q |
| 20 | 0.76; s | 15.24; q | 0.76; s | 15.24; q | 0.74; s | 15.27; q | 0.77; s | 15.36; q |
| 21 | 2.75;<br>2.39 | 34.79; t | 2.76; m<br>2.54; m | 34.90; t | 2.68;<br>2.38 | 34.97; t | 2.68; m<br>2.50; m | 34.07; t |
| 22 | - | 178.0; s | - | 177.5; s | - | 173.2; s | - | 173.4; s |
| 23 | | | | | 3.65; s | 51.58; q | 3.69; s | 51.66; q |

Performing carboiodination of **184** with iodoacetic acid and its esters (methyl and ethyl) under the DLP initiation conditions resulted in the formation of similar iodides **201**, **202**, **204** as major reaction products (Figure 3.4). According to 2D NMR all carbons and protons were assigned, see Table 3.1. 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 the final

addition of iodine at the distal methyl from cycle A of the substrate. These distal iodides **203** and **205** have been identified in the reaction products derived from all involved alkylation agents, but their yield was different. The highest yield of the distal iodide **205** was observed when ethyl iodoacetate was used. Following our assumption that steric effects govern the radical translocations, we investigated alkylation of **184** 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 **211**, which formed along with the alkylated sulfone **210**.

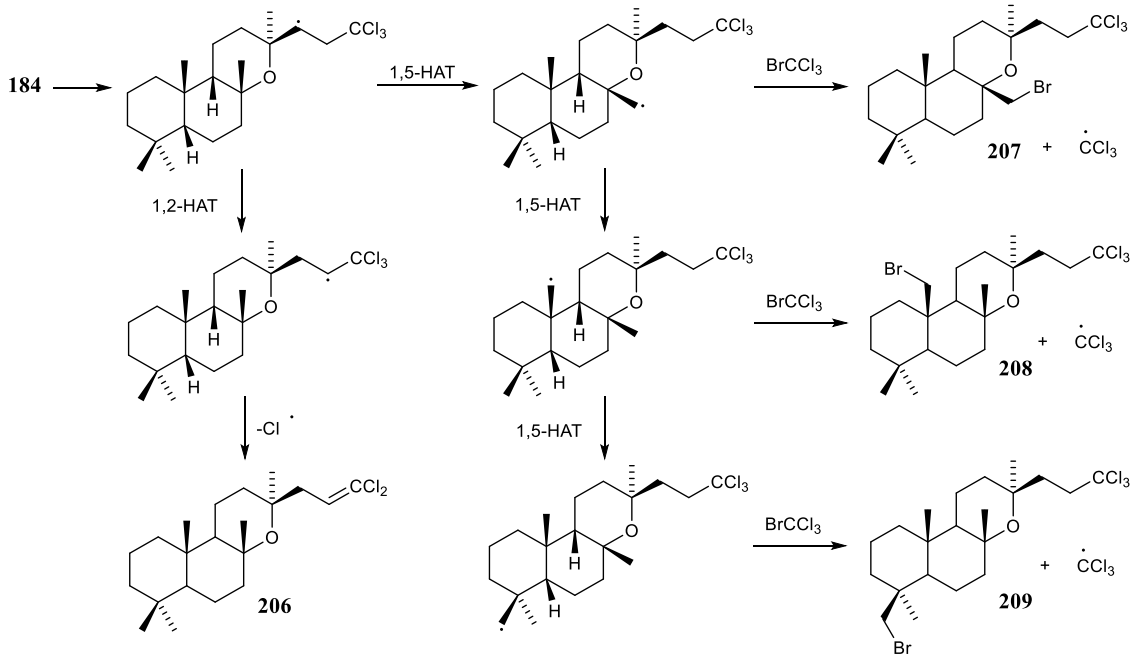



**Fig. 3.5. Suggested mechanism for the triple radical translocation.**

Switching to the $BrCCl_3$ alkylation gave a better overall yield of radical translocation products. Moreover, the identification of products **207** and **208** deriving from all the successive radical shifts was made possible by a careful HPLC of the reaction products and following NMR studies. In fact, the yield of these intermediate-translocated bromides was quite substantial. Their identification represents a solid proof to the reaction mechanism which involves a sequence of three 1,5-HAT (Figure 3.5). To the best of our knowledge, there is only one example of a double 1,5-HAT described in the literature [163]. Thus, our results represent the longest ever observed 1,5-HAT sequence. It is also noteworthy mentioning, that formation of vinylic dichloride **206** involves a very rare 1,2-HAT [164], which in this case can be explained by the use of chlorine radical elimination. Submission of **184** to radical carboazidation conditions led to the synthesis of the corresponding azide **200**. No elimination products have been detected in this case. Following modification of azide group, especially the reduction into amine can lead to

interesting nitrogen-containing compounds which are GABA-terpenic hybrids. Such compounds have been sporadically reported in SAR studies [165, 166] and this field remains a current priority in medicinal chemistry area [167].

### 3.3. Carboazidation of natural compound Forskolin

Forskolin is a secondary metabolite isolated from *Coleus forskohlii* plant [168] and shows a myriad of therapeutic activities [169], such as antihypertensive [170] and broncho-spasmolytic [171]. 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 **183** and diverse strategies have been demonstrated for its total and semisynthesis [172].

Carboazidation of forskolin with ethyl iodoacetate and pyridinsulfonyl azide under DTBHN initiation conditions resulted in the formation of azide **212** in 68% yield (Figure 3.6). 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 **200** and a peak at 79.9 ppm for compound **212**.

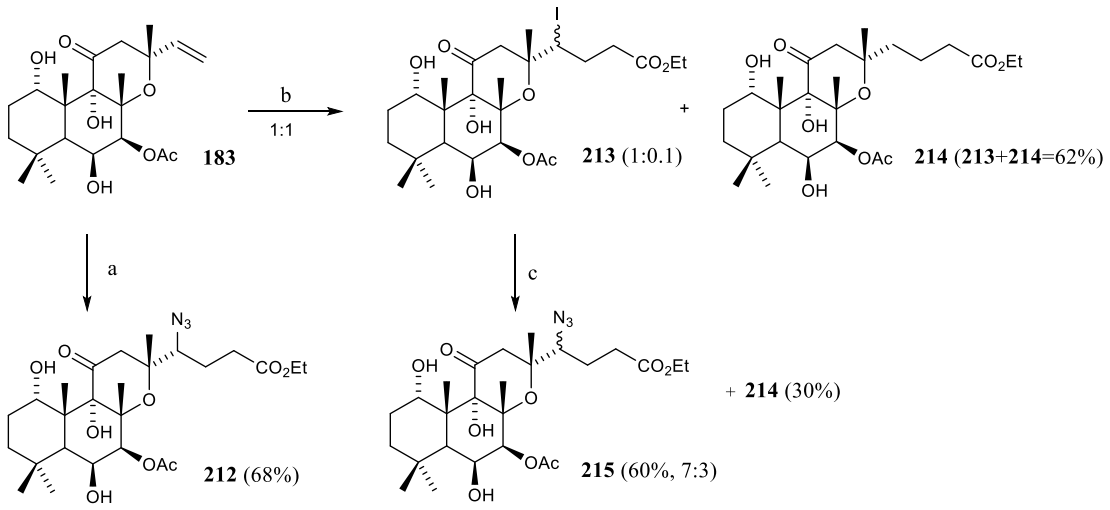



**Fig. 3.6. Radical transformation of forskolin.**

*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 **213** and reduced compound **214** in 62% combined yield. All attempts to separate individual compounds **213** and **214** failed. According to NMR data, the mixture of epimeric iodides **213** 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 the formation of azides **215** in 44 % yield with the ratio 70:30 and the reduced product **214** in 28% yield. Previous attempts to separate individually compounds **213** and **214** changed the ration of the mixture **215**. The major compound in the azides mixture **215** 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 **212** 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 first example of atom transfer radical addition (ATRA) was developed by Kharasch several decades ago [82, 83]. He reported a bromine atom transfer addition of an electrophilic carbon-centered radical onto a terminal bond in which both a carbon-carbon and carbon-bromine bond are formed. Many papers were reported after Kharasch method, such as ATRA mediated by metal, tributyl hydride or AIBN [84]. However, all these methods are harsh and suffer from drawbacks such as toxicity of tin hydride, the difficulty of purification and huge excess of the alkene. We used very mild conditions and tin-free procedure developed by Renaud [173, 174].

The carbohydrogenation of olefin upon initiation with triethylborane and air [175] 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. Some of the radical precursors were synthesized. For example, iodophenyl sulfone was obtained from sodium benzenesulfinate. The iodoacetyl-dihydrocholesterol and iodoacetyl-isoborneol were synthesized from the corresponding alcohols by iodoacetylation reaction [151]. The isoborneol was treated with iodoacetic anhydride in dichloromethane and DMAP.

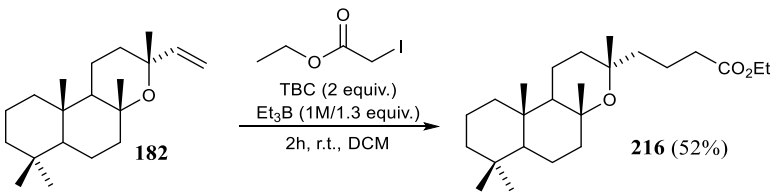



**Fig. 3.7. Carbohydrogenation of manoyl oxide with ethyl iodoacetate.**

Carbohydrogenation of manoyl oxide with ethyl iodoacetate, TBC and triethylborane in dichloromethane afforded the desired product **216** in 52% yield after 2 h (Figure 3.7). According to NMR data, the significant peaks were registered in the $^1H$ spectrum at 4.20 ppm ($CH_2$-23) as

quartet, 2.26 ppm ($CH_2$-21) as triplet of doublet, 1.25 ppm ($CH_3$-24) as triplet and as singlets at 1.21 ppm ($CH_3$-16), 1.10 ppm ($CH_3$-17), 0.84 ppm ($CH_3$-19), 0.78 ppm ($CH_3$-18) and 0.75 ppm ($CH_3$-20). The carbonyl group was registered at 174.00 ppm in the carbon spectrum, at 60.12 ppm (C-23), at 14.28 ppm (C-24) and 15.37 ppm (C-20).

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 **217** in 58% yield (Figure 3.8). The reaction of the olefin with iodophenyl sulfone provided the product **218** in moderate yield. We tried as well to perform C-C coupling with other isoprenic iodoacetates as radical precursors, such as acetyl-iodocholesterol and acetyl-iodoisoborneol. Unfortunately, carbohydrogenation reaction of **184** 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 no improvement was observed.

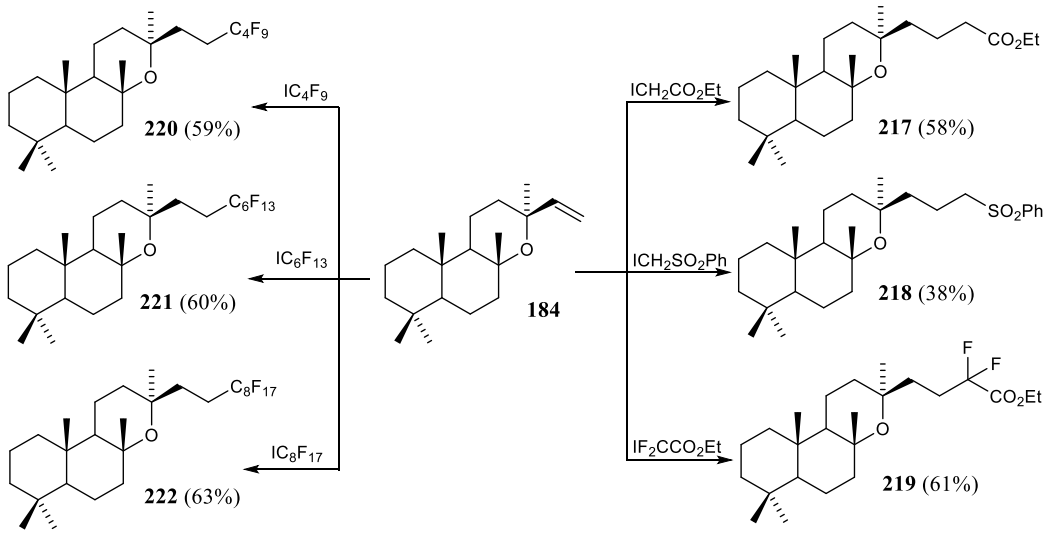



**Fig. 3.8. Carbohydrogenation of *epi*-manoyl oxide.**
*Reagents and conditions*: iodides (1.2 equiv.), olefin (1 equiv.), TBC (2 equiv.), $Et_3B$ 1M in pentane (1.3 equiv.) in DCM, r.t., 2 h.

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 in excellent yields. The treatment of *epi*-manoyl oxide with ethyl difluoroiodoacetate, 4-*tert*-butylcatechol and triethylborane afforded the product **219** in 61% yield. According to NMR spectral data, we can see the splitting of some protons and

carbons peaks. For example, carbonyl from the ethyl group at 164.49 ppm was split into triplet and methylene from C-15 at 29.72 ppm into triplet too, while quaternary carbon is missing. In the proton NMR spectrum, methylene group was split into different doublets. One of them at 3.36 ppm is a doublet, and the second one at 3.35 is a doublet of doublets. According to the literature [176] and our $^{19}F$ NMR spectra, $CF_2$ group gave two peaks at -105.21 ppm and -106.55 ppm.

The carbohydrogenation of olefin with nanofluoro-1-iodobutane gave the desired product **220** in 59% yield. In the carbon spectra we observed that C-15 (25.77 ppm) was split into triplet again, as in the case with ethyl difluoroiodoacetate. But, in this case the fluorinated chain ($CF_2$-$CF_2$-$CF_2$-$CF_3$) was not observed. In the hydroalkylation reactions with perfluoroalkyl iodide, only $^{19}F$ NMR spectra and HRMS helped us to determine all the products and the fluorinated chain.

The fluorine NMR spectra is a bit more complex than with the difluoroacetate, $CF_3$ group appeared at -81 ppm as triplet, but $CF_2$ groups (-114.49; -123.97; and -125.98 ppm) as multiplets. These data indicated that the product contains the fluorinated chain.

Treatment of olefin **184** with perfluoro-1-iodohexane, in dichloromethane afforded the product **221** in 60% (Figure 3.8). The $^{13}C$ and $^{1}H$ NMR data confirm that this compound contains fluorinated chain. The peaks in the carbon spectrum are the same peaks as in the example above. We observed triplet for $CH_2$ group at 25.86 ppm and doublets at 3.65 ppm and 3.37 ppm. Using the $^{19}F$ NMR data, the fluorinated chain was described.

In the case of the perfluorooctyl iodide, the fluorine NMR was very complex and displayed $CF_3$ (-81.08 ppm) as doublet, $CF_2$ (-114.49 and 125.98 ppm) as multiplet and another $CF_2$ (-121.68; -121.89; -122.69 ppm) as singlet. The desired product **222** was obtained in 63% yield. For all fluorinated products, the sign of the optical rotation changed to negative values. The hydroalkylation of **184** with trifluoroiodomethane ($CF_3I$) failed.

### 3.5. Carboazidation of isocopalic related diterpenoids

Spongiane diterpenoids are natural compounds isolated from 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 [177, 178].

Methyl *ent*-isocopalate, the tricyclic diterpene intermediate is used as a good precursor in the total synthesis of natural compounds [179]. The first synthesis of *ent*-isocopalate was reported by Cimino [180], starting from grindelic acid in five steps (45% yield). Later, another

approach to the synthesis of methyl *ent*-isocopalate was reported [181]. The tricyclic diterpene was obtained in 61% overall yield, starting from sclareol, commercially available and inexpensive compound [182, 183].

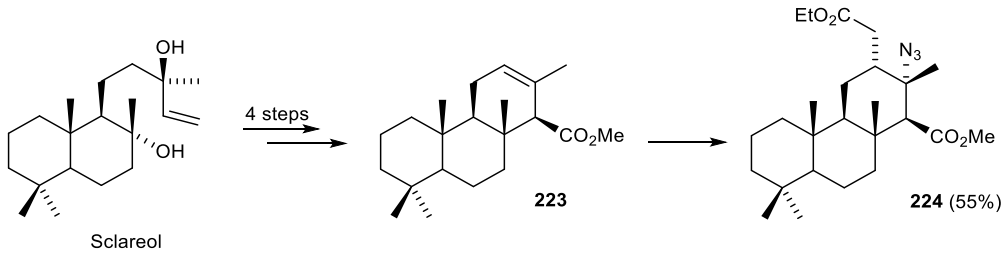



**Fig. 3.9. Carboazidation of methyl *ent*-isocopalate 223.**
*Reagents and conditions:* $ICH_2CO_2Et$ (2 equiv.), $3\text{-}PySO_2N_3$ (3 equiv.), $Bu_6Sn_2$ (1.5 equiv.), DTBHN (0.03 equiv.), benzene, 10 h, Δ.

In the continuation of our studies, two other isocopalate diterpenoids **223** and **225** have been investigated as substrates for ATRA processes. Carboazidation of methyl *ent*-isocopalate **223** with ethyl iodoacetate and phenyl sulfonyl azide under DTBHN initiation conditions resulted in the formation of azide **224** in 55% yield (Figure 3.9). According to NMR spectra, the most important signals are the following: in $^1H$ spectrum $CH_2$-22 was split into two different doublet of doublets at 2.64 ppm and 2.16 ppm; CH-12 appeared as a multiplet at 2.38 ppm; methyls as a singlet at 3.55 ppm (Me-16), 1.66 ppm (Me-17), 1.04 ppm (Me-18), 0.74 ppm (Me-21), 0.70 ppm (Me-20), 0.69 ppm (Me-19) and as a triplet Me-25 at 1.16 ppm; in $^{13}C$ spectrum tertiary azide appeared at 64.94 ppm and CH-12 at 42.0 ppm. The relative stereochemistry of azide **224** 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 3.10).

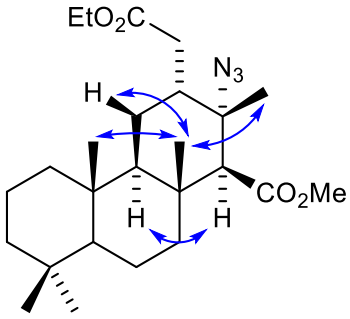



**Fig. 3.10. NOESY correlation of compound 224.**

As we know, the free hydroxyl group can interfere with radical chains and our alcohol was protected with a silyl group. Protection of -OH group was performed with *tert*-butyl dimethyl silyl chloride and imidazole in DMF at room temperature for 12 h. Treatment of

protected diterpenoid **226** 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 **228** in 40% yield. Stereochemistry of the tertiary azide **229** was not determined. Following hydrogenation of azide **228** resulted into lactam **229** in quantitative yield. Cyclization of amine group with carbonyl is faster than with the hydroxyl group (Figure 3.11) [184].

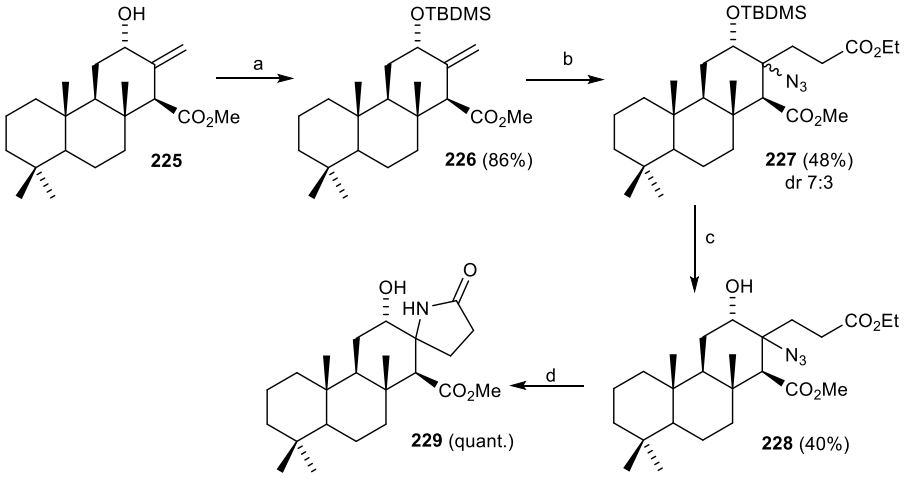



**Fig. 3.11. Carboazidation of hydroxy *ent*-isocopalate.**

*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.

### 3.6. Conclusions to chapter 3

In summary, this chapter demonstrates the application of the free radical transformations for efficient structural modification of manoyl oxides, forskolin and isocopalic acid derivatives. We demonstrate the first example of an ATRA reaction that is accompanied by radical translocation *via* successive 1,5-HAT, which leads to remote functionalization of the terpenic scaffold. The triple 1,5-HAT sequence is an unprecedented radical remote functionalization. Progress in advanced functionalization can lead to biological activities, which could be complementary to the properties of other relevant representatives of manoyl oxides family.

We demonstrate that radical carboazidation reaction can give good results with alkene having a non-terminal double bond, such as methyl *ent*-isocopalate. This is a very mild reaction and forskolin was azidated without any modification of its numerous functional groups.

Carbohydrogenation of *epi*-manoyl oxide has provided good results with a wide range of iodides. The reactions of olefin with perfluroalkyl iodides as radical precursors afforded the fluorinated compounds in very good yields, which could be tested for biological activity and implemented in medicine or radiology. All synthesized compounds can be involved in following cytotoxicity anti-inflammatory and antifungal assays.

### 3.7. Experimental Part

**General Procedure 1**: To a mixture of CuI (0.02 mmol), DIPEA (0.04 mmol) and AcOH (0.04 mmol) in $CH_2Cl_2$ (2 mL) was added a mixture of alkyne (1 mmol) and azide (1 mmol) at room temperature. The resulting mixture was stirred 2 h. After this time the reaction mixture was purified by FC (pentane/EtOAc).

**General Procedure 2:** DTBHN (0.03 mmol) was added every 2 h to a solution of iodoester (1.5 mmol), olefin (1 mmol), $PhSO_2N_3$ or 3-$PySO_2N_3$ (3 mmol) and $Bu_6Sn_2$ (1.5 mmol), in dry $C_6H_6$ (5.0 mL) at reflux under $N_2$. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by FC (pentane/EtOAc).

**General Procedure 3:** DLP (0.05 mmol) was added every 2 h to a solution of iodine (1.5 mmol) and olefin (1 mmol) in dry $C_6H_6$ (5.0 mL) at reflux under $N_2$. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (pentane/EtOAc).

**General Procedure 4:** To a solution of alkene (1 equiv.) and iodide (1.2 equiv.) in $CH_2Cl_2$ (10 mL/0.5 mmol of iodide) was added 4-*tert*-butylcatechol or 4-methoxycatechol (2 equiv.) followed by $Et_3B$ (1.3 equiv., 1M solution in hexane). The resulting solution was stirred at room temperature in presence of air and protected from moisture by a $CaCl_2$ guard tube. After 2 h, the reaction mixture was filtered over short pad of neutral $Al_2O_3$ using $Et_2O$ to trap the catechol derivative and boron containing side products. The resulting crude filtrate was concentrated under reduce pressure and after purification by FC (pentane/EtOAc).

*(3S,4aR,10aS)-3-(2-azidoethyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromene (185)*

To a solution of *epi*-manoyl oxide **184** (300 mg, 1.03 mmol) and *N, N*-dimethylacetamide (0.01 mL, 0.11 mmol) in DCM (2 mL) was added dropwise catecholborane (0.33 mL, 3.0 mmol) at 0℃ under nitrogen atmosphere. The resulting mixture was heated under reflux for 5 h, then *t*-BuOH (0.2 mmol) was added at 0℃ to solvolyze the excess of cathecolborane. After the evaporation of solvent under vacuum, DMF (2 mL), 3-$PySO_2N_3$ (569 mg, 3.1 mmol), DTBHN

(18 mg, 0.103 mmol) were added and the solution was stirred at 80℃. After 2 h the solution turned black and was filtered through a pad of $Al_2O_3$ to remove polar borane containing residues using $Et_2O$ as eluent. The filtrate was washed with water, dried over $Na_2SO_4$ and concentrated. The crude product was purified by column chromatography (hexane/EtOAc 98:2) afforded the azide **185** (137 mg, 40%) as a white powder. $[a]_D^{20}$= 9.4º (*c*= 0.64, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2924, 2094, 1720, 1463, 1375, 1265, 993, 727. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.27-3.47 (*m*, $CH_2$-15); 2.00-2.10 (*m*, $CH_2$-14); 1.25 (*s*, $CH_3$-17); 1.18 (*s*, $CH_3$-16); 0.84 (*s*, $CH_3$-20); 0.78 (*s*, $CH_3$-19); 0.76 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 75.32, 71.90, 65.85, 57.33, 56.45, 50.81, 47.68, 43.45, 42.11, 39.53, 39.15, 37.78, 36.95, 33.31, 33.25, 30.20, 24.24, 21.26, 19.95, 18.55, 15.68, 15.23. **GCMS** m/z calculated for $[C_{20}H_{35}N_3O]^+$: 333.28; found 331.0 [M-$H_2$]. Elemental analysis calculated for $C_{20}H_{35}N_3O$ (333.28): C, 72.03; H, 10.58; N, 12.60; O, 4.80; found C, 72.05; H, 11.00; N, 12.62; O, 4.83.

*2-(1-(2-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)-ethyl)-1H-1,2,3-triazol-4-yl)-propan-2-ol (186)*

According to general procedure 1 from azide **185** (100 mg, 0.3 mmol) and 2-methyl-3-butyn-2-ol (26 µL, 0.28 mmol). The crude mixture was purified by FC (pentane/EtOAc 80:20) and afforded compound **186** (118 mg, 94%) as a colorless oil. $[a]_D^{20}$= 1.84º (*c*= 5.1, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2926, 1457, 1375, 1078, 907, 728, 646. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.42 (*s*, CH-5´); 4.34-4.53 (*m*, $CH_2$-15); 1.60 (*s*, $CH_3$-7´); 1.30 (*s*, $CH_3$-17); 1.17 (*s*, $CH_3$-16); 0.84 (*s*, $CH_3$-20); 0.77 (*s*, $CH_3$-19); 0.75 (*s*, $CH_3$-18). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 118.93, 75.49, 71.69, 57.09, 56.46, 46.79, 43.49, 42.10, 41.60, 39.14, 37.66, 36.98, 33.32, 33.26, 30.46, 30.16, 24.32, 21.28, 19.97, 18.53, 15.68, 15.17. **$^1$H NMR with $Et_3N$** (300 MHz, $CDCl_3$) *δ* (ppm) 7.41 (*bs*, CH-5´); 4.32-4.51 (*m*, $CH_2$-15); 2.55 (*q*, *J*=7 Hz, $Et_3N$); 1.59 (*s*, $CH_3$-7´); 1.28 (*s*, $CH_3$-17); 1.16 (*s*, $CH_3$-16); 1.00 (*t*, *J*=7 Hz, $Et_3N$); 0.82 (*s*, $CH_3$-20); 0.76 (*s*, $CH_3$-19); 0.73 (*s*, $CH_3$-18). **$^{13}$C NMR with $Et_3N$** (75 MHz, $CDCl_3$) δ (ppm) 155.77, 118.93, 75.40, 71.63, 57.09, 56.44, 46.67, 45.89 ($Et_3N$), 43.47, 42.07, 41.59, 39.11, 37.66, 36.94, 33.28 (2C), 30.54, 30.52, 30.13, 24.28, 21.24, 19.93, 18.50, 15.65, 15.14, 11.06 ($Et_3N$). **HRMS (ESI**) calculated for $[C_{25}H_{43}N_3O_2]^+$: 418.3437; found 418.3428.

*Ethyl 1-(2-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)-ethyl)-1H-1,2,3-triazole-4-carboxylate (187)*

According to general procedure 1 from azide **185** (100 mg, 0.3 mmol) and ethyl propiolate (29 µL, 0.28 mmol). The reaction mixture was purified by FC (pentane/EtOAc 85:15) giving triazole **187** (123 mg, 95%) as a white powder. $[a]_D^{20}$= 1.4º (*c*= 1.5, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2922, 2864,

1722, 1464, 1375, 1198, 911, 775, 728. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 8.06 (*s*, CH-5´); 4.47-4.63 (*m*, $CH_2$-15); 4.41 (*q*, *J* = 7.1 Hz, $CH_2$-7´); 1.39 (*t*, *J* = 7.1 Hz, $CH_3$-8´); 1.29 (*s*, $CH_3$-17); 1.19 (*s*, $CH_3$-16), 0.85 (*s*, $CH_3$-20), 0.78 (*s*, $CH_3$-19), 0.76 (*s*, $CH_3$-18). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 160.87, 140.23, 127.29, 75.54, 71.59, 61.25, 56.81, 56.49, 47.17, 43.50, 42.10, 41.70, 39.13, 37.41, 37.01, 33.33, 33.27, 30.10, 24.41, 21.29, 19.97, 18.53, 15.64, 15.13, 14.34. **HRMS (ESI)** calculated for $[C_{25}H_{41}N_3O_3]^+$: 432.3227; found 432.3221.

*1-(2-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)-ethyl)-4-phenyl-1H-1,2,3-triazole (188)*

According to general procedure 1 from azide **185** (100 mg, 0.3 mmol) and phenyl acetylene (19 µL, 0.28 mmol). The reaction mixture was purified by FC (pentane/EtOAc 85:15) and afforded triazole **188** (117 mg, 90%) as a white powder. $[a]_D^{20}$= 0.69º (*c*= 0.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2922, 2358, 1457, 1376, 1144, 1045, 762, 693, 419. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.81-7.84 (*m*, CH-7´); 7.74 (*s*, CH-5´); 7.39-7.44 (*m*, CH-8´); 7.29-7.34 (*m*, CH-9´); 4.44-4.63 (*m*, $CH_2$-15); 2.2-2.4 (*m*, $CH_2$-14); 1.34 (*s*, $CH_3$-17), 1.22 (*s*, $CH_3$-16), 0.86 (*s*, $CH_3$-20), 0.80 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-18). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 147.72, 130.72, 128.82 (2C), 128.08 (2C), 125.72, 119.49, 75.53, 71.74, 57.07, 56.50, 46.93, 43.55, 42.13, 41.71, 39.17, 37.62, 37.02, 33.35, 33.29, 30.22, 24.41, 21.31, 20.01, 18.56, 15.69, 15.20. **HRMS (ESI)** calculated for $[C_{25}H_{41}N_3O_3]^+$: 436.3315; found 436.3322.

*1-(2-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)-ethyl)-1H-1,2,3-triazole (189)*

To a solution of azide **185** (100 mg, 0.3 mmol), propiolic acid (16 µL, 0.26 mmol) in DMF (1 mL), were added CuI (11 mg, 0.06 mmol), Na ascorbate (24 mg, 0.12 mmol) and DBU (22 µL, 0.15 mmol). The reaction mixture was stirred at 60 ºC for 3 h under $N_2$. The mixture was diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. The crude product was purified by FC (hexane/EtOAc 80:20) and afforded **189** (89 mg, 83%) as a colorless oil. $[a]_D^{20}$= 2.5º (*c*= 1.6, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2921, 2362, 1464, 1374, 1073, 989, 798, 458. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.68 (*d*, *J*= 1.0 Hz, CH-4´); 7.53 (*d*, *J* = 1.0 Hz, CH-5´); 4.41-4.61 (*m*, $CH_2$-15); 2.31-2.41;1.88-2.03 (*m*, $CH_2$-14); 1.31 (*s*, $CH_3$-17); 1.19 (*s*, $CH_3$-16); 0.85 (*s*, $CH_3$-20); 0.78 (*s*, $CH_3$-19); 0.76 (*s*, $CH_3$-18). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 133.69, 123.20, 75.50, 71.69, 57.07, 56.49, 46.69, 43.53, 42.12, 41.67, 39.16, 37.61, 37.00, 33.33, 33.28, 30.18, 24.34, 21.30, 19.99, 18.55, 15.68, 15.18. **HRMS (ESI)** calculated for $[C_{25}H_{41}N_3O_3]^+$: 360.2996; found 360.3009.

*2-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)-ethan-1-amine (190)*

A solution of azide **185** (53 mg, 0.15 mmol) and 10% Pd/C (10% w/w) in dry EtOAc (2 mL) was stirred for 24 h at room temperature under $H_2$ (1 atm). The catalyst was filtered off, the solvent was removed under reduced pressure and the crude purified by FC ($CH_2Cl_2$/MeOH 90:10) giving the amine **190** (33 mg, 72%) as a white powder. $[a]_D^{20} = 5.9°$ (*c*= 1.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3300, 2924, 1720, 1463, 1375, 1283, 1265, 993, 727. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 44.39 (*bs*, $NH_2$), 2.85-3.01 (*m*, $CH_2$-15), 1.27 (*s*, $CH_3$-17), 1.13 (*s*, $CH_3$-16), 0.84 (*s*, $CH_3$-20), 0.77 (*s*, $CH_3$-19), 0.76 (*s*, $CH_3$-18). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 75.37, 72.88, 56.49, 55.95, 43.64, 42.98, 42.11, 39.06, 37.52, 37.05, 36.23, 33.35, 33.24, 29.63, 24.85, 21.33, 19.98, 18.53, 15.45, 15.07. **HRMS (ESI)** calculated for $[C_{20}H_{37}NO]^+$: 308.2941; found 308.2948.

According to general procedure 3 from manoyl oxide **182** (40 mg, 0.14 mmol), iodoacetic acid (26 mg, 0.14 mmol) and DLP (12 mg, 0.03 mmol). The reaction mixture was refluxed for 8 h. The crude product was methylated with an etheric solution of diazomethane and after purified by column chromatography (pentane/EtOAc 98:2) and gave the mixture of esters **192** and **193** (19 mg, 38%, **192**:**193**=1:3, $^1$H NMR), along with a complex mixture of iodinated products (44 mg). The latter mixture was purified on HPLC to give a sample of iodides **191** (50%).

*Methyl 4-iodo-4-((3R,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (mixture of epimers, 50:50%) (191)*

Pale-yellow viscous liquid, **IR** (ν, $cm^{-1}$): 2947, 2925, 2864, 2324, 2077, 1741, 1462, 1440, 1388, 1377, 1262, 1195, 1176, 1119, 1098, 10791053, 1033, 996, 963. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.93 and 3.96 (*t*, *J*= 2.7 Hz, CH-14), 3.67 and 3.68 (*s*, $CH_3$-23), 1.38 and 1.39 (*s*, $CH_3$-16), 1.24 and 1.25 (*s*, $CH_3$-17), 0.85 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.75 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.53, 173.34 (*s*, C-23); 76.04, 75.85 (*s*, C-8); 73.94 (*s*, C-13); 57.82, 57.43 (*d*, C-9); 56.49, 56.43 (*d*, C-5); 54.03, 53.92 (*d*, C-14); 51.56 (*q*, C-24), 42.74, 42.69 (*t*, C-7), 42.19, 42.18 (*t*, C-3); 39.17 (*t*, C-1); 36.87, 36.86 (*s*, C-10); 37.95, 35.71 (*t*, C-12); 35.18, 35.10 (*t*, C-21); 33.31, 33.29 (*q*, C-19, overlap with *s*, C-4); 30.17, 30.11 (*t*, C-15); 25.88, 23.04 (*q*, C-16); 24.57, 24.47 (*q*, C-17); 21.28 (*q*, C-18); 19.90, 19.86 (*t*, C-6); 18.62, 18.61 (*t*, C-2); 15.73, 15.69 (*q*, C-20); 15.66, 15.57 (*t*, C-11).

Colorless viscous liquid, **IR** (ν, $cm^{-1}$): 2928, 2867, 2309, 1741, 1460, 1441, 1388, 1376, 1255, 1194, 1171, 1119, 1101, 1080, 1047, 1029, 972, 960 (of the mixture).

*Methyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-benzo[f]chromen-3-yl) butanoate (minor compound, 25%) (192)*

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.46 (*dd*, *J*= 6.3; 3.8 Hz, CH-11), 3.66 (*s*, $CH_3$-23), 2.27-2.31 (*m*, $CH_2$-21), 2.10 (*dd*, AMX, $J_{AM}$= 16.3, $J_{AX}$= 6.00 Hz, $CH_2$-12), 1.94 (*dd*, AMX, $J_{AM}$= 16.3, $J_{MX}$= 3.7 Hz, $CH_2$-12), 1.40 (*s*, $CH_3$-17), 1.20 (*s*, $CH_3$-16), 1.06 (*s*, $CH_3$-20), 0.86 (*s*, $CH_3$-18), 0.83 (*s*, $CH_3$-19). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 174.39 (*s*, C-22), 152.41 (*s*, C-9), 112.64 (*d*, C-11), 74.22 (*s*, C-8), 71.78 (*s*, C-13), 54.19 (*d*, C-5), 51.37 (*q*, C-24), 43.21 (*t*, C-7), 42.04 (*t*, C-3), 41.00 (*t*, C-14), 39.67 (*s*, C-10), 38.72 (*t*, C-1), 35.15 (*t*, C-12), 34.65 (*t*, C-21), 33.78 (*s*, C-4), 33.32 (*q*, C-19), 30.57 (*q*, C-17), 28.27 (*q*, C-16), 22.27 (*q*, C-20), 21.65 (*q*, C-18), 20.21 (*t*, C-6), 19.97 (*t*, C-15), 19.13 (*q*, C-2).

*Methyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (193)*

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.66 (*s*, $CH_3$-23), 2.27-2.31 (*m*, $CH_2$-21), 1.26 (*s*, $CH_3$-17), 1.20 (*s*, $CH_3$-16), 0.85 (*s*, $CH_3$-19), 0.78 (*s*, $CH_3$-18), 0.75 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 174.39 (*s*, C-22), 74.68 (*s*, C-8), 72.59 (*s*, C-13), 58.29 (*d*, C-9), 56.50 (*d*, C-5), 51.35 (*q*, C-23), 45.02 (*t*, C-14), 43.15 (*t*, C-7), 42.25 (*t*, C-3), 39.24 (*t*, C-1), 36.92 (*s*, C-10), 36.43 (*t*, C-12), 34.57 (*t*, C-21), 33.34 (*s*, C-4), 33.32 (*q*, C-19), 27.59 (*q*, C-16), 24.83 (*q*, C-17), 21.28 (*q*, C-18), 19.89 (*t*, C-6), 19.37 (*t*, C-15), 18.66 (*t*, C-2), 15.74 (*q*, C-20), 15.43 (*t*, C-11).

According to general procedure 3 from manoyl oxide (98 mg, 0.33 mmol), ethyl iodoacetate (39 µL, 0.33 mmol) and DLP (50 mg, 0.126 mmol). The reaction was refluxed for 18 h. The crude product was purified by column chromatography (pentane/EtOAc 98:2) and gave epimer **194** (63 mg, 45%) and the mixture of esters **195** and **196** (13 mg, 10%, **195**:**196**=6:4, $^{1}$H NMR).

*Ethyl (4R)-4-iodo-4-((3R,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (194)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 0.64°$ (*c*= 0.28, MeOH), **IR** (ν, $cm^{-1}$): 3450, 2925, 2867, 1736, 1459, 1376, 1177, and 1031. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.12 (*q*, *J*= 7 Hz, $CH_2$-23), 3.95 (*dd*, *J*= 11.3; 2 Hz, CH-14), 1.37 (*s*, $CH_3$-16), 1.25 (*t*, *J*= 7 Hz, $CH_3$-24), 1.24 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.78 (*s*, $CH_3$-18), 0.74 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 172.89 (*s*, C-22), 76.01 (*s*, C-8), 73.93 (*s*, C-13), 60.35 (*t*, C-23), 57.42 (*d*, C-9), 56.45 (*d*, C-5), 54.13 (*d*, C-14), 42.69 (*t*, C-7), 42.17 (*t*, C-3), 39.13 (*t*, C-1), 37.84 (*t*, C-12), 36.84 (*s*, C-10), 35.40 (*t*, C-21), 33.29 (*q*, C-19), 33.27 (*s*, C-4), 30.10 (*t*, C-15), 24.55 (*q*, C-17), 23.05 (*q*, C-16),

21.27 (*q*, C-18), 19.88 (*t*, C-6), 18.59 (*t*, C-2), 15.65 (*q*, C-20), 15.54 (*t*, C-11), 14.24 (*q*, C-24). Elemental analysis calculated for $C_{24}H_{41}IO_3$ (504.49): C, 57.14; H, 8.19; found: C, 57.22; H, 8.25.

*Mixture of ethyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-benzo[f]chromen-3-yl)butanoate 195 (60%) and ethyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)butanoate 196 (40%).*
Colorless viscous liquid, **IR** (ν, $cm^{-1}$): 3902, 3741, 3590, 3463, 3361, 3238, 2944, 2632, 2494, 2333, 2191, 2080, 1984, 1737, 1692, 1457, 1377, 1264, 1180, 1030.

*Ethyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-benzo[f]chromen-3-yl) butanoate (major compound, 60%) (195)*
**$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.46 (AMX, *dd*, $J_1$= 6 Hz, $J_2$= 4 Hz, CH-11), 4.11 (*q*, *J*= 7.1 Hz, $CH_2$-23), 2.28 (*t*, *J*= 7.6 Hz, $CH_2$-21), 2.26 (*t*, *J*= 7.5 Hz, $CH_2$-21), 2.10 (AMX, *dd*, $J_{AM}$= 16.2 Hz, $J_{AX}$= 6 Hz, $CH_2$-12), 1.95 (AMX, *dd*, $J_{AM}$= 16.2 Hz, $J_{MX}$= 4 Hz, $CH_2$-12), 1.37 (*s*, $CH_3$-16), 1.26 (*bs*, $CH_3$-16), 1.25 (*t*, *J*= 7.1 Hz, $CH_3$-24), 1.20 (*s*, $CH_3$-17), 1.06 (*s*, $CH_3$-17), 0.86 (*s*, $CH_3$-19), 0.85 (*s*, $CH_3$-19), 0.83 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-20), 0.76 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) (major compound **187**)*: 173.72 (*s*, C-22), 152.36 (*s*, C-9), 112.61 (*d*, C-11), 74.17 (*s*, C-7), 71.76 (*s*, C-13), 60.08 (*t*, C-23), 54.13 (*d*, C-5), 43.17 (*t*, C-7), 41.98 (*t*, C-3), 40.97 (*t*, C-14), 38.66 (*t*, C-1), 35.08 (*t*, C-12), 34.88 (*t*, C-21), 33.74 (*s*, C-4), 33.27 (*q*, C-19), 30.53 (*q*, C-17), 28.24 (*q*, C-16), 22.24 (*q*, C-20), 21.62 (*q*, C-18), 20.17 (*t*, C-6), 19.95 (*t*, C-15), 19.09 (*t*, C-2), 14.26 (*q*, C-24).

*Ethyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (196)*
**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) (minor compound **196**)*: 173.93, 74.63, 72.56, 60.05, 58.23, 56.45, 44.99, 43.14, 42.20, 39.63, 39.19, 36.38, 34.78, 33.30, 27.53, 24.79, 21.24, 19.85, 19.33, 18.61, 15.70, 15.38, 14.26.*Assigned on the basis of 2D NMR spectra of **195** and **196** the mixture.

According to general procedure 2 from manoyl oxide (66 mg, 0.22 mmol), ethyl iodoacetate (5.5 µL mg, 0.22 mmol), $PhSO_2N_3$ (312 mg, 1.704 mmol), $Bu_6Sn_2$ (0.4 mL, 0.84 mmol) and DTBHN (1.2 mg, 0.007 mmol). The reaction mixture was refluxed for 9 h. The crude product was purified by column chromatography (pentane/EtOAc 99:1) and afforded the starting material (21 mg, 30%) and a mixture of **195** and **196** (31 mg, 35%, **195**:**196**=1:1, $^1$H NMR).

According to general procedure 3 from manoyl oxide (29 mg, 0.1 mmol), bromotrichloromethane (20 mg, 0.1 mmol) and DLP (10 mg, 0.025 mmol). The reaction was refluxed for 10 h. The crude product was purified by HPLC gave the starting material (9 mg, 31%), bromides **197** (5.2 mg, 18%) along with pure **198** (10.2 mg, 38%, brsm) and **199** (8.2 mg, 22%).

*(3R,4aR,10aS)-3-(1-bromo-3,3,3-trichloropropyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromene (major epimer, 75%) (197)*

Colorless viscous liquid, $[\alpha]_D^{20} = 7.33°$ (*c*= 0.03, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2948, 2866, 1463, 1379, 1119, 1099, 1079, 1032, 959. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.99 (*dd*, *J*= 7.8; 0.8 Hz, CH-14), 3.73 (*dd*, *J*= 15.8; 1.2 Hz, $CH_2$-15), 3.06 (*q*, *J*= 7.9 Hz, $CH_2$-15), 1.32 (*s*, $CH_3$-16), 1.25 (*s*, $CH_3$-17), 0.89 (*dd*, *J*= 12.1; 2.5 Hz, CH-5), 0.84 (*s*, $CH_3$-19), 0.78 (*s*, $CH_3$-18), 0.76 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 98.61 (*s*, C-21), 76.45 (*s*, C-8), 74.40 (*s*, C-13), 58.82 (*d*, C-14), 57.23 (*d*, C-9), 57.36 (*t*, C-15), 56.55 (*d*, C-5), 42.76 (*t*, C-7), 42.16 (*t*, C-3), 39.15 (*t*, C-1), 36.94 (*s*, C-10), 36.72 (*t*, C-12), 33.32 (*q*, C-19), 33.27 (*s*, C-4), 24.71 (*q*, C-17), 22.26 (*q*, C-16), 21.27 (*q*, C-18), 19.84 (*t*, C-6), 18.56 (*t*, C-2), 15.55 (*q*, C-20), 15.28 (*t*, C-11). Elemental analysis calculated for $C_{21}H_{34}BrCl_3O$ (488.76): C, 51.61; H, 7.01; found: C, 51.70; H, 7.11.

*(3R,4aR,10aS)-3-(1-bromo-3,3,3-trichloropropyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromene (minor epimer, 25%) (197)*

Identified in the mixture of epimers. **IR** (ν, $cm^{-1}$): 2926, 2668, 1463, 1388, 1378, 1120, 1108, 1078, 1056, 1033, 996, 967, 796. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) (subtracted from the spectrum of the mixture containing the major epimer): 3.95 (*dd*, *J*= 7.1; 1.4 Hz, CH-14), 3.73 (*d*, *J*= 15.9 Hz, $CH_2$-15), 3.18 (*dd*, *J*= 8.9; 7.1Hz, $CH_2$-15), 1.47 (*s*, $CH_3$-16), 1.40 (*s*, $CH_3$-17), 0.86 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.76 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) (subtracted from the spectrum of the mixture containing the major epimer): 98.52 (*s*, C-21), 76.34 (*s*, C-8), 75.19 (*s*, C-13), 58.59 (*d*, C-5), 58.50 (*t*, C-15), 58.13 (*t*, C-14), 56.51 (*d*, C-5), 42.73 (*t*, C-7), 42.14 (*t*, C-3), 39.15 (*t*, C-1), 36.95 (*t*, C-10), 34.3 (*s*, C-4), 33.28 (*q*, C-19), 27.40 (*t*, C-12), 26.40 (*q*, C-16), 24.42 (*q*, C-17), 21.27 (*q*, C-18), 19.84 (*t*, C-6), 18.6 (*t*, C-2), 15.17 (*q*, C-11).

*(3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-3-(3,3,3-trichloropropyl)-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-benzo[f]chromene (198)*

Colorless viscous liquid, $[\alpha]_D^{20} = 3.18°$ (*c*= 0.54, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2928, 2868, 1714, 1459, 1388, 1376, 1341, 1282, 1261, 1139, 1093, 1067, 1054, 1028, 1013, 975, 962, 879, 809, 789,

771, 751. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.51 (*dd*, *J*= 6.2; 3.6 Hz, CH-11), 1.40 (*s*, $CH_3$-17), 1.24 (*s*, $CH_3$-16), 1.0 (*s*, $CH_3$-20), 0.92 (*dd*, *J*= 12.2; 2.2 Hz, CH-5), 0.84 (*s*, $CH_3$-19), 0.83 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 153.00 (*s*, C-9), 112.60 (*d*, C-11), 101.05 (*s*, C-21), 74.55 (*s*, C-8), 71.11 (*s*, C-13), 54.00 (*d*, C-5), 50.50 (*t*, C-15), 43.00 (*t*, C-7), 41.95 (*t*, C-3), 39.67 (*s*, C-10), 38.75 (*t*, C-1), 37.70 (*t*, C-14), 35.74 (*t*, C-12), 33.73 (*s*, C-4), 33.38 (*q*, C-19), 30.78 (*q*, C-17), 28.76 (*q*, C-16), 22.31 (*q*, C-20), 21.61 (*q*, C-18), 20.11 (*t*, C-6), 19.09 (*t*, C-2). Elemental analysis calculated for $C_{21}H_{33}Cl_3O$ (407.84): C, 61.84; H, 8.16; found: C, 61.92; H, 8.27.

*(3R,4aR,10aS)-3,4a,7,7,10a-pentamethyl-3-(3,3,3-trichloropropyl)-dodecahydro-1H-benzo[f]chromene (199)*

Colorless viscous liquid, $[\alpha]_D^{20} = 0.80°$ (*c*= 0.20, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2927, 2866, 1465, 1446, 1388, 1377, 1120, 1102, 1079, 1045, 1030, 1003, 971, 959, 786. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 1.27 (*s*, $CH_3$-17), 1.26 (*s*, $CH_3$-16), 0.95 (*dd*, *J*= 12; 2 Hz, CH-5), 0.86 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.76 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 101.11 (*s*, C-21), 74.90 (*s*, C-8), 71.71 (*s*, C-13), 58.13 (*d*, C-9), 56.50 (*d*, C-5), 50.18 (*t*, C-15), 43.03 (*t*, C-7), 42.21 (*t*, C-3), 41.78 (*t*, C-14), 39.23 (*t*, C-1), 37.32 (*s*, C-4), 36.90 (*s*, C-10), 36.69 (*t*, C-12), 33.32 (*q*, C-19), 28.00 (*q*, C-16), 24.70 (*q*, C-17), 21.28 (*q*, C-18), 19.85 (*t*, C-6), 18.63 (*t*, C-2), 15.72 (*q*, C-20), 15.36 (*t*, C-11). Elemental analysis calculated for $C_{21}H_{35}Cl_3O$ (409.86): C, 61.54; H, 8.61; found: C, 61.61; H, 8.69.

*Ethyl (4R)-4-azido-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f] chromen-3-yl) butanoate (200)*

According to general procedure 2 from *epi*-manoyl oxide (98 mg, 0.33 mmol), ethyl iodoacetate (39 µL, 0.33 mmol), $PhSO_2N_3$ (181 mg, 0.99 mmol) and $Bu_6Sn_2$ (0.25 mL, 0.49 mmol) and DTBHN (1.7 mg, 0.01 mmol). The reaction mixture was refluxed for 9 h. The crude product was purified by column chromatography (pentane/EtOAc 99:1) and gave the starting material (29 mg, 30%), and azide **200** (55 mg, 57% brsm) as a crystalline powder. Colorless viscous liquid, $[\alpha]_D^{20} = 119.6°$ (*c*= 1.53, $CHCl_3$), **IR** (ν, $cm^{-1}$): 2980, 2937, 2870, 2845, 2098, 1735, 1447, 1388, 1376, 1334, 1260, 1158, 1096, 1079, 10.43, 1026, 992, 958. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.13 (*q*, *J*=7 Hz, $CH_2$-23), 3.28 (*d*, *J*=11 Hz, CH-14), 1.78 (*d*, *J*=12 Hz, CH-7), 1.26 (*t*, *J*= 7 Hz, $CH_3$-24,), 1.23 (*s*, $CH_3$-16), 1.13 (*s*, $CH_3$-17), 0.85 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.74 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.02 (*s*, C-22), 75.91 (*s*, C-13), 75.65 (*s*, C-8), 70.56 (*d*, C-14), 60.61 (*t*, C-23), 56.66 (*d*, C-5), 53.92 (*d*, C-9), 43.84 (*t*, C-7), 42.93 (*t*, C-3), 39.02 (*t*, C-1), 36.93 (*s*, C-10), 33.33 (*q*, C-19), 33.14 (*s*, C-4), 32.21 (*t*, C-21), 29.65 (*t*, C-12),

25.45 (*q*, C-16), 24.91 (*q*, C-17), 24.87 (*t*, C-15), 21.22 (*q*, C-18), 20.07 (*t*, C-6), 18.48 (*t*, C-2), 15.21 (*q*, C-20), 14.34 (*t*, C-11), 14.29 (*q*, C-24). Elemental analysis calculated for $C_{24}H_{41}N_3O_3$ (419.60): C, 68.70; H, 9.85; found: C, 68.88; H, 9.93.

According to general procedure 3 from *epi*-manoyl oxide (50 mg, 0.17 mmol), iodoacetic acid (32 mg, 0.17 mmol) and DLP (14 mg, 0.034 mmol). The reaction was refluxed for 8 h. The crude mixture was purified by column chromatography (pentane/EtOAc 90:10) and afforded epimers of **201** (44% of major epimer and 16 % of minor epimer).

*4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoic acid (major epimer) (201)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 41.5°$ (*c*= 0.21, MeOH), **IR** (ν, $cm^{-1}$): 2980, 2924, 2870, 1709, 1456, 1446, 1388, 1377, 1133, 1073, 1060, 986, 958. NMR – see Table 3.1. Elemental analysis calculated for $C_{22}H_{37}IO_3$ (476.44): C, 55.46; H, 7.83; found: C, 55.49; H, 7.92. *****The absolute stereochemistry at C-14 was not determined.

*4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoic acid (minor epimer) (201)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 8.6°$ (*c*= 0.52, MeOH), **IR** (ν, $cm^{-1}$): 2923, 2870, 1708, 1457, 1446, 1388, 1377, 1144, 1125, 1092, 1076, 1043, 1026, 989, 963. NMR – see Table 3.1. Elemental analysis calculated for $C_{22}H_{37}IO_3$ (476.44): C, 55.46; H, 7.83; found: C, 55.40; H, 7.87. *****The absolute stereochemistry at C-14 was not determined.

According to general procedure 3 from *epi*-manoyl oxide (104 mg, 0.36 mmol), iodoacetic acid (67 mg, 0.36 mmol) and DLP (29 mg, 0.072 mmol). The reaction mixture was refluxed for 8 h and after immediately was methylated with an etheric solution of diazomethane. The methylated product was purified by column chromatography (pentane/EtOAc 98:2) and gave epimers of **202** (70 mg, 41% of major epimer and 27 mg, 18% of minor epimer) and iodide **203** (25 mg, 17%).

*Methyl 4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (major epimer) (202)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 28.4°$ (*c*= 0.34, MeOH), **IR** (ν, $cm^{-1}$): 2946, 2990, 2870, 1741, 1448, 1388, 1378, 1362, 1143, and 1073. NMR – see Table 3.1. Elemental analysis calculated for $C_{23}H_{39}IO_3$ (490.47): C, 55.32; H, 8.02; found: C, 55.36; H, 8.10.

*Methyl 4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (minor epimer)(202)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 4.4°$ (*c*= 0.14, MeOH), **IR** (ν, $cm^{-1}$): 2924, 2854, 1742, 1458, 1439, 1377, 1156, and 1077. NMR – see Table 3.1. Elemental analysis calculated for $C_{23}H_{39}IO_3$ (490.47): C, 55.32; H, 8.02; found: C, 55.34; H, 8.09.

*Methyl 4-((3R,4aR,7S,10aS)-7-(iodomethyl)-3,4a,7,10a-tetramethyldodecahydro-1H-benzo[f] chromen-3-yl) butanoate (203)*

Colorless viscous liquid, $[\alpha]_D^{20} = 28.4°$ (*c*= 0.34, MeOH), **IR** (ν, $cm^{-1}$): 2977, 2942, 2872, 1740, 1451, 1376, 1202, 1164, 1142, and 1134. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.65 (*s*, $CH_3$-23), 3.58 (*d*, *J*= 9.8 Hz, CH-18), 3.15 (*dd*, *J*= 9.8; 1.8 Hz, CH-18), 1.22 (*s*, $CH_3$-17), 1.09 (*s*, $CH_3$-16), 1.01 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 174.09 (*s*, C-22), 74.52 (*s*, C-8), 73.07 (*s*, C-13), 57.71 (*d*, C-9), 55.44 (*d*, C-5), 51.44 (*q*, C-23), 43.43 (*t*, C-7), 40.48 (*t*, C-14), 39.11 (*t*, C-3), 39.10 (*t*, C-1), 37.39 (*t*, C-12), 36.90 (*s*, C-10), 36.64 (*s*, C-4), 34.52 (*t*, C-21), 30.01 (*q*, C-16), 33.43 (*q*, C-19), 24.05 (*q*, C-17), 20.11 (*t*, C-15), 19.93 (*t*, C-6), 19.49 (*t*, C-18), 17.82 (*t*, C-2), 16.42 (*q*, C-20), 15.35 (*t*, C-11). Elemental analysis calculated for $C_{23}H_{39}IO_3$ (490.47): C, 55.32; H, 8.02; found: C, 55.37; H, 8.01.

According to general procedure 3 from *epi*-manoyl oxide (153 mg, 0.53 mmol), ethyl iodoacetate (63 μL, 0.53 mmol) and DLP (53 mg, 0.13 mmol). The reaction mixture was refluxed for 10 h. The crude was purified by column chromatography (pentane/EtOAc 98:2) and gave epimers of **204** (84 mg, 32% of major epimer and 43 mg, 16% of minor epimer) and iodide **205** (79 mg, 30%).

*Ethyl 4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)butanoate (major epimer) (204)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 1.07°$ (*c*= 0.13, MeOH), **IR** (ν, $cm^{-1}$): 3670, 2967, 2298, 1737, 1454, 1441, 1407, 1376, 1242, 1171, 1066, 1050, 882. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.19 (*dd*, *J*= 11.2; 1.6 Hz, CH-14), 4.13 (*q*, *J*= 7 Hz, $CH_2$-23), 1.34 (*s*, $CH_3$-16), 1.26 (*t*, *J*= 7 Hz, $CH_3$-24), 1.17 (*s*, $CH_3$-17), 0.93 (*dd*, *J*= 12; 2 Hz, CH-5), 0.85 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.76 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 172.78 (*s*, C-22), 75.83 (*s*, C-8), 74.78 (*s*, C-13), 60.32 (*t*, C-23), 56.54 (*d*, C-5), 55.07 (*d*, C-9), 48.75 (*d*, C-14), 43.32 (*t*, C-7), 42.10 (*t*, C-3), 38.96 (*t*, C-1), 37.03 (*s*, C-10), 35.93 (*t*, C-12), 35.38 (*t*, C-21), 33.34 (*q*, C-19), 33.13 (*s*, C-4), 30.21 (*t*, C-15), 25.35 (*q*, C-16), 24.98 (*q*, C-17), 21.35 (*q*, C-18), 20.07 (*t*, C-6),

18.46 (*t*, C-2), 15.28 (*q*, C-20), 14.84 (*t*, C-11), 14.21 (*q*, C-24). Elemental analysis calculated for $C_{24}H_{47}IO_3$ (504.21): C, 57.14; H, 8.19; found: C, 57.11; H, 8.23.

*Ethyl 4-iodo-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl)butanoate (minor epimer) (204)*

Pale-yellow viscous liquid, $[\alpha]_D^{20}$ =17.72° (*c*= 0.32, MeOH), **IR** (ν, $cm^{-1}$): 2980, 2936, 2869, 2342, 1734, 1461, 1444, 1388, 1376, 1182, 1125, 1094, 1078, 1034, 991. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.29 (*dd*, *J*= 12; 2 Hz, CH-14), 4.14 (*q*, *J*= 7 Hz, $CH_2$-23), 1.34 (*s*, $CH_3$-17), 1.31 (*s*, $CH_3$-16), 1.27 (*t*, *J*=7 Hz, $CH_3$-24), 0.94 (*dd*, *J*= 12; 2.3 Hz, CH-5), 0.86 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.78 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 172.82, 76.18, 74.73, 60.45, 56.54, 55.16, 54.21, 43.54, 42.10, 39.07, 37.09, 35.38, 33.34, 33.16, 31.55, 30.31, 28.74, 24.35, 21.35, 19.99, 18.46, 15.36, 15.28, 14.25. Elemental analysis calculated for $C_{24}H_{47}IO_3$ (504.21): C, 57.14; H, 8.19; found: C, 57.20; H, 8.25.

*Ethyl 4-((3R,4aR,7S,10aS)-7-(iodomethyl)-3,4a,7,10a-tetramethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (205)*

Colorless viscous liquid, $[\alpha]_D^{20}$ = -1.32° (*c*= 0.47, MeOH), **IR** (ν, $cm^{-1}$): 2965, 2927, 2870, 1735, 1463, 1452, 1375, 1260, 1203, 1192, 1164, 1129, 1102, 1080, 1042, 1023, 989. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.12 (*q*, *J*= 7.2 Hz, $CH_2$-23), 3.59 (*d*, *J*= 9.8 Hz, $CH_2$-18), 3.16 (*dd*, *J*= 9.8; 1.8 Hz, $CH_2$-18), 1.25 (*t*, *J*= 7.2 Hz, $CH_3$-24), 1.23 (*s*, $CH_3$-17), 1.1 (*s*, $CH_3$-16), 1.02 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.69 (*s*, C-22), 73.09 (*s*, C-13), 74.58 (*s*, C-8), 60.21 (*t*, C-23), 57.75 (*d*, C-9), 55.47 (*d*, C-5), 43.52 (*t*, C-7), 40.48 (*t*, C-14), 39.14 (*t*, C-1), 39.09 (*t*, C-3), 37.31 (*t*, C-12), 36.94 (*s*, C-10), 36.67 (*s*, C-4), 34.90 (*t*, C-21), 32.46 (*q*, C-19), 30.09 (*q*, C-16), 24.11 (*q*, C-17), 20.20 (*t*, C-15), 19.97 (*t*, C-6), 19.48 (*t*, C-18), 17.86 (*t*, C-2), 16.46 (*q*, C-20), 15.39 (*t*, C-11), 14.27 (*q*, C-24). Elemental analysis calculated for $C_{24}H_{47}IO_3$ (504.21): C, 57.14; H, 8.19; found: C, 57.19; H, 8.26.

According to general procedure 3 from *epi*-manoyl oxide (93.6 mg, 0.32 mmol), bromotriclhoromethane (63.5 mg, 0.32 mmol) and DLP (32 mg, 0.08 mmol). The reaction was refluxed 10 h. The crude product was purified by HPLC afforded dichloride **206** (10 mg, 10% brsm), bromide **207** (22 mg, 16%), bromide **208** (17 mg, 13%) and bromide **209** (48 mg, 36%), along with 15% (14 mg) of recovered starting material.

*(3S,4aR,10aS)-3-(3,3-dichloroallyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f] chromene (206)*

Colorless viscous liquid, $[\alpha]_D^{20} = 20.13°$ (*c*= 0.15, $CHCl_3$), **IR** (ν, $cm^{-1}$): 2926, 2866, 1737, 1465, 1376, 1096, 1078, 991. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.02 (*dd*, *J*= 7.7; 6.0 Hz, CH-15), 2.56 (*dd*, *J*= 15.6; 6.2 Hz, $CH_2$-14), 2.28 (*dd*, *J*= 15.6; 7.9 Hz, $CH_2$-14), 0.76 (*s*, $CH_3$-18), 1.29 (*s*, $CH_3$-17), 1.12 (*s*, $CH_3$-16), 0.94 (*dd*, *J*= 12; 2.5 Hz, CH-5), 0.89 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 127.62 (*d*, C-15), 120.40 (*s*, C-21), 75.38 (*s*, C-8), 72.67 (*s*, C-13), 57.49 (*d*, C-9), 56.52 (*d*, C-5), 43.44 (*t*, C-7), 42.20 (*t*, C-3), 41.24 (*t*, C-14), 39.23 (*t*, C-1), 37.30 (*t*, C-12), 36.93 (*s*, C-10), 33.33 (*s*, C-4), 33.32 (*q*, C-19), 30.65 (*q*, C-16), 24.28 (*q*, C-17), 21.29 (*q*, C-18), 20.00 (*t*, C-6), 18.61 (*t*, C-2), 15.69 (*q*, C-20), 15.42 (*t*, C-11). Elemental analysis calculated for $C_{21}H_{34}Cl_2O$ (372.20): C, 67.55; H, 9.18; found: C, 67.61; H, 9.24.

*(3S,4aR,10aS)-4a-(bromomethyl)-3,7,7,10a-tetramethyl-3-(3,3,3-trichloropropyl) dodecahydro-1H-benzo[f]chromene (207)*

Colorless viscous liquid, $[\alpha]_D^{20}$ = -14.23° (*c*= 0.17, $CHCl_3$), **IR** (ν, $cm^{-1}$): 2925, 2869, 2850, 1731, 1463, 1376, 1041, 787, 693. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.76 (*d*, *J*= 11.2 Hz, $CH_2$-17), 3.56 (*dd*, *J*= 11.2; 2.0 Hz, $CH_2$-17), 1.24 (*s*, $CH_3$-16), 0.99 (*dd*, *J*= 12.4; 1.9 Hz, CH-5), 0.86 (*s*, $CH_3$-19), 0.81 (*s*, $CH_3$-20), 0.74 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 100.84 (*s*, C-21), 74.58 (*s*, C-8), 72.55 (*s*, C-13), 56.91 (*d*, C-5), 53.63 (*d*, C-9), 50.34 (*t*, C-15), 41.90 (*t*, C-3), 40.71 (*t*, C-17), 40.31 (*t*, C-14), 39.56 (*t*, C-7), 39.05 (*t*, C-1), 37.22 (*s*, C-10), 33.19 (*q*, C-19), 33.20 (*s*, C-4), 33.19 (*t*, C-12), 28.43 (*q*, C-16), 21.23 (*q*, C-18), 19.50 (*t*, C-6), 18.51 (*t*, C-2), 15.80 (*q*, C-20), 14.47 (*t*, C-11). Elemental analysis calculated for $C_{21}H_{34}BrCl_3O$ (488.76): C, 51.61; H, 7.01; found: C, 51.65; H, 7.09.

*(3S,4aR,10aR)-10a-(bromomethyl)-3,4a,7,7-tetramethyl-3-(3,3,3-trichloropropyl)-dodecahydro-1H-benzo[f]chromene (208)*

Colorless viscous liquid, $[\alpha]_D^{20} = 7.37°$ (*c*= 0.16, $CHCl_3$), **IR** (ν, $cm^{-1}$): 2972, 2929, 2866, 1465, 1452, 1377, 1104, 1080, 1042, 995, 790. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.92 (*dd*, *J*= 11.3; 1.2 Hz, $CH_2$-20), 3.65 (*dd*, *J*= 11.3; 1.7 Hz, $CH_2$-20), 1.53 (*s*, $CH_3$-17), 1.13 (*s*, $CH_3$-16), 0.90 (*s*, $CH_3$-19), 0.84 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 100.71 (*s*, C-21), 75.01 (*s*, C-8), 72.52 (*s*, C-13), 59.62 (*d*, C-9), 58.09 (*d*, C-5), 50.95 (*t*, C-15), 41.69 (*t*, C-3), 41.00 (*s*, C-10), 40.57 (*t*, C-12), 36.60 (*s*, C-14), 36.34 (*t*, C-20), 35.93 (*t*, C-1), 34.27 (*q*, C-19), 33.14 (*s*, C-4), 30.56 (*q*, C-16), 23.51 (*q*, C-17), 22.26 (*q*, C-18), 19.78 (*t*, C-11), 18.52 (*t*, C-11), 17.95 (*q*, C-2).

*(3S,4aR,7S,10aS)-7-(bromomethyl)-3,4a,7,10a-tetramethyl-3-(3,3,3-trichloropropyl) dodecahydro-1H-benzo[f]chromene (209)*

Colorless viscous liquid, $[\alpha]_D^{20} = 9.00°$ (*c*= 0.26, $CHCl_3$), **IR** (ν, $cm^{-1}$): 2970, 2930, 2865, 1465, 1452, 1377, 1105, 1080, 1041, 994, 787, 692. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.75 (*d*, *J*= 10.0 Hz, $CH_2$-18), 3.31 (*dd*, *J*= 10.0; 1.6 Hz, $CH_2$-18), 1.30 (*s*, $CH_3$-17), 1.15 (*s*, $CH_3$-16), 1.04 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 100.78 (*s*, C-21), 74.94 (*s*, C-8), 72.07 (*s*, C-13), 57.68 (*d*, C-9), 57.25 (*d*, C-5), 50.78 (*t*, C-15), 43.63 (*t*, C-7), 41.55 (*t*, C-18), 39.18 (*t*, C-1), 38.02 (*t*, C-12), 37.81 (*t*, C-14), 37.73 (*s*, C-4), 37.00 (*t*, C-3), 36.90 (*s*, C-10), 30.47 (*q*, C-16), 29.64 (*q*, C-19), 24.22 (*q*, C-17), 19.91 (*t*, C-6), 17.91 (*q*, C-2), 16.51 (*q*, C-20), 15.43 (*t*, C-11). Elemental analysis calculated for $C_{21}H_{34}BrCl_3O$ (488.76): C, 51.61; H, 7.01; found: C, 51.58; H, 7.10.

According to general procedure 3 from *epi*-manoyl oxide (51 mg, 0.18 mmol), iodomethylsulfonyl benzene (50.6 mg, 0.18 mmol) and DLP (18 mg, 0.045 mmol). The reaction mixture was refluxed 10 h and after the crude was purified by column chromatography (pentane/EtOAc 93:7) and gave the starting material (42 mg, 75%), iodide **210** (4.7 mg, 28% brsm) and iodide **211** (6.2 mg, 36% brsm).

*(3S,4aR,10aS)-3-((R)-1-iodo-3-(phenylsulfonyl)-propyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromene (210)*

Pale-yellow viscous liquid, $[\alpha]_D^{20} = 45.6°$ (*c*= 0.24, MeOH), **IR** (ν, $cm^{-1}$): 2925, 2857, 1447, 1321, 1308, 1149, 1087, and 1073. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.93 (*m*, CH-2´), 7.67 (*m*, CH-4´), 7.58 (*m*, CH-3´), 4.11 (*dd*, *J*= 11.5; 1.9 Hz, CH-14), 1.26 (*s*, $CH_3$-16), 1.01 (*s*, $CH_3$-17), 0.89 (*dd*, *J*= 12.2; 2.4 Hz, CH-5), 0.85 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-18), 0.73 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 139.19 (*s*, C-1´), 133.69 (*d*, C-4´), 129.30 (*d*, C-2´, C-6´), 128.16 (*d*, C-3´, C-5´), 76.01 (*s*, C-13), 74.62 (*s*, C-8), 57.22 (*t*, C-21), 56.57 (*d*, C-5), 54.97 (*d*, C-9), 45.33 (*t*, C-14), 43.24 (*t*, C-7), 42.10 (*t*, C-3), 38.98 (*t*, C-1), 37.02 (*s*, C-10), 35.75 (*t*, C-12), 33.19 (*s*, C-4), 32.32 (*q*, C-19), 28.50 (*t*, C-15), 25.25 (*q*, C-16), 24.80 (*q*, C-17), 21.33 (*t*, C-18), 19.98 (*t*, C-6), 18.47 (*t*, C-2), 15.83 (*t*, C-11), 15.23 (*q*, C-20). Elemental analysis calculated for $C_{27}H_{41}IO_3S$ (572.59): C, 56.64; H, 7.22; found: C, 56.71; H, 7.31.

*(3S,4aR,7S,10aS)-7-(iodomethyl)-3,4a,7,10a-tetramethyl-3-(3-(phenylsulfonyl)-propyl)-dodecahydro-1H-benzo[f]chromene (211)*

Colorless viscous liquid, $[\alpha]_D^{20} = -0.2$ (*c*= 1.26, MeOH), **IR** (ν, $cm^{-1}$): 3388, 2921, 2850, 1708, 1667, 1628, 1449, 1216, 1072, 1052, 908, 855. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 7.91 (*m*,

CH-2´), 7.64 (*m*, CH-4´), 7.57 (*m*, CH-3´), 3.57 (*d*, *J*= 9.8 Hz, $CH_2$-18), 3.14 (*dd*, *J*= 9.9; 1.6 Hz, $CH_2$-18), 1.08 (*s*, $CH_3$-17), 1.05 (*s*, $CH_3$-16), 1.00 (*s*, $CH_3$-19), 0.75 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 139.13 (*s*, C-1´), 133.60 (*d*, C-4´), 129.24 (*d*, C-2´, C-6´), 128.06 (*d*, C-3´, C-5´), 74.65 (*s*, C-8), 72.63 (*s*, C-13), 57.21 (*d*, C-5), 56.76 (*t*, C-21), 56.75 (*d*, C-9), 43.41 (*t*, C-7), 39.64 (*t*, C-14), 39.07 (*t*, C-1), 39.02 (*t*, C-3), 36.90 (*s*, C-10), 36.90 (*t*, C-12), 36.63 (*s*, C-4), 32.43 (*q*, C-19), 29.63 (*q*, C-16), 23.96 (*q*, C-17), 19.92 (*t*, C-6), 19.33 (*q*, C-18), 18.02 (*t*, C-15), 17.80 (*t*, C-2), 16.38 (*q*, C-20), 15.24 (*t*, C-11). Elemental analysis calculated for $C_{27}H_{41}IO_3S$ (572.59): C, 56.64; H, 7.22; found: C, 56.68; H, 7.30.

*Ethyl (4S)-4-((3R,5S,6S,10S,10aR,10bS)-5-acetoxy-6,10,10b-trihydroxy-3,7,7,10a-tetramethyl-1-oxododecahydro-1H-benzo[f]chromen-3-yl)-4-azidobutanoate (212)*

According to general procedure 2 from forskolin (100 mg, 0.25 mmol), ethyl iodoacetate (44 µL, 0.37 mmol), 3-$PySO_2N_3$ (137 mg, 0.75 mmol), $Bu_6Sn_2$ (187 µL, 0.37 mmol) and DTBHN (6 mg, 0.075 mmol). The reaction mixture was refluxed for 6 h and after purified by column chromatography (pentane: EtOAc 60:40) afforded the azide **212** (92 mg, 68%) as a yellowish oil. $[\alpha]_D^{20}$ = -9.0° (*c*= 2.0, $CHCl_3$). **IR** (ν, cm$^{-1}$): 2928, 2132, 1733, 1372, 1233, 1173, 1039, 989, 699. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 5.44 (*d*, *J*= 3.7 Hz, CH-7), 4.91 (*s*, OH), 4.40 (*bs*, CH-6), 4.33 (*bs*, CH-1), 4.14 (*q*, *J*= 7.1 Hz, $CH_2$-25), 3.92 (*dd*, *J*=11; 3.5 Hz, CH-14), 2.32-2.56 (*m*, $CH_2$-12), 2.17 (*s*, $CH_3$-22), 1.49 (*s*, $CH_3$-16), 1.46 (*s*, $CH_3$-20), 1.22-1.27 (*m*, $CH_3$-26, $CH_3$-17 and $CH_2$-2), 1.09 (*s*, $CH_3$-18), 1.04 (*s*, $CH_3$-19). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 201.44 (*s*, C-11), 172.87 (*s*, C-24), 169.82 (*s*, C-21), 84.56 (*s*, C-9), 79.88 (*d*, C-14), 79.07 (*s*, C-8), 76.80 (*d*, C-7), 73.04 (*d*, C-1), 70.62 (*s*, C-13), 69.64 (*d*, C-6), 60.67 (*t*, C-25), 50.54 (*d*, C-12), 43.48 (*s*, C-10), 42.96 (*d*, C-5), 35.77 (*t*, C-3), 34.56 (*s*, C-4), 33.44 (*q*, C-19), 29.47 (*t*, C-15), 25.69 (*t*, C-23), 24.97 (*q*, C-16), 24.94 (*q*, C-17), 24.45 (*t*, C-2), 21.37 (*q*, C-18), 21.15 (*q*, C-22), 19.49 (*q*, C-20), 14.18 (*q*, C-26). **HRMS (ESI)** calculated for [$C_{26}H_{41}O_9$] -$N_3$: 497.2744; found 497.2745.

To a solution of forskolin **183** (50 mg, 0.17 mmol) in dry dichloromethane was added ethyl iodoacetate (24 µL, 0.2 mmol) and triethylborane (0.22 mL, 0.22 mmol). The reaction mixture was stirred at room temperature for 2 h and after filtered over short pad of neutral $Al_2O_3$ using $Et_2O$. The resulting mixture was purified by FC (pentane/EtOAc 80:20) gave the mixture of iodine **213** (32%, 90:10) and reduced product **214** (30%). The small amount of the both products was isolated for the characterization.

**IR** (ν, cm$^{-1}$) for compound **213** and **214**: 2934, 2863, 1733, 1445, 1374, 1258, 1181, 1073, 988, 957.

*Ethyl (4S)-4-((3R,4aR,5S,6S,10S,10aR,10bS)-5-acetoxy-6,10,10b-trihydroxy-3,4a,7,7,10a-pentamethyl-1-oxododecahydro-1H-benzo[f]chromen-3-yl)-4-iodobutanoate (major) (213)*

**$^{1}$H NMR** (300 MHz, $C_6D_6$) δ (ppm) 5.83 (*d, J*= 3.7 Hz, CH-7), 4.61 (*bs*, C-6), 4.36 (*bs*, CH-1), 3.97 (*q, J*= 7.1 Hz, $CH_2$-25), 3.77 (*d, J*= 16 Hz, CH-14), 1.86 (*s*, $CH_3$-22), 1.86 (*s*, $CH_3$-16), 1.57 (*s*, $CH_3$-20), 1.38 (*s*, $CH_3$-17), 1.31 (s, $CH_3$-18), 0.99 *(t, J*= 7 Hz, $CH_3$-22), 0.89 (*s*, $CH_3$-19). **$^{13}$C NMR** (75 MHz, $C_6D_6$) δ (ppm) 205.68, 172.23, 168.92, 82.66, 82.24, 76.89, 76.51, 74.27, 69.93, 59.85, 51.21, 51.08, 42.98, 42.78, 36.08, 34.99, 34.11, 32.47, 30.53, 27.25, 26.65, 24.03, 23.13, 20.46, 19.90, 13.90. **HRMS (ESI)** calculated for $[C_{24}H_{42}O_3]^+$: 625.1878; found 625.1868.

*Ethyl 4-((3S,4aR,5S,6S,10S,10aR,10bS)-5-acetoxy-6,10,10b-trihydroxy-3,4a,7,7,10a-pentamethyl-1-oxododecahydro-1H-benzo[f]chromen-3-yl)butanoate (214)*

**$^{1}$H NMR** (300 MHz, $C_6D_6$) δ (ppm) 5.77 (*d, J*= 4.0 Hz, CH-7), 4.95 (*bs*, C-6), 4.90 (*bs*, CH-1), 3.96 (*q, J*= 7.1 Hz, $CH_2$-25), 1.75 (*s*, $CH_3$-22), 1.70 (*s*, $CH_3$-16), 1.54 (*s*, $CH_3$-20), 1.31 (*s*, $CH_3$-17), 1.21 (*s*, $CH_3$-18), 0.99 (*t, J*= 7 Hz, $CH_3$-22), 0.88 (*s*, $CH_3$-19). **$^{13}$C NMR** (75 MHz, $C_6D_6$) δ (ppm) 203.30, 172.21, 168.96, 84.14, 83.35, 76.07, 74.88, 69.62, 64.09, 59.93, 43.24, 42.23, 38.78, 38.72, 35.96, 34.18, 33.41, 32.49, 26.73, 25.62, 24.10, 20.41(3C), 19.59 and 13.92. **HRMS (ESI)** calculated for $[C_{26}H_{42}O_9]^-$: 497.2743; found 497.2745.

To a solution of the mixture **213** and **214** (53 mg) in DMF (3 mL) was added $NaN_3$ (14 mg, 0.2 mmol). The reaction was heated at 80 °C overnight. The reaction mixture was washed with brine and extracted with EtOAc. The crude was purified by FC (pentane/EtOAc 60:40) afforded the azide **215** (35 mg, 60%) and unreacted **214** (15 mg, 30%).

*Ethyl 4-((3R,4aR,5S,6S,10S,10aR,10bS)-5-acetoxy-6,10,10b-trihydroxy-3,4a,7,7,10a-pentamethyl-1-oxododecahydro-1H-benzo[f]chromen-3-yl)-4-azidobutanoate (215)*

**IR** (ν, $cm^{-1}$): 2917, 1733, 1448, 1372, 1234, 1040, 989, 783. **$^{1}$H NMR** (300 MHz, $C_6D_6$) δ (ppm) (major) 5.64 (*d, J*= 3.7 Hz, CH-7), 5.05 (*s*, OH), 4.77 (*bs*, C-6), 4.42 (*bs*, CH-1), 3.89 (*q, J*= 7.1 Hz, $CH_2$-25), 3.51 (*d, J*= 10 Hz, CH-14), 1.73 (*s*, $CH_3$-22), 1.68 (*s*, $CH_3$-16), 1.51 (*s*, $CH_3$-20), 1.37 (*s*, $CH_3$-17), 1.08 (*s*, $CH_3$-18), 1.05 (*s*, $CH_3$-19), 0.92 (*t, J*= 7 Hz, $CH_3$-22). **$^{1}$H NMR** (300 MHz, $C_6D_6$, minor) 5.56 (*d, J*= 3.7 Hz, CH-7), 5.10 (*s*, OH), 4.75 (*bs*, C-6), 4.42 (*bs*, CH-1), 3.89 (*q, J*= 7.1 Hz, $CH_2$-25), 3.51 (*d, J*= 10 Hz, CH-14), 1.75 (*s*, $CH_3$-22), 1.70 (*s*, $CH_3$-16), 1.57 (*s*, $CH_3$-20), 1.36 (*s*, $CH_3$-17), 1.07 (*s*, $CH_3$-18), 1.02 (*s*, $CH_3$-19), 0.92 (*t, J*= 7 Hz, $CH_3$-22). **$^{13}$C NMR** (75 MHz, $C_6D_6$) δ (ppm) (major) 201.50, 172.91, 169.77, 85.21, 79.95, 79.79, 77.56, 73.80, 70.99, 70.13, 60.45, 50.72, 44.47, 43.72, 36.74, 35.17, 33.99, 30.03, 26.66, 25.61, 25.53, 21.35, 21.07, 20.89, 20.19, 14.54. **$^{13}$C NMR** (75 MHz, $C_6D_6$, minor) 200.94, 172.34, 170.53,

86.02, 79.98, 79.77, 77.78, 73.21, 70.93, 70.26, 60.84, 50.72, 44.76, 43.60, 36.92, 35.27, 33.99, 30.69, 26.71, 25.42, 21.74, 21.11, 20.89, 20.48, 14.56. **HRMS (ESI)** calculated for $[C_{26}H_{41}O_9]$ - $N_3$: 497.2718; found 497.2717.

*Ethyl 4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (216)*

According to general procedure 4 from manoyl oxide (50 mg, 0.17 mmol), ethyl iodoacetate (24 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAc 96:6) gave the compound **216** (33 mg, 52%) as a colorless oil. $[\alpha]_D^{20} = 8.5°$ (*c*= 1.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2922, 1734, 1373, 1154, 1027, 990, 802. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.10 (*q*, *J*= 7.1 Hz, $CH_2$-23), 2.26 (*td*, *J*= 10.4; 2.8 Hz, $CH_2$-21), 1.25 (*t*, *J*= 6.9 Hz, $CH_3$-24), 1.21 (*s*, $CH_3$-16), 1.10 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.78 (*s*, $CH_3$-18), 0.75 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 174.00, 74.67, 72.59, 60.12, 58.23, 56.41, 44.96, 43.06, 42.18, 39.16, 36.84, 36.31, 34.75, 33.33, 33.29, 27.57, 24.82, 21.27, 19.85, 19.33, 18.62, 15.74, 15.37, 14.28. **HRMS (ESI)** calculated for $[C_{24}H_{42}O_3]$ $Na^+$: 401.3017; found 401.3026.

*Ethyl 4-((3R,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (217)*

According to general procedure 4 from *epi*-manoyl oxide (50 mg, 0.17 mmol), ethyl iodoacetate (24 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAc 96:6) gave the compound **217** (37 mg, 58%) as a colorless oil. $[\alpha]_D^{20} = 14.5°$ (*c*= 2, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2922, 1734, 1373, 1154, 1027, 990, 802. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.10 (q, *J*= 7.1 Hz, $CH_2$-23), 2.26 (*t*, *J*= 7.1 Hz, $CH_2$-21), 1.24 (t, *J* = 6.9 Hz, $CH_3$-24), 1.23 (*s*, $CH_3$-16), 1.10 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.78 (*s*, $CH_3$-18), 0.75 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 173.73, 74.92, 72.96, 60.18, 57.61, 56.47, 43.57, 42.17, 40.62, 39.18, 37.34, 36.95, 34.96, 33.36, 33.27, 30.14, 24.25, 21.30, 20.26, 20.00, 18.60, 15.70, 15.31, 14.28. **HRMS (ESI)** calculated for $[C_{24}H_{42}O_3]$ $Na^+$: 401.3017; found 401.3026.

*(3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-3-(3-(phenylsulfonyl)propyl)dodecahydro-1H-benzo[f]chromene (218)*

According to general procedure 4 from *epi*-manoyl oxide (30 mg, 0.1 mmol), benzyl sulfonylmethyl iodide (33 mg, 0.12 mmol), *tert*-butylcatechol (33 mg, 0.2 mmol), $Et_3B$ (0.13 mL, 0.13 mmol). The crude mixture was purified by FC (pentane/EtOAc 90:10) gave the

compound **218** (17 mg, 38%, brsm) and starting material (50%). **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 7.89-7.99 (*m*, CH-23), 7.63-7.67 (*m*, CH-25), 7.65-7.53 (*m*, CH-24), 3.06 (*t*, *J* = 7.2 Hz, $CH_2$-21), 1.09 (*s*, $CH_3$-16), 1.04 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.77 (*s*, $CH_3$-18), 0.73 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 139.1, 133.62, 129.26, 128.11, 75.02, 72.52, 57.04, 56.84, 56.45, 43.49, 42.13, 39.81, 39.13, 36.95, 36.86, 33.33, 33.26, 30.00, 24.12, 21.30, 19.96, 18.56, 18.11, 16.64, 15.63. (The product contains a small amount of benzyl sulfonylmethyl). **HRMS (ESI)** calculated for $[C_{27}H_{42}O_3S]^+$: 447.2924; found 447.2927.

*Ethyl 2,2-difluoro-4-((3S,4aR,10aS)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromen-3-yl) butanoate (219)*

According to general procedure 4 from *epi*-manoyl oxide (50 mg, 0.17 mmol), ethyl difluoro iodoacetate (25 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAc 96:6) afforded compound **219** (43 mg, 61%) as a yellowish oil. $[\alpha]_D^{20}$ = -28.1° (*c*= 0.9, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2925, 1766, 1464, 1372, 1189, 1046, 1082, 778. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.31 (*tq*, *J*= 7.1, 3.0 Hz, $CH_2$-23), 3.63 (*d*, *J*= 10.9 Hz, $CH_2$-15), 3.35 (*dd*, *J*= 10.9, 2.3 Hz, $CH_2$-15), 1.35 (*t*, *J*= 7.1 Hz, $CH_3$-24), 1.25 (*s*, $CH_3$-16), 1.18 (*s*, $CH_3$-17), 0.86 (*s*, $CH_3$-19), 0.80 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-20). **$^{13}$C NMR** [$^{19}$F] (100 MHz, $CDCl_3$) δ (164.82, 164.49, 164.16), 114.29, 73.86, 72.54, 62.73, 56.96, 51.45, 41.91, 41.71, 38.94, 37.37, 35.96, 33.24, 33.20, 32.20, 29.72 (t), 27.22, 21.35, 20.01, 19.60, 18.50, 15.59, 14.51, 14.06. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ -105.21 (*dt*, *J*= 255.4, 16.3 Hz), -106.55 (*dt*, *J*= 255.5, 17.2 Hz). **HRMS (ESI)** calculated for $[C_{24}H_{40}F_2O_3]Na^+$: 437.2830; found 437.2838.

*(3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-3-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-dodecahydro-1H-benzo[f]chromene (220)*

According to general procedure 4 from *epi*-manoyl oxide (50 mg, 0.17 mmol), nonafluoro-1-iodobutane (35 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAC 98:2) afforded the compound **220** (51 mg, 59%) as a yellowish oil. $[\alpha]_D^{20}$ = -41.7° (*c*= 1.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2926, 2359, 2342, 1464, 1217, 1131, 1023, 878, 721. **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.62 (*d*, *J*= 10.9 Hz, $CH_2$-15), 3.34 (*dd*, *J*= 10.9, 2.1 Hz, $CH_2$-15), 1.25 (*s*, $CH_3$-16), 1.19 (*s*, $CH_3$-17), 1.12-1.25 (*m*, $CH_3$-16), 0.86 (*s*, $CH_3$-19), 0.81 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 73.89, 72.13, 56.96, 51.07, 41.89, 41.64, 38.90, 37.38, 34.80, 33.25, 33.19, 32.19, 27.10, 25.77 (t), 21.36, 19.83, 19.61, 18.49, 15.53, 14.47. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -81.08

(*s*, 3F), -114.49 (*m*, 2F), -123.97 – -124.29 (*m*, 2F), -125.98 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{24}H_{35}F_9O]^+$: 509.2445; found 509.2460.

*(3S,4aR,10aS)-3,4a,7,7,10a-pentamethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) dodecahydro-1H-benzo[f]chromene (221)*

According to general procedure 4 from *epi*-manoyl oxide (50 mg, 0.17 mmol), perfluoro-1-iodohexane (45 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAc 98:2) afforded the compound **221** (62 mg, 60%) as a yellowish oil. $[\alpha]_D^{20} =$ -33.9° (*c*= 1.7, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2933, 2359, 2341, 1464, 1235, 1190, 1144, 1058, 668. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.62 (*d*, *J*= 11.0 Hz, $CH_2$-15), 3.34 (*dd*, *J*= 10.9, 2.1 Hz, $CH_2$-15), 1.19 (*s*, $CH_3$-17), 1.11-1.24 (*m*, $CH_3$-16), 0.86 (*s*, $CH_3$-19), 0.81 (*s*, $CH_3$-18), 0.79 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 73.89, 72.14, 56.96, 51.07, 41.89, 41.64, 38.89, 37.38, 34.83, 33.24, 33.19, 32.19, 27.10, 25.86 (t), 21.36, 19.82, 19.61, 18.49, 15.52, 14.47. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -81.08 (*d*, *J*= 15.6 Hz, 3F), -114.49 (*m*, 2F), -121.88 (*m*, 2F), -122.83 (*m*, 2F), -123.19 (*m*, 2F), -126.17 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{26}H_{35}F_{13}O]^+$: 609.2375; found 609.2389.

*(3S,4aR,10aS)-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-3,4a,7,7,10a-pentamethyldodecahydro-1H-benzo[f]chromene (222)*

According to general procedure 4 from *epi*-manoyl oxide (50 mg, 0.17 mmol), perfluorooctyl iodide (55 µL, 0.2 mmol), *tert*-butylcatechol (56 mg, 0.34 mmol), $Et_3B$ (0.22 mL, 0.22 mmol). The crude mixture was purified by FC (pentane/EtOAc 98:2) afforded the compound **222** (76 mg, 63%) as a yellowish oil. $[\alpha]_D^{20} =$ -17.2° (*c*= 2, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2933, 2359, 2342, 1237, 1201, 1145, 1058, 654. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 3.62 (*d*, *J*= 11.0 Hz, $CH_2$-15), 3.35 (*dd*, *J*= 10.9, 1.9 Hz, $CH_2$-15), 1.19 (*s*, $CH_3$-17), 1.11-1.24 (*m*, $CH_3$-16), 0.81 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18), 0.77 (*s*, $CH_3$-20). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 73.89, 72.14, 56.97, 51.07, 41.89, 41.64, 38.90, 37.38, 34.82, 33.24, 33.19, 32.19, 27.10, 25.87, 21.35, 19.81, 19.61, 18.49, 15.52, 14.48. **$^{19}$F NMR** (282 MHz, $CDCl_3$) δ (ppm) -81.08 (*d*, *J*= 15.6 Hz, 3F), -114.49 (*m*, 2F), -121.68 (*s*, 2F), -121.89 (*s*, 4F), -122.69 (*s*, 2F), -123.14 (*s*, 2F), -125.98 (*m*, 2F). **HRMS (ESI)** calculated for $[C_{26}H_{35}F_{13}O]^+$: 709.2332; found 709.2333.

*Methyl (1S,4aR,4bS,10aR)-3-azido-2-(2-ethoxy-2-oxoethyl)-2,4b,8,8,10a-pentamethyl-tetradecahydrophenanthrene-1-carboxylate (224)*

According to general procedure 2 from methyl *ent*-isocopalate **223** (30 mg, 0.09 mmol), ethyl iodoacetate (22 µL, 0.188 mmol), $PhSO_2N_3$ (51 mg, 0.28 mmol), $Bu_6Sn_2$ (71 µL, 0.14 mmol) and

DTBHN (0.5 mg, 0.0028 mmol). The reaction mixture was refluxed for 10 h and after purified by FC (pentane: EtOAc 95:5) afforded the azide **224** (22 mg, 55%) as a yellowish oil. $[\alpha]_D^{20} =$ 22.1° (*c*= 0.8, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2932, 2099, 1734, 1307, 1119, 1028. **$^1$H NMR** (300 MHz, $CDCl_3$) δ (ppm) 4.05 (*q*, *J*= 7.1 Hz, $CH_2$-24), 3.55 (*s*, $CH_3$-16), 2.64 (*dd*, *J*= 15.7, 6.0 Hz, $CH_2$-22), 2.38 (*m*, CH-12), 2.16 (*dd*, *J*= 15.9, 7.6 Hz, $CH_2$-22), 2.19 (*s*, CH-14), 1.66 (*s*, $CH_3$-17), 1.16 (*t*, *J*= 7.2 Hz, $CH_3$-25), 1.04 (*s*, $CH_3$-18), 0.74 (*s*, $CH_3$-21), 0.70 (*s*, $CH_3$-20), 0.69 (*s*, $CH_3$-19). **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ (ppm) 172.88, 172.13, 64.96, 60.58, 60.10, 56.84, 52.42, 51.35, 42.03, 41.94, 41.41, 39.49, 38.95, 37.11, 34.94, 33.31, 33.26, 23.20, 21.46, 21.30, 18.42, 17.92, 16.42, 16.04, 14.26. **HRMS (ESI)** calculated for $[C_{25}H_{41}N_3O_4]^+$: 448.3182; found 448.3170.

*Methyl (1S,3S,4aR,4bS,10aR)-3-((tert-butyldimethylsilyl)oxy)-4b,8,8,10a-tetramethyl-2-methylenetetradecahydrophenanthrene-1-carboxylate (226)*

To a solution of alcohol **225** (100 mg, 0.3 mmol) and imidazole (82 mg, 1.2 mmol) in DMF (3 mL) at 0°C was added *tert*-butyldimethylsilyl chloride (90 mg, 0.6 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried, concentrated. The crude was purified by column chromatography (pentane/EtOAC 98:2) to give the ether **226** (115 mg, 86%). **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.84 (*d*, *J*= 43.7 Hz, $CH_2$-16), 4.27 (*s*, CH-12), 3.61 (*s*, $CH_3$-21), 3.28 (*s*, CH-14), 1.00 (*s*, $CH_3$-17), 0.89 (*s*, $CH_3$-25), 0.84 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-20), 0.03 (*s*, $CH_3$-22), 0.00 (*s*, $CH_3$-23). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 172.23, 145.48, 109.35, 73.37, 57.37, 56.69, 51.70, 50.86, 41.98, 40.26, 39.99, 39.62, 37.20, 33.34, 33.28, 30.86, 25.81, 21.51, 18.68, 18.51, 18.11, 16.21, 14.30, -4.67, -5.10.

*Methyl (1S,3S,4aR,4bS,10aR)-2-azido-3-((tert-butyldimethylsilyl)oxy)-2-(3-ethoxy-3-oxopropyl)-4b,8,8,10a-tetramethyltetradecahydrophenanthrene-1-carboxylate (227)*

According to general procedure 2 from silyl **226** (100 mg, 0.22 mmol), ethyl iodoacetate (31 µL, 0.26 mmol), 3-$PySO_2N_3$ (121 mg, 0.66 mmol), $Bu_6Sn_2$ (166 µL, 0.33 mmol) and DTBHN (1 mg, 0.0051 mmol). The reaction mixture was refluxed for 12 h. The crude mixture was purified by column chromatography (pentane/EtOAc 98:2) afforded the mixture of 2 azides **227** (61 mg, 48%) ratio 7:3 according to $^1$H NMR. **IR** (ν, $cm^{-1}$): 2956, 2927, 2872, 2852, 2098, 1735, 1462, 1388, 1368, 1253, 1164, 1048, 834, 774. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.10 (*q*, *J*= 71. Hz, $CH_2$-24), 3.66 (*s*, $CH_3$-16), 2.98 (*s*, CH-12), 1.25 (*m*, $CH_3$-25), 1.17 (*s*, $CH_3$-18), 0.95 (*s*, $CH_3$-29), 0.91 (*s*, $CH_3$-21), 0.83 (*s*, $CH_3$-20), 0.78 (*s*, $CH_3$-19), 0.15 (*s*, $CH_3$-26), 0.08 (*m*, $CH_3$-

27). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) (major) 173.69, 172.08, 72.69, 66.83, 60.47, 57.40, 56.79, 51.25, 50.09, 42.08, 41.01, 39.48, 30.03, 37.01, 33.24, 29.56, 27.20, 26.52, 26.33, 25.89, 25.75, 21.31, 19.97, 18.45, 16.61, 16.31, 14.22, -3.00, -4.20. **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) (minor) 172.63, 172.59, 70.37, 64.73, 60.52, 59.09, 56.96, 51.12, 50.80, 42.14, 41.13, 39.98, 38.74, 37.25, 33.29, 28.89, 27.59, 26.01, 21.34, 18.49, 18.04, 16.01, 16.37, 14.19, -3.00, -4.20.

*Methyl (1S,3S,4aR,4bS,10aR)-2-azido-2-(3-ethoxy-3-oxopropyl)-3-hydroxy-4b,8,8,10a-tetramethyltetradecahydrophenanthrene-1-carboxylate (228)*

To a solution of azide **227** (92 mg, 0.16 mmol) in THF (3 mL) was added TBAF (125 mg, 0.48 mmol). The reaction mixture was stirred overnight at 0°C to room temperature. Upon completion, the solvent was removed under reduced pressure and the crude was purified by column chromatography (pentane/EtOAc 95:5) affording the azido-alcohol **228** (30 mg, 40%) as a white powder. $[a]_D^{20} = 8.05°$ (*c*= 0.9, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3428, 2938, 2101, 1717, 1377, 1171, 1017, 907. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.12 (*t*, *J*= 7.2 Hz, $CH_2$-24), 3.89 (*t*, *J*= 2.8 Hz, CH-12), 3.67 (*s*, $CH_3$-21), 3.00 (*s*, CH-14), 2.69-2.77 (*m*, $CH_2$-15), 2.29-2.47 (*m*, $CH_2$-22), 2.10-2.18 (*m*, $CH_2$-15), 1.25 (*t*, *J* = 7.1 Hz, $CH_3$-25), 1.18 (*s*, $CH_3$-16), 0.83 (*s*, $CH_3$-17), 0.81 (*s*, $CH_3$-19), 0.79 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.29, 172.06, 70.31, 68.26, 60.69, 58.01, 56.56, 51.52, 49.95, 41.94, 40.87, 39.42, 39.04, 36.84, 33.26, 33.24, 29.28, 26.34, 25.01, 21.25, 18.39, 17.95, 16.44, 16.24, 14.19.

*Methyl (1S,3S,4aR,4bS,10aR)-3-hydroxy-4b,8,8,10a-tetramethyl-5'-oxododecahydro-1H-spiro[phenanthrene-2,2'-pyrrolidine]-1-carboxylate (229)*

A solution of azide **228** (30 mg, 0.065 mmol) and 10% Pd/C (10% w/w) in dry EtOAc (2 mL) was stirred for 48 h at room temperature under $H_2$ (1 atm). The catalyst was filtered off, the solvent was removed under reduced pressure and the crude purified by FC ($CH_2Cl_2$/MeOH 95:5) gave lactam **229** (25 mg, quant.) as a colorless oil. $[a]_D^{20} = 35.4°$ (*c*= 1.17, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3361, 2935, 1730, 1688, 1456, 1369, 1202, 756. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 6.64 (*bs*,-NH), 3.73 (*s*, CH-12), 3.63 (*s*, $CH_3$-21), 3.04-3.14 (*m*, CH-15) 2.76 (*s*, CH-14), 2.35-2.65 (*m*, $CH_2$-22), 1.13 (*s*, $CH_3$-16), 0.86 (*s*, $CH_3$-17), 0.83 (*s*, $CH_3$-19), 0.81 (*s*, $CH_3$-18). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 177.64, 172.57, 72.60, 64.66, 57.02, 56.61, 51.21, 50.08, 41.97, 40.83, 39.57, 38.93, 36.84, 33.29, 30.45, 29.72, 26.10, 25.27, 21.30, 18.44, 17.91, 16.31, 15.74.

# 4. SYNTHESIS OF SOME TERPENOIDS *VIA* CATIONIC REARRANGEMENTS

The broad range of terpenoids is due to the tremendous diversity of isomerizations 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. 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 [185].

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

Verrucosins A **230** and B **231** are two acylglycerols isolated for the first time from *Doris verrucosa* mollusks collected in the Mediterranean Sea (Figure 4.1) [186, 187]. Diterpenoids **230** and **231** 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 [188]. 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 **230** and **231** has been previously suggested [189]. We elaborated a synthetic scheme for the synthesis of bicyclic framework of ent-verucosins via a cationic-induces rearrangement of available iso-copalic derivatives.

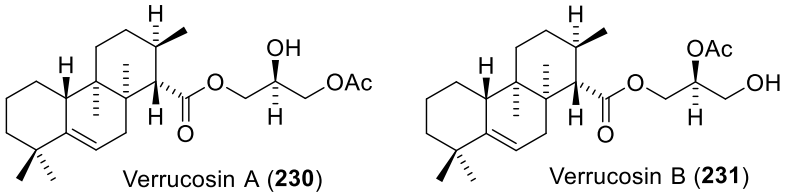



**Fig. 4.1. Natural verrucosins A and B.**

(-)-Sclareol **232** served as a starting compound, which was converted into the methyl ester of *ent*-isocopalic acid **223**, according to the known procedure [190, 191]. The latter compound was in turn transformed into the methyl ester of 12$\alpha$-hydroxy-*ent*-isocopal-13(16)-en-15-oic acid **225** and 12$\alpha$-hydroxy-*ent*-isocopal-13(14)-en-15-oic acid **233**, according to the reported two-step sequence [192]. Afterward, the mixture of alcohols **225** and **233** was treated

with 6N $H_2SO_4$ in dioxane, which led to the formation of some lactone **234** (37%) along with major unreacted $\Delta^{13,14}$ alcohol **233** and a minor amount of the rearranged compound **235** in 7% yield. According to NMR data, the most important signals of compound **234** are: in $^1$H NMR appeared as a multiplets at 5.71 ppm (CH-12), 4.64 ppm (metylene C-16) and 0.89 ppm (CH-5); and as a singlets of the methyls groups: 0.90 ppm (C-20), 0.84 ppm (C-17), geminal dimethyls at 0.88 ppm (C-18) and 0.83 ppm (C-19); and the methine C-14 as a broad singlet at 4.64 ppm. In the $^{13}$C NMR spectrum the $CH_3$-18 was registered at 33.4 ppm, $CH_3$-19 at 21.6 ppm, $CH_3$-20 at 15.3 ppm and $CH_3$-17 at 14.9 ppm, but the CH-12 at 121.0 ppm, $CH_2$-16 at 69.8 ppm, the quaternary C-13 at 129.6 ppm and C-15 at 175.4 ppm.

According to NMR analysis of rearranged alcohol **235**, the significant signals were registered in $^1$H spectrum at: 3.65 ppm ($CH_3$-21), 2.2 ppm (methine C-14), 1.16 ppm ($CH_3$-16), 1.10 ppm ($CH_3$-18), 0.87 ppm ($CH_3$-17), 0.84 ppm ($CH_3$-19) and 0.82 ppm ($CH_3$-20) a singlets; at 3.43 ppm ($CH_2$-12, with *J*= 4.4 Hz) as a doublet; the peaks in $^{13}$C spectrum were: 173.57 ppm for carbonyl group (C-15), 72.3 ppm for methane (C-12) and for methyl groups 51.2 ppm (C-21), 16.2 ppm (C-16), 21.6 ppm (C-17), 33.2 ppm (C-18), 21.3 ppm (C-19) and 16.3 ppm (C-20).

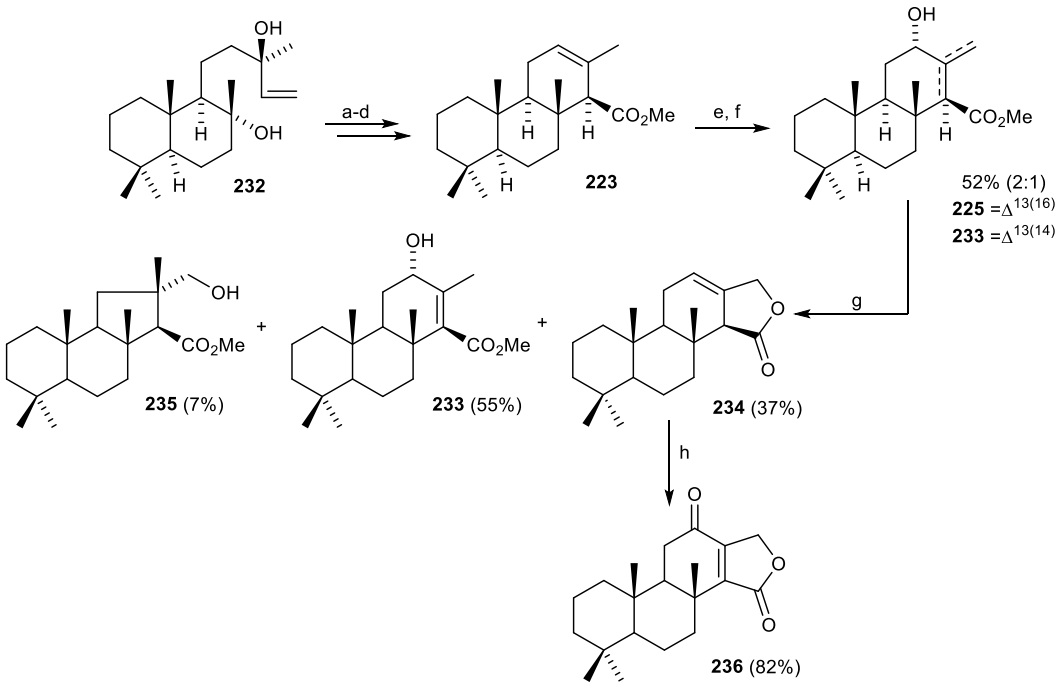



**Fig. 4.2. Isomerization of isocopalic diterpenes.**

*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 $^o$C, 15 min, then $Et_3N$, 92%; **e.** *m*-CPBA, $CH_2Cl_2$, 0 $^o$C, 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 $\gamma$-lactone **234** with sodium chromate led to spongiane $\alpha,\beta$-unsaturated keto-lactone **236** in 82% yield, functionalized in C-12 position [193]. According to the IR data of the keto-lactone **236** confirms the presence of the conjugated double bond (1688 $cm^{-1}$) and the carbonyl group of the ester group (1033, 1764 $cm^{-1}$). In the $^{1}H$ NMR spectrum, the singlet signals of the C-19 methyl groups appeared at 0.85 ppm, C-18 at 0.88 ppm, of the C-17 at 1.29 ppm, the C-5 at 0.93 ppm and the C-9 at 1.83 ppm as a doublet of the doublets, the methylene group C-16 at 4.83 ppm as a singlet. In the $^{13}C$ NMR spectrum of the compound 8 the methylene groups were registered for C-1 at 39.4 ppm, C-2 (17.9 ppm), C-3 (41.7 ppm), C-6 (18.2 ppm), C-7 (35.1 ppm), C-11 (35.2 ppm) and C-16 (67.3 ppm), the methyls at 33.1 ppm (C-18), 21.2 ppm (C-19), 19.2 ppm (C-17) and 15.9 ppm for C-20, for the trisubstituted carbons at 56.3 ppm (C-5) and 56.1 ppm (C-9), but for the tetrasubstituted carbons at 33.2 ppm(C-4), 37.5 ppm (C-8), 36.9 ppm (C-10), 196.9 ppm (C-12), 148.8 ppm (C-13), 152.5 ppm (C-14), and 170.9 ppm for the carbonyl group C-15.

The reaction of ester **225** 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 **234** in only 4% yield and compound **237** in 67% yield (Figure 4.4). According to elemental analysis, IR and NMR spectra, the major compound **237** was identified as a diterpenic diene ester with the molecular formula $C_{21}H_{32}O_2$. The NMR data of compound **237** were assigned (see Table 4.1) based on its 1D ($^{1}H$, $^{13}C$, DEPT-135) and 2D homo- ($^{1}H/^{1}H$ COSY-45, $^{1}H/^{1}H$ NOESY) and heteronuclear ($^{1}H/^{13}C$ HSQC and $^{1}H/^{13}C$ HMBC) correlation spectra (Figure 4.3).

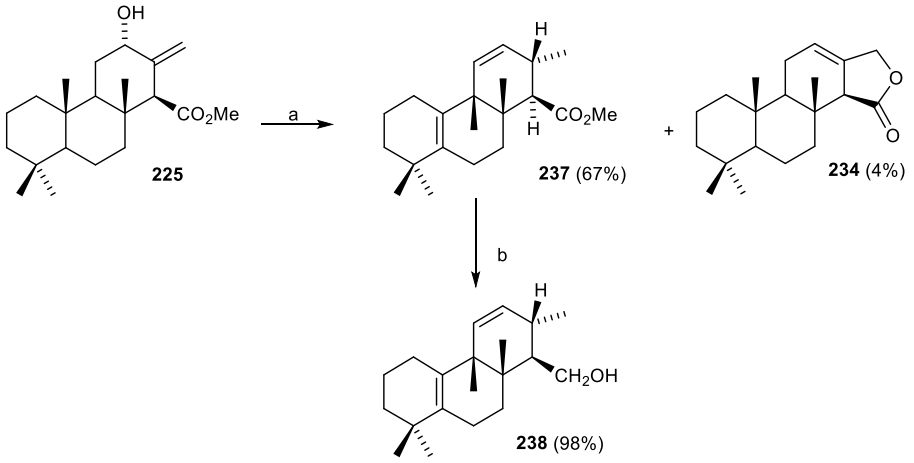



**Fig. 4.3. Isomerization of diterpenic alcohol 225.**

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

Thus, the $^{1}$H NMR spectrum displayed singlets of tertiary methyl groups: at 0.98 ppm (C-17) and 0.994 ppm (C-20), geminal dimethyl at 0.986 and 0.988 ppm, (C-18 and C-19), signals of one secondary methyl group at 0.88 ppm (C-16) that appears as a doublet of multiplets with *J* = 6.7 Hz due to splitting of CH-13, CH-12 and CH-14 nuclei, a downfield singlet of the methyl ester group at 3.69 ppm as well as deshielded signals of two $sp^2$ methines: 5.38 ppm (dd, *J*= 10.1; 1.2 Hz, CH-12) and 5.45 ppm (br. d, *J*= 10.1, CH-11). The assignment of signals that characterize methylene protons belonging both to ring A (complex splitting patterns $H_2$-1-$H_2$-2-$H_2$-3) and B (splitting patterns $H_2$-6-$H_2$-7) is depicted in Table 4.1, being to a certain degree impeded by couplings and signal overlapping.

**Table 4.1. $^{1}$H and $^{13}$C data of compound 237 in $CDCl_3$.**

| No, C | δ $^{1}$H; m/J, Hz | δ $^{13}$C; m | | δ $^{1}$H; m/J, Hz | δ $^{13}$C; m |
|---|---|---|---|---|---|
| $1_{ax}$ | 1.90; m | 27.1; t | 10 | - | 133.4; s |
| $1_{eq}$ | 2.00; m | | 11 | 5.45; br.d/10.1 | 133.5; s |
| 2 | 1.58; m | 20.0; t | 12 | 5.38; dd/10.1; 1.2 | 129.1; d |
| $3_{ax}$ | 1.36; td/12.3; 3.6 | 39.8; t | 13 | 2.48; m | 31.5; d |
| $3_{eq}$ | 1.44; dddd/12.5; 4.9; 3.3; 1.5 | | 14 | 2.48; m | 51.3; d |
| 4 | - | 33.9; s | 15 | - | 175.9; s |
| 5 | - | 131.5; s | 16 | 0.88; m | 19.9; q |
| $6_{ax}$ | 2.35; m | 20.8; t | 17 | 0.97; s | 18.7; q |
| $6_{eq}$ | 1.90; m | | 18 | 0.986; s | 27.9; q |
| $7_{ax}$ | 1.65; ddd/14.0; 12.5; 6.3 | 30.1; t | 19 | 0.988; s | 28.8; q |
| $7_{eq}$ | 1.23; dd/14.0; 6.3 | | 20 | 0.994; s | 22.3; q |
| 8 | - | 36.8; s | 21 | 3.69; s | 51.0; q |
| 9 | - | 42.7; s | | | |

The $^{13}$C NMR data (Table 4.1) exhibited twenty-one carbon signals, which were assigned by DEPT as six methyls, five $sp^3$ methylenes, two $sp^3$ and two $sp^2$ methines, three $sp^3$ and three $sp^2$, including one ester, quaternary carbons. The presence of two double bonds, one of which being disubstituted and another tetrasubstituted, was corroborated by the $^{13}$C NMR data [133.5 (C-11), 129.1 (C-12), 131.5 (C-5) and 133.4 ppm (C-10)]. The rearranged carbon framework of compound **237** becomes obvious with a detailed analysis of its HMBC spectrum. Thus, the observed correlations from both C-6 and C-1 to two $sp^2$ hybridized carbons (C-5, 131.5 ppm and C-10, 133.4 ppm) were indicative of $\Delta^{5,10}$ localization, which was also supported by the correlations of $CH_3$-19/C-5 and $CH_3$-18/C-5. The migration of the C-20 methyl from the C-10 to C-9 position was ascertained by the $CH_3$-20/C-10, $CH_3$-20/C-9,$CH_3$-20/C-11 and $CH_3$-20/C-8 cross-peaks in the HMBC spectrum, while the presence of the $\Delta^{11,12}$ function was especially proven by long-range correlations between $CH_3$-16/C-12, $CH_3$-20/C-11, CH-12/C-14, CH-11 and CH-12/C-9 and by mutual HMBC correlations as indicated in Figure 4.4.

During elucidation of the stereochemistry at the C-13 asymmetric center of compound **237** a problem emerged, caused by the overlapped signals of methines C-13 and C-14 that appeared in the $^{1}$H NMR spectrum as a multiplet centered at 2.48 ppm. In light of this, interpretation of its $^{1}$H–$^{1}$H NOESY spectrum only furnished inconclusive data for the identification of the configuration at C-13. Therefore, we decided to solve this problem by correlation of the NMR data of compound **237** with that of its reduction product, compound **238**. In the $^{1}$H NMR spectrum of compound **238** signals of the C-13 and C-14 nuclei were well-separated: 1.39 ppm (dt, *J*= 10.5, 3.6 Hz, CH-14$_{ax}$) and 2.03 ppm (m, *J*= 10.5, 7.0, 1.6, 1.3 Hz, CH-13$_{ax}$). The large coupling constant (10.5 Hz) between the vicinal methine protons under discussion demonstrated their *trans*-diaxial interaction, which was confirmed by molecular modeling. Finally, the (*R*) relative configuration at C-13 was deduced from the NOESY correlation between CH$_3$-17/CH-13 and the lack of CH$_3$-17/CH-14 correlation.

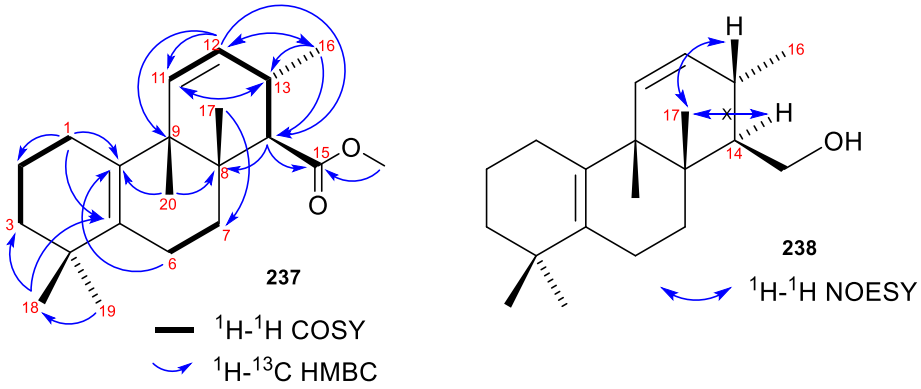



**Fig. 4.4. Key 2D correlations for the compounds 237 and 238.**

Based on these data, it was possible to confirm that the acid promoted isomerization of the methyl ester of 12$\alpha$-hydroxy-*ent*-isocopal-13(16)-en-15-oic **225** acid furnished a diene ester with a rearranged framework **237**. A plausible path for its formation involving the electrophilic isomerization of compound **225** is depicted in Figure 4.5.

Thus, after protonation of ester **225** carbocation A is formed, which through a 1,3-hydride shift (H-11$\beta$ moves to C-13) generates carbocation B. A second hydride shift forms carbocation C, which after angular methyl migration and dehydration forms carbocation D, which is stabilized by deprotonation to afford the methyl ester of (8*S*,9*R*,13*R*,14*R*)-4,4,8,9,13-pentamethyl-20(10-9)-abeo-*ent*-isocopal-5(10),11(12)-dien-15-oic acid **237**. The fact that this mechanistic explanation relies upon a rare 1,3-hydride shift [194] forced us to consider other alternatives. For example, an acid-induced dehydration could compete with the formation of intermediate A and bring about the formation of a diene **239**. However, subsequent re-

protonation and rearrangement would lead to a trisubstituted compound **240**, the isomer of **237**. Its isomerization to a less favored disubstituted olefin proceeding with total facial selectivity of the protonation at C-13 seems less probable. There are also similar reports on terpene synthesis which have been shown to occur *via* such rearrangements. For example, Urones and collaborators postulated the formation of a carbonium ion very similar to A upon treatment of the related epoxide with a Lewis acid. Its subsequent conversion involved a skeletal rearrangement *via* ring contraction [195].

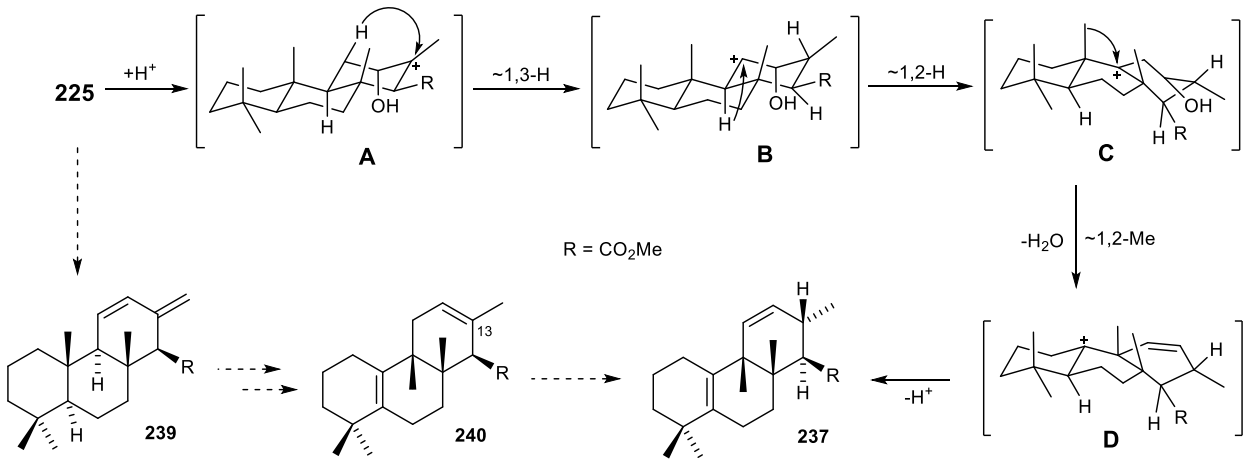



**Fig. 4.5. Proposed reaction mechanism for the acid-promoted isomerization of 225 into 237.**

Taking into consideration the above mentioned statement, we can synthesize the diene **237** from epoxide **241** in the same conditions of the reaction as we did with alcohol **225** (Figure 4.6). In this case, the yield is lower than above, but the yield of $\gamma$-lactone **234** 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 **241** in 2-nitropropane with 5 equiv. $FSO_3H$ in mild conditions at -78$^oC$, led to the formation of the aldehyde **242** (70% yield) and compound **243** (5% yield) in only 30 min. The aldehyde **242** was also synthesized from epoxide **241** by Basabe et. al [199], 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 **241** [196, 197] under mild conditions provided the new compound **243** with a very interesting rearranged skeleton, which was not observed in the reaction with $BF_3$*$Et_2O$.

According to the NMR data of aldehyde **242**, the $^1H$ NMR spectrum displayed singlets of tertiary methyl groups: 1.34 ppm (C-16), 0.87 ppm (C-17) and 0.82 ppm (C-20), germinal dimethyls at 1.11 ppm and 0.84 ppm (C-18 and C-19) and methyl for the ester group at 3.61 ppm (C-21), and the methine for the aldehyde was registered at 9.45 ppm (C-12) as a singlet too. The

$^{13}$C NMR data exhibited twenty-one carbon signals, which were assigned by DEPT as six methylenes, four methines, six methyls and five quaternary carbons. The methyl groups were registered at: 20.65 ppm (C-16), 16.76 ppm (C-17), 33.49 ppm (C-18), 21.24 ppm (C-19), 15.79 ppm (C-20) and 50.99 ppm (C-21); quaternary carbon from ester group at 171.92 ppm and aldehyde at 202.81 ppm.

The structure of the other compound **243** with the hyrtiosane skeleton was determined according to NMR data and IR spectroscopy. The significant signals were registered in $^{1}$H spectrum at: 3.53 ppm (C-21), 1.33 ppm (C-16), 0.835 ppm (C-17), 0.80 ppm (C-20) the methyl groups and at 1.11 ppm (C-18), 0.83 ppm (C-19) the geminal dimethyl groups; the methines C-12 at 4.90 ppm and C-14 at 2.15 ppm as a singlets. However, in the carbon spectrum, the significant peaks were identified at: 15.79 ppm (C-20), 24.13 ppm (C-17) and 28.16 ppm (C-16) for tertiary methyls; 33.39 ppm (C-18) and 21.29 ppm (C-19) for geminal dimethyl and 58.20 ppm (C-21) for the methoxy group; 175.65 ppm (C-15) for quaternary carbon and 111.58 ppm (C-12).

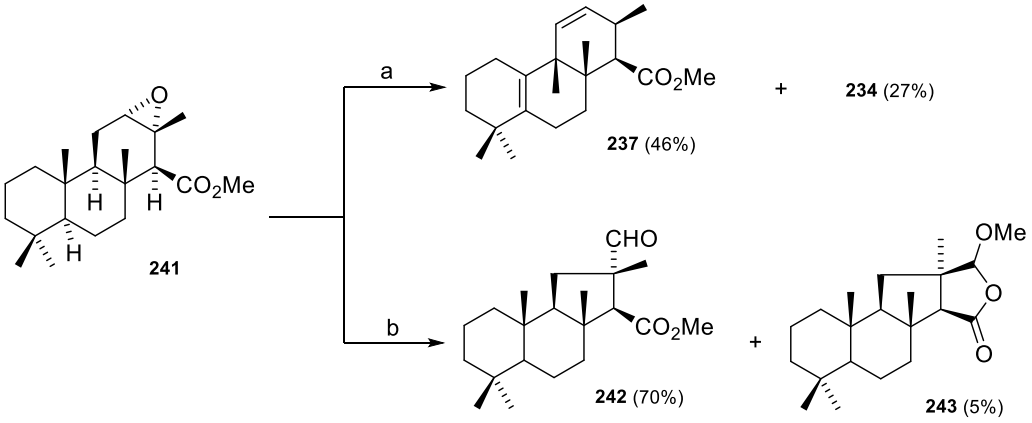



**Fig. 4.6. Skeletal rearrangements of epoxide 241 under acidic conditions.**
*Reagents and conditions:* **a.** *p*-TsOH/$CHCl_3$, Δ, 3 h; **b.** $FSO_3H$, 2-$NO_2$Pr, MeOH, -78 $^{o}$C.

### 4.2. The acid-induced rearrangement of homodrimanic epoxide

Terpenoids of the halimanic structure are widely distributed in natural sources [198]. Biosynthetically, they are considered intermediates between labdanes and clerodanes [199], since they all arise from enzymatic cyclization of geranylgeranyl diphosphate to a labda-13-en-8-yl diphosphate cation, which can then be deprotonated to give a labdadienyl diphosphate or can undergo rearrangements to afford halimane and clerodane (Figure 4.7).

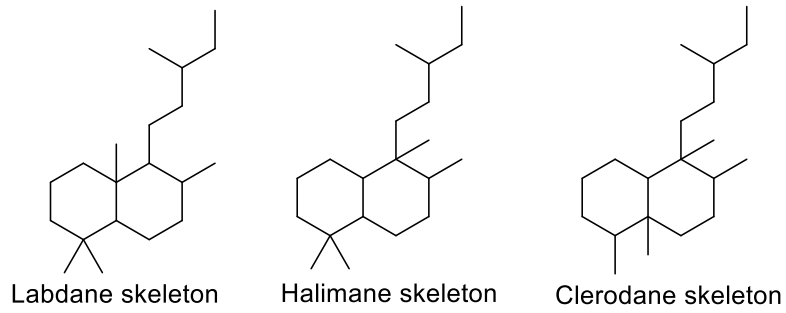



**Fig. 4.7. Terpenes with labdanic, halimanic and clerodanic skeletons.**

The synthesis of austrodoric acid, a perhydrindanic sesquiterpenoid isolated from a *Austrodoris Querguelensis* [200] has been reported starting from homodrimanic epoxide **246** [200]. When we used pillared clay for the rearrangement of **112** we obtained the same compounds as in [201], but with a totally opposite selectivity. The prevailing rearrangement products **247**-**249** represented the bicyclic fragment of halimanes (Fig. 4.8).

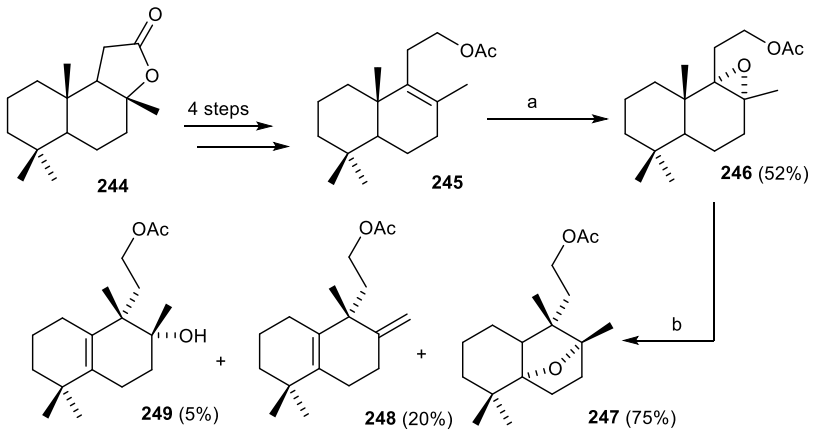



**Fig. 4.8. Isomerization of homodrimane epoxide 246.**

*Reagents and conditions:* **a.** *m*-CPBA, $CH_2Cl_2$, 0 $^oC$, 12 h; **b.** pillared clay, 2-$NO_2$Pr, 100 $^oC$, 2 h.

The starting material for the rearrangement reaction can be easily synthesized from commercially available sclareolide **244** *via* a short synthetic sequence [200]. The tertrasubstituted acetate **245** was treated with *meta*-chloroperbenzoic acid in dichloromethane and led to the formation of epoxide **246** in 52% yield. The isomerization of epoxide **246** led to the formation of a mixture of several compounds. The reaction with Al-H-Na-Lar pillared clay [202] as a heterogeneous catalyst, on heating in 2-nitropropane at 100 $^oC$ results in a substantial prevalence of the oxide **247** (75% yield), over olefin **248** (20%) and alcohol **249** (5%) (Figure 4.8). The structural assignment was performed based on extensive NMR experiments on pure compounds (see Table 4.2), as well as based on IR spectroscopy and MS spectrometry data.

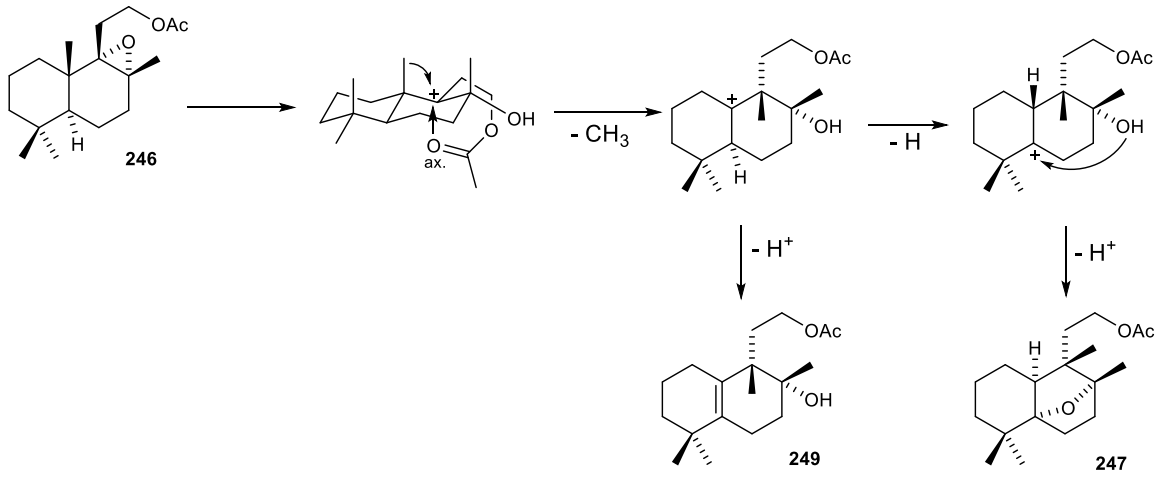



**Fig. 4.9. Proposed mechanism of epoxide 246 opening.**

**Table 4.2. $^{1}$H and $^{13}$C of compounds 247, 248 and 249.**

| | **247** | | **248** | | **249** | |
|---|---|---|---|---|---|---|
| No, C | δ $^{1}$H; m/J, Hz | δ $^{13}$C; m | δ $^{1}$H; m/J, Hz | δ $^{13}$C; m | δ $^{1}$H; m/J, Hz | δ $^{13}$C; m |
| 1 | n.a. | 24.73; t | 2.02; m<br>2.25; m | 26.97; t | 1.93; m | 26.44; t |
| 2 | n.a. | 22.43; t | 1.66; m | 19.32; t | 1.58; m | 19.78; t |
| 3 | n.a. | 37.91; t | 1.44; m | 39.15; t | 1.40; m | 39.70; t |
| 4 | - | 35.60; s | - | 34.67; s | - | 34.28; s |
| 5 | - | 90.29; s | - | 140.97; s | - | 134.85; s |
| 6 | n.a. | 23.22; t | 2.14; m | 21.86; t | 2.09; m | 22.71; t |
| 7 | n.a. | 34.71; t | 1.45; m<br>1.55; m | 34.94; t | 1.74; m<br>1.59; m | 33.42; t |
| 8 | - | 88.73; s | - | 125.96; s | - | 73.91; s |
| 9 | - | 42.23; s | - | 35.95; s | - | 44.65; s |
| 10 | 1.79; m | 48.98; d | - | 151.94; s | - | 132.00; s |
| 11 | n.a. | 39.40; t | 1.69; m | 37.04; t | 1.89; m<br>1.77; m | 35.35; t |
| 12 | 4.06; ddd/12; 9.4; 5.8<br>4.14; ddd/10.4; 9.3; 6.4 | 61.97; t | 4.00; dt/11.1; 7.6; 1.0<br>4.10; dt/10.9; 7.6; 1.0 | 62.09; t | 4.11; dt/10.5; 5.1; 1.0<br>4.21; dt/10.5; 6.4; 1.0 | 63.67; t |
| 13 | 1.27; s | 16.69; q | 4.85; s<br>5.02; s | 105.26; t | 1.13; s | 24.41; q |
| 14 | 0.78; s | 17.49; q | 1.10; s | 26.66; q | 0.98; s | 20.71; q |
| 15 | 1.01; s | 26.00; q | 1.04; s | 28.16; q | 0.96; s | 28.50; q |
| 16 | 1.10; s | 21.36; q | 1.03; s | 27.96; q | 0.99; s | 28.42; q |
| 17 | - | 171.24; s | - | 171.09; s | - | 171.15; s |
| 18 | 2.04; s | 21.12; q | 2.04; s | 21.05; q | 2.02; s | 21.15; q |

Opening of the epoxy ring can follow two possible directions, either at C-8 or at C-9. The isomerization reaction of the epoxide **246** at C-9 is described in Figure 4.9. Based on the direct substituent character on these atoms, the stability of all resulting carbenium ions is relatively equal. But if the participation of the lateral chain acetate (AcO) group is considered one of them,

some differences can be observed. The main factors that cause the stabilization effect of the lateral AcO group are the size and the position of the carbonyl atom in the transition state. According to the resulting products, the axial position of the oxygen atom should be considered favorable. From this perspective, isomerization of epoxide **246** and epoxide opening at C-9 leads to the formation of the compounds with halimane skeleton and is favored by the six-membered transition state.

### 4.3. Conclusions to chapter 4

To conclude, we show in this chapter functionalization of natural compounds *via* cationic reactions, more exactly through the isomerization or/and skeleton rearrangements [203].

On the isomerization of several terpenoids under acidic conditions, nine new compounds with halimane, hyrtiosane and verrucosin skeleton were synthesized. The reaction with a solid heterogeneous catalyst provides a biomimetic protocol for the efficient synthesis of the halimanic bicyclic fragment in optically active form. Pillared clay showed a remarkable ability to selectively promote this challenging transformation.

As well, the first biomimetic synthesis of the diene diterpenoid **237-**a with the *ent*-verrucosin A/B skeleton has been performed by electrophilic isomerization of methyl 12$\alpha$-hydroxy-*ent*-isocopal-13(16)-en-15-oate **225**. The presented method opens the possibility of the synthesis of bioactive diterpenoids possessing this unique rearranged framework. The most interesting point of this isomerization reaction is that the *ent*-verrucosin was alternatively obtained from methyl *ent*-isocopal-12$\alpha$-13$\alpha$-epoxy-15$\beta$-oic acid **241**.

### 4.4. Experimental part

To a solution of the mixture of alcohol **225** and **233** (774 mg, 2.31 mmol) in dioxane (127 mL) was added $H_2SO_4$ 6N (11.3 mL) and was refluxed for the 4 h. The reaction mixture was cooled and extracted with $Et_2O$, washed with brine, water and dried on $Na_2SO_4$. The crude was purified by column chromatography (pentane/EtOAc 90:10) gave the lactone **234** (286 mg, 37%), alcohol **233** (426 mg, 55%) and rearranged alcohol **235** (8 mg, 7%).

*(3aS,3bR,9aS)-3b,6,6,9a-tetramethyl-3a,3b,4,5,5a,6,7,8,9,9a,9b,10-dodecahydrophenanthro[1,2-c]furan-3(1H)-one (234)*

$[\alpha]_D^{25}$ = +3.94° (c= 2.23, $CHCl_3$), **IR** ($\nu$, $cm^{-1}$): 1003, 1135, 1763, 2927. **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ (ppm) 5.71 (*m*, CH-12), 4.64 (*m*, $CH_2$-16), 2.76 (*bs*, CH-14), 2.54 (*dd*, *J*= 10.2, 3.1 Hz, $CH_2$-$7_{eq}$), 2.13 (*dm*, *J*= 18.5 Hz, $CH_2$-$11_{eq}$), 1.97 (*tm*, *J*= 14.2 Hz, $CH_2$-$11_{ax}$), 1.60 (*m*, $CH_2$-2 and

$CH_2$-$1_{eq}$), 1.38 (*m*, $CH_2$-6 and $CH_2$-$3_{eq}$), 1.34 (*m*, $CH_2$-$7_{ax}$), 1.29 (*m*, CH-9), 1.13 (*td*, *J*= 13.5, 4.4 Hz, $CH_2$-$3_{ax}$), 0.90 (*s*, $CH_3$-20), 0.89 (*m*, CH-5), 0.88 (*s*, $CH_3$-18), 0.84 (*s*, $CH_3$-17), 0.84 (*m*, $CH_2$-$1_{ax}$), 0.83 (*s*, $CH_3$-19). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 175.4 (*s*, C-15), 129.6 (*s*, C-13), 121.0 (*d*, C-12), 69.8 (*t*, C-16), 56.7 (*d*, C-5), 54.3 (*d*, C-9), 54.2 (*d*, C-14), 41.8 (*t*, C-3), 40.0 (*t*, C-7), 39.8 (*t*, C-1), 37.5 (*s*, C-10), 34.5 (*s*, C-8), 33.4 (*q*, C-18), 33.2 (*s*, C-4), 22.5 (*t*, C-11), 21.6 (*q*, C-19), 18.4 (*t*, C-6), 18.3 (*t*, C-2), 15.3 (*q*, C-20), 14.9 (*q*, C-17).

*Methyl (3S,4bS,10aR)-3-hydroxy-2,4b,8,8,10a-pentamethyl-3,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene-1-carboxylate (233)*

$[\alpha]_D^{25}$ = -30.8° (c= 1.34, $CHCl_3$). **IR** (ν, $cm^{-1}$): 1018, 1196, 1218, 1725, 2924, 3231. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.08 (*td*, *J*= 8.4, 1.3 Hz, CH-12), 3.73 (*s*, $CH_3$-21), 2.11 (*qd*, *J*= 12.5, 7.2, 1.3 Hz, $CH_2$-$11_{eq}$), 1.68 (*d*, *J* = 0.72, $CH_3$-16), 1.45 (*m*, $CH_2$-$11_{ax}$), 1.24 (*s*, $CH_3$-17), 0.87 (*s*, $CH_3$-20), 0.84 (*m*, CH-5), 0.83 (*s*, $CH_3$-18), 0.80 (*s*, $CH_3$-19). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 170.3 (*s*, C-15), 141.4 (*s*, C-14), 133.0 (*s*, C-13), 72.3 (*d*, C-12), 56.3 (*d*, C-5), 54.1 (*d*, C-9), 51.2 (*q*, C-21), 42.0 (*t*, C-3), 39.5 (*t*, C-1), 38.2 (*t*, C-7), 38.1 (*s*, C-8), 37.2 (*s*, C-10), 33.23 (*s*, C-4), 33.2 (*q*, C-18), 28.6 (*t*, C-11), 21.6 (*q*, C-17), 21.3 (*q*, C-19), 18.4 (*t*, C-2), 18.3 (*t*, C-6), 16.3 (*q*, C-20), 16.2 (*q*, C-16).

*Methyl (2S,3S,3aR,9aS)-2-(hydroxymethyl)-2,3a,6,6,9a-pentamethyldodecahydro-1H-cyclopenta[a]naphthalene-3-carboxylate (235)*

$[\alpha]_D^{25}$ = -10.8° (c= 0.6, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3531, 2927, 1736, 1457, 1438, 1387, 1282, 1271, 1193, 1165, 1027, 910. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.65 (*s*, $CH_3$-21), 3.43 (*d*, *J*= 4.4 Hz, $CH_2$-12), 2.2 (*s*, CH-14), 1.16 (*s*, $CH_3$-16), 1.10 (*s*, $CH_3$-18), 0.87 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.82 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 173.57, 73.61, 62.27, 60.31, 57.38, 51.02, 45.28, 44.05, 42.45, 40.94, 40.27, 36.81, 34.28, 33.50, 33.06, 23.09, 21.26, 18.85, 18.30, 16.48, 15.77.

To a solution of lactone **234** (77 mg, 0.25 mmol) in benzene (1.5 mL) were added AcOH (0.3 mL), $Ac_2O$ (0.3 mL) and $Na_2Cr_2O_4$ (86 mg). The reaction mixture was stirred for 48 h at 80°C. After the mixture was diluted with solution 5% KOH (50 mL), extracted with $Et_2O$, washed with brine and water, dried on $Na_2SO_4$ and concentrated. The crude was purified by column chromatography (pentane/EtOAC 97:3) to give the keto-lactone **236** (63mg, 82%).

*(3bR,9aS)-3b,6,6,9a-tetramethyl-1,3b,4,5,5a,6,7,8,9,9a,9b,10-dodecahydrophenanthro[1,2-c]furan-3,11-dione (236)*

$[\alpha]_D^{17}$ = -13.37° (c= 0.47, $CHCl_3$). **IR** (ν, $cm^{-1}$): 1033, 1689, 1764. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.83 (*s*, $CH_2$-16), 2.72 (*m*, $CH_2$-$7_{eq}$), 2.62 (*dd*, *J*= 3.2, 17.4 Hz, $CH_2$-$11_{eq}$), 2.47 (*dd*, *J*= 14.1, 17.4 Hz, $CH_2$-$11_{ax}$), 1.83 (*dd*, *J*= 3.2, 14.0 Hz, CH-9), 1.74 (*m*, $CH_2$-2), 1.63 (*m*, $CH_2$-$1_{eq}$ and $CH_2$-$6_{eq}$), 1.47 (*m*, $CH_2$-$6_{ax}$ and $CH_2$-$7_{ax}$), 1.42 (*m*, $CH_2$-$3_{eq}$), 1.29 (*s*, $CH_3$-17), 1.15 (*m*, $CH_2$-$3_{ax}$), 0.97 (*s*, $CH_3$-20), 0.93 (*dd*, *J*= 12.3, 2.0 Hz, CH-5), 0.88 (*s*, $CH_3$-18), 0.86 (*m*, $CH_2$-$1_{ax}$), 0.85 (*s*, $CH_3$-19). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 196.9 (*s*, C-12), 170.9 (*s*, C-15), 152.5 (*s*, C-14), 148.8 (*s*, C-13), 67.3 (*t*, C-16), 56.3 (*d*, C-5), 56.1 (*d*, C-9), 41.7 (*t*, C-3), 39.4 (*t*, C-1), 37.5 (*s*, C-8), 36.9 (*s*, C10), 35.2 (*t*, C-11), 35.1 (*t*, C-7), 33.2 (*s*, C-4), 33.1 (*q*, C-18), 21.2 (*q*, C-19), 19.2 (*q*, C-17), 18.2 (*t*, C-6), 17.9 (*t*, C-2), 15.9 (*q*, C-20).

To a solution of alcohol **225** (95 mg, 0.28 mmol) in $CHCl_3$ (35 mL) was added pTSA (145 mg, 0.84 mmol). The reaction mixture was refluxed for 4 h and extracted with $CHCl_3$, washed with brine, water, dried and concentrated. The crude was purified by column chromatography (pentane/EtOAc 99:1) to give diene **237** (64 mg, 67%) and *γ*-lactone **234** (4 mg, 4%).

*Methyl (1R,2R,4aR,10aS)-2,4a,8,8,10a-pentamethyl-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthrene-1-carboxylate (237)*

$[\alpha]_D^{25}$ = 37.7° (c= 1.33, $CHCl_3$). IR (ν, $cm^{-1}$): 1164, 1732. Elemental analysis for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; found: C, 79.81; H, 10.14. $^1$H and $^{13}$C NMR see Table 4.1.

To a solution of ester **237** (10 mg, 0.032 mmol) in anhydrous THF (5 mL) was treated with $LiAlH_4$ (15 mg, 0.40 mmol) under stirring. After 3 h at reflux, the reaction was cooled and quenched with ethyl acetate (0.1 mL). The reaction product was subsequently treated with a 10% $H_2SO_4$ solution (2 mL), extracted with $Et_2O$ and washed with brine, sat. $NaHCO_3$ solution and brine, dried, concentrated. The crude product was purified by column chromatography (pentane/EtOAc 99:1) to give alcohol **238** (9 mg, 98%).

*((1R,2S,4aR,10aS)-2,4a,8,8,10a-pentamethyl-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthren-1-yl)methanol (238)*

Colorless viscous oil. $[a]_D^{25}$ = 31.5 (c= 0.61, $CHCl_3$). **IR** (ν, $cm^{-1}$): 1360, 1460, 2925. 3375. **$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 5.35 (*dd*, *J*= 10.1, 1.3 Hz, CH-11), 5.31 (*dd*, *J*= 10.1, 1.6 Hz, CH-12), 3.82 (*dd*, *J*= 11.5, 3.8 Hz, $CH_2$-$15_B$), 3.66 (*dd*, *J*= 11.5, 3.3 Hz, $CH_2$-$15_A$), 2.03 (*m*, *J*=

10.5, 7.0, 1.6, 1.3 Hz, CH-13), 1.87 (*m*, $CH_2$-1 and $CH_2$-6), 1.63 (*ddd*, *J*= 14.0, 5.9, 1.7 Hz, $CH_2$-$7_{eq}$), 1.55 (*m*, *J*= 14.0, 12.6, 5.9 Hz, $CH_2$-$7_{ax}$), 1.47 (*m*, $CH_2$-2), 1.43 (*br s*, OH), 1.39 (*dt*, *J*= 10.5, 3.6 Hz, CH-$14_{ax}$), 1.36 (*dddd*, *J*= 12.5, 5.1, 3.3, 1.3 Hz, $CH_2$-$3_{eq}$), 1.26 (*td*, *J*= 12.5, 3.3 Hz, $CH_2$-$3_{ax}$), 0.99 (*d*, *J*= 7.0 Hz, $CH_3$-16), 0.91 (*s*, $CH_3$-18), 0.907 (*s*, $CH_3$-20), 0.86 (*s*, $CH_3$-19), 0.75 (*s*, $CH_3$-17). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 134.6 (*d*, C-10), 133.3 (*s*, C-11), 131.2 (*s*, C-5), 130.6 (*d*, C-12), 62.9 (*s*, C-15), 45.0 (*d*, C-14), 43.3 (*s*, C-9), 39.8 (*t*, C-3), 36.4 (*s*, C-8), 33.9 (*s*, C-4), 31.1 (*d*, C-13), 28.9 (*q*, C-19), 28.6 (*t*, C-7), 27.8 (*q*, C-18), 27.2 (*t*, C-1), 22.5 (*q*, C-20), 21.2 (*t*, C-6), 20.2 (*q*, C-16), 20.0 (*t*, C-2), 19.6 (*q*, C-17).

To a solution of epoxide **241** (114 mg, 0.34 mmol) in $CHCl_3$ (22 mL) was added pTSA (210 mg, 1.22 mmol). The reaction mixture was refluxed for 4 h and extracted with $CHCl_3$, washed with sat. $NaHCO_3$ solution, brine, dried and concentrated. The crude was purified by column chromatography (pentane/EtOAc 99:1) to give diene **237** (52 mg, 46%) and γ-lactone **234** (31 mg, 27%).

To a solution of epoxide **241** (100 mg, 0.15 mmol) in $^{i}PrNO_2$ (0.5 mL) was added $FSO_3H$ (0.04 mL) at -78°C. The reaction was stirred for 30 min and then quenched with MeOH (0.3 mL). The mixture was extracted with $Et_2O$ and water, drying on $Na_2SO_4$ and concentrated. The crude was purified by column chromatography (pentane/EtOAc 95:5) to give the aldehyde **242** (70 mg, 70%) and furanolactone **243** (5 mg, 5%).

*Methyl (2S,3S,3aR,9aS,9bR)-2-formyl-2,3a,6,6,9a-pentamethyldodecahydro-1H-cyclopenta[a]naphthalene-3-carboxylate (242)*

$[a]_D^{25}$ = -11.07 (c= 1.2, $CHCl_3$). **IR** (ν, $cm^{-1}$): 3392, 2934, 1727, 1457, 1382, 1359, 1160, 1024, 895. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 9.45 (*s*, CH-12), 3.61 (*s*, $CH_3$-21), 2.79 (*s*, CH-14), 1.34 (*s*, $CH_3$-16), 1.11 (*s*, $CH_3$-18), 0.87 (*s*, $CH_3$-17), 0.84 (*s*, $CH_3$-19), 0.82 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 202.81 (*s*, C-12), 171.92 (*s*, C-15), 59.94 (*d*, C-14), 57.73 (*d*, C-9), 57.17 (*d*, C-5), 52.77 (*s*, C-13), 50.99 (*q*, C-21), 45.72 (*s*, C-8), 42.32 (*t*, C-3), 40.59 (*t*, C-7), 40.06 (*t*, C-1), 36.95 (*s*, C-10), 33.49 (*q*, C-18), 33.08 (*t*, C-11), 32.98 (*s*, C-4), 21.24 (*q*, C-19), 20.65 (*q*, C-16), 18.82 (*t*, C-2), 18.22 (*t*, C-6), 16.76 (*q*, C-17), 15.79 (*q*, C-20).

*(6aR,6bS,9aR,10aR,10bS)-9-methoxy-4,4,6a,9a,10b-pentamethyltetradecahydro-7H-benzo[4,5]indeno[1,2-c]furan-7-one (243)*

$[a]_D^{25}$ = -77.9 (c= 0.7, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2925, 2868, 2337, 1766, 1457, 1387, 1174, 1132, 973. **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 4.90 (*s*, CH-12), 3.53 (*s*, $CH_3$-21), 2.15 (*s*, CH-14),

1.33 (*s*, $CH_3$-16), 1.08 (*s*, $CH_3$-18), 0.835 (*s*, $CH_3$-17), 0.830 (*s*, $CH_3$-19), 0.80 (*s*, $CH_3$-20). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ (ppm) 175.65 (*s*, C-15), 111.58 (*d*, C-12), 64.59 (*d*, C-14), 60.15 (*d*, C-9), 58.20 (*q*, C-21), 56.41 (*d*, C-5), 47.73 (*s*, C-13), 46.31 (*s*, C-8), 42.28 (*t*, C-3), 40.03 (*t*, C-1), 37.14 (*s*, C-10), 36.17 (*t*, C-7), 33.39 (*q*, C-18), 33.02 (*s*, C-4), 30.61 (*t*, C-11), 28.16 (*q*, C-16), 24.13 (*q*, C-17), 21.29 (*q*, C-19), 18.82 (*t*, C-2), 18.34 (*t*, C-6), 15.79 (*q*, C-20).

To a solution of acetate **245** (100 mg, 0.36 mmol) in dry $CH_2Cl_2$ (2 mL) was added m-CPBA (125 mg, 0.72 mmol) at 0$^o$C. After stirring for 1 h at 0$^o$C, the reaction mixture was extracted with $Et_2O$, quenched with $Na_2S_2O_3$ (5%), washed with $NaHCO_3$ solution and brine, dried over $Na_2SO_4$. The crude was purified by column chromatography (pentane/EtOAc 90:10) to give the epoxide **246** in 52% yield.

*2-((1aR,7aS,7bS)-1a,4,4,7a-tetramethyloctahydronaphtho[1,2-b]oxiren-7b(1aH)-yl)ethyl acetate (246)*

**$^1$H NMR** (400 MHz, $CDCl_3$) δ (ppm) 3.95 (*t*, $CH_2$-11, *J*= 8.2 Hz), 1.91 (*s*, $CH_3$-13), 1.11 (*s*, $CH_3$-14), 0.87 (*s*, $CH_3$-17), 0.71(*s*, $CH_3$-16), 0.67 (*s*, $CH_3$-15) [201].

To a solution of epoxyacetate **246** (88 mg, 0.3 mmol) in 2-nitropropane (8 mL) was added Al-H-Na-Lar pillared clay (300 mg) and stirred for 2 h at 100 $^o$C. The solid catalyst was decanted and washed with $Et_2O$. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography (pentane/EtOAc 95:15) provided acetate **247** (66 mg, 75%), **248** (17 mg, 20%) and **249** (4.5 mg, 5%).

*2-((1S,2R,4aS)-1,2,5,5-tetramethyloctahydro-2H-2,4a-epoxynaphthalen-1-yl)ethyl acetate (247)*
Colorless viscous liquid; $[\alpha]_D^{25}$= 23.03 (c= 0.33, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2967, 2930, 2870, 1742, 1365, 1238, 1074, 1034, 854. NMR: see Table 4.2. **EIMS**: m/z (%) = 294 (15) [M+], 276 (2), 234 (10), 219 (10), 207 (60), 179 (70), 161 (60), 149 (20), 133 (25), 119 (50), 107 (55), 93 (40), 79 (35), 67 (25), 55 (25), 43 (100). Elemental analysis calculated for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; found: C, 73.35; H, 10.08.

*(R)-2-(1,5,5-trimethyl-2-methylene-1,2,3,4,5,6,7,8-octahydronaphthalen-1-yl)ethyl acetate (248)*
Colorless viscous liquid; $[\alpha]_D^{25}$= 54.3 (c= 0.35, $CHCl_3$). **IR** (ν, $cm^{-1}$): 2925, 1742, 1460, 1364, 1234, 1034, 880. NMR: see Table 4.2. **EIMS**: m/z (%) = 276 (10) [M+], 261 (2), 216 (10), 202 (30), 190 (50), 175 (100), 159 (15), 145 (20), 131 (20), 119 (45), 105 (20), 91 (20), 77 (10), 55 (10), 43 (20). Elemental analysis calculated for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; found: C, 78.23; H, 10.20.

*2-((1S,2R)-2-hydroxy-1,2,5,5-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-yl)ethyl acetate (249)*

Colorless viscous liquid; $[\alpha]_D^{25}$= 34.4 (c= 0.25, $CHCl_3$). **IR** ($\nu$, $cm^{-1}$): 3460, 2927, 1737, 1461, 1364, 1239, 1142, 1082, 1031, 964, 913. NMR: see Table 4.2. **EIMS**: m/z (%) = 294 (1) [M+], 276 (2), 261 (1), 234 (10), 219 (7), 201 (15), 189 (45), 175 (10), 161 (15), 145 (7), 133 (15), 119 (100), 105 (15), 91 (15), 77 (7), 55 (7), 43 (20). Elemental analysis calculated for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; found: C, 73.35; H, 10.15.

## 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 15$\alpha$-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 15$\alpha$-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. Carbohydrogenation of methyl 15$\alpha$-hydroxy-*ent*-kaur-16-en-19-oate allowed an efficient synthesis of C-17 alkylated derivatives, including fluoroalkylated products, which showed a simultaneous dehydration under reaction conditions to generate an endocyclic double bond [chapter 2, § 2.3].

4. 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].
5. 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].
6. 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].
7. The synthesis of 13-*epi*-manoyl oxide fluorinated derivatives has been performed for the first time basing on free radical carbohydrogenation [chapter 3, § 3.4].
8. 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].
9. Broadening the structural diversity of available isocopalic compounds has been demonstrated on the example of cationic isomerization of methyl isocopalate **225**, which led under acidic conditions to the one-step generation of tricyclic verucosin skeleton **237** [chapter 4, § 4.1].
10. 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].
11. 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 crystallographic 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 **135** 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 **143** 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, a

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.

Approval of scientific results of the current work has been ensured by reporting at nine international or national scientific conferences with posters and oral communications. The following can be mentioned: The XXIVth session of scientific communications (România, **2013**); The 55th International Conference (Moldova, **2014**); The XVIII-th International Conference Physical methods in Coordination and Supramolecular Chemistry (Moldova, **2015**); The Scientific Conference of Doctoral students (Moldova, **2016** and **2017**); The 12th National Symposium with International Participation "Medicinal Plants-Present and Perspectives (România, **2016**); International Symposium on Bioorganic Chemistry (Germany, **2017**); Summer school 'Trends in Organic Synthesis' (Switzerland, **2017**); International Conference "Achievements and Perspectives of Modern Chemistry" (Moldova, **2019**). The research presented in the current thesis has been published in three papers and one patent application.

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# Anexx 1. Patent application

05/ 00

AGENŢIA DE STAT PENTRU PROPRIETATEA INTELECTUALĂ A REPUBLICII MOLDOVA

DIRECŢIA BREVETE

F-01-BI-046-I-04-0327

STATE AGENCY ON INTELLECTUAL PROPERTY OF THE REPUBLIC OF MOLDOVA

PATENTS DIRECTION

AGEPI

IDNO 1015601000112

Rechizite bancare (MDL): Beneficiar: MF-Trezoreria de Stat, Agenţia de Stat pentru Proprietatea Intelectuală, Contul IBAN: MD55TRPAAA142310A15851AA, Contul bancar: 33114001, Banca beneficiară: Ministerul Finaţelor- Trezoreria de Stat, Codul băncii: TREZMD2X

nr. **8094**

din **2019.07.12**

**KULCIŢKI Veaceslav, Institutul de Chimie str. Academiei nr. 3, MD-2028, Chişinău, Republica Moldova**

Ca rezultat al examinării cererii de brevet de invenţie cu:
Nr. intrare: 6507
Data intrare: 2019.06.21
Titlul: **Derivat ent-kauranic şi utilizarea acestuia**

Secţia Gestionare Documente a stabilit:
materialele cererii corespund prevederilor art. 34 din Legea nr. 50/2008 privind protecţia invenţiilor (în continuare Lege) şi cererea este înscrisă în Registrul naţional de cereri de brevet de invenţie cu:
(21) Nr. depozit: a 2019 0052
(22) Data depozit: 2019.06.21
(71) Solicitant(ţi): INSTITUTUL DE CHIMIE, MD; KATHOLIEKE UNIVERSITEIT LEUVEN, BE
(72) Inventator(i): KULCIŢKI Veaceslav, MD; GÎRBU Vladilena, MD; PRUTEANU Elena, MD; RENAUD Philippe, CH; DAELEMANS Dirk, BE; MOLLO Ernesto, IT; DEFRANOUX Fanny, FR; UNGUR Nicon, MD

Vă informăm că în conformitate cu prevederile art. 32 din Lege este necesar să depuneţi la AGEPI, în termen de 3 luni de la data de depozit a cererii, **traducerea** documentelor cererii (descrierea, figurile, revendicările, rezumatul) în limba română.

Dacă solicitantul nu va depune în termenul indicat **traducerea** documentelor cererii, cererea va fi respinsă în temeiul art. 48 din Lege.

Vă rugăm să prezentaţi materialele cererii (descriere, revendicări, rezumat) în format electronic la adresa brevete@agepi.gov.md.

Vă informăm că în conformitate cu art. 31 din Lege puteţi să brevetaţi invenţia revendicată în străinătate prin depunerea unei cereri internaţionale conform Tratatului de Cooperare în domeniul Brevetelor (PCT).

Cererea internaţională trebuie să fie depusă la AGEPI în termen de 12 luni de la data de depozit sau de prioritate a cererii.

Informaţii mai detaliate puteţi găsi la adresele: http://www.wipo.int/pct/en/ şi http://agepi.gov.md/ro/inventions/international.

Şef Secţie Gestionare Documente interimar GHIŢU Irina

## DECLARATION ON THE ASSUMPTION OF RESPONSIBILITY

I, the undersigned, Vladilena GÎRBU, declare on my own responsibility that the materials presented in the thesis are the result of my own research and scientific achievements. I realize that otherwise will suffer the consequences in accordance with the legislation in force.

Vladilena GÎRBU

Date: 5.09.2019

Signature:

## AUTHOR'S CV


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| Telephone | +37368221184 |
| Email | vgirbu1@gmail.com |
| Date of birth | 27 October 1989 |


*Work experience*

| | |
|---|---|
| 01/2008–09/2008 | **Sales assistant**<br>Maxiplant SRL, Chisinau (Moldova) |
| 04/2012–09/2012 | **Sales manager**<br>Vistarcom SRL, Chisinau (Moldova) |
| 07/2013–09/2013 | **Analytical Chemist**<br>Savoare Farm SRL, Chisinau (Moldova)<br>-responsible for the analysis and quality of alcohol |
| 10/2012–Present | **Junior scientific researcher**<br>Institute of Chemistry, Chisinau (Moldova)<br>-organic synthesis<br>-chemistry of natural products<br>-analytical chemistry |

*Education and training*

| | |
|---|---|
| 09/1995–06/2007 | **Diploma of high school** Chisinau (Moldova) |
| 09/2008–06/2012 | **Diploma of bachelor's in chemical technology and biotechnologies**<br>State University of Moldova, Chisinau (Moldova)<br>Disciplines: English; organic, analytical and inorganic chemistry; management; technological and food chemistry; thermochemistry; polymers, electrochemistry; philosophy... |
| 09/2012–06/2014 | **Diploma of master in exact Sciences**, specialization Chemistry, University of the Academy of Sciences of Moldova, Chisinau (Moldova)<br>Synthesis of natural compounds, inorganic chemistry, thermodynamics, separation techniques by chromatography, 1D and 2D NMR, GCMS, organic chemistry lab. |
| 11/2014–02/2019 | **PhD student in bioorganic chemistry, chemistry of natural and physiologically active compounds**<br>State University 'Dimitrie Cantemir', Chisinau (Moldova)<br>Collaboration with University of Bern, Department of Chemistry and biochemistry. Synthesis of natural products, radical chemistry. |
| 11/2015–02/2016 | **Internship in Organic Chemistry**<br>University of Bern, Department of Chemistry and Biochemistry, Bern (Switzerland) |

| | |
|---|---|
| | -working in radical chemistry and natural compounds |
| 09/2017–09/2018 | **Trainee in Organic Chemistry**<br>University of Bern, Bern (Switzerland)<br>-radical transformations of terpenes |

*Publications*

Publications in journals-3 articles
Publications at international conferences-13 abstracts
Publications at national conferences-4 abstracts
Patent- 1

*Research Projects*

▪New synthesis routes for obtaining terpenic compunds with biological activity. Project 12.819.08.05F (2012-2013) of the Supreme Council for Science and Technological Development of the Republic of Moldova.
▪Radical mediated modification of natural products. SCOPES 2013-2016 Joint Research Project IZ73Z0_152346 / 1, ISF, Switzerland.
▪Synthesis of terpenic polyfunctionalized derivatives by radical reactions. PhD project, starting from 2014 to 2017. University of Moldovan Academy of Sciences.
▪Non-conventional green procedures for renewable raw materials processing. STCU 5984 research project (2015-2017), Ukraine.
▪Elaboration of methods for obtaining valuable terpenoids by valorization of renewable resources from Republic of Moldova (2015-2018). Project 15.817.02.14A of the Supreme Council for Science and Technological Development of the Republic of Moldova.

*Computer skills*

Competent with most Microsoft Office programs, as well as web-based search engines and chemistry specialized software (ChemOffice, Spinworks, Origin, MestReNova).

*Language skills*

Romanian, Russian-native languages; English-Intermediate level; German-level A2.2