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SYNTHESIS OF TERPENIC COMPOUNDS WITH ADVANCED FUNCTIONALIZATION VIA BIOMIMETIC METHODS

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KULCIŢKI VEACESLAV

SINTEZA COMPUŞILOR TERPENICI CU FUNCŢIONALIZARE AVANSATĂ PRIN METODE BIOMIMETICE

SPECIALITATEA 143.01 CHIMIE ORGANICĂ

Teză de doctor habilitat în chimie

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Doctor habilitat în chimie, conferenţiar-cercetător, specialitatea 143.01 chimie organică

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Doctor în chimie, conferenţiar-cercetător, specialitatea 143.04 chimie bioorganică; chimia compuşilor naturali şi fiziologic activi

CHIŞINĂU, 2017

To the memory of my teacher Iurii Revenco, who has laid the foundations of my knowledge in chemistry and inspired my love for the miraculous world of chemical magic.

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ADNOTARE

Numele de familie, prenumele autorului: Veaceslav KULCIŢKI
Titlul tezei: Sinteza Compuşilor Terpenici cu Funcţionalizare Avansată prin Metode Biomimetice
Gradul ştiinţific solicitat: Doctor habilitat în chimie / **Localitatea:** or. Chişinău
Anul perfectării tezei: 2016/**Structura tezei:** Introducere, 5 capitole, dintre care primul reprezintă sinteza datelor literare, iar următoarele 4 capitole includ rezultatele cercetărilor experimentale proprii la subiectul tezei, urmate de concluzii generale şi recomandări, bibliografia cu 266 de titluri, 219 pagini de text de bază, 121 figuri şi 7 tabele.
Numărul de publicaţii la temă: rezultatele obţinute au fost publicate în 42 lucrări ştiinţifice
Cuvinte-cheie: chimie organică, sinteză organică, terpenoide, ciclizare, regrupare, funcţionalizare, biomimetic, prenilare / **Domeniul de cercetare:** chimia organică
Scopul şi obiectivele lucrării: În virtutea faptului că majoritatea compuşilor terpenici care reprezintă interes practic au schelete carbonice complexe şi funcţionalizare avansată cu heteroatomi, scopul primordial al acestei lucrări a fost elaborarea metodelor de sinteză a diverse clase de compuşi terpenici prin combinarea flexibilă a proceselor biomimetice de oligomerizare, ciclizare, regrupare şi funcţionalizare dirijată. Obiectivele specifice ale lucrării au inclus sinteza compuşilor terpenici din diferite serii oligomerice cu funcţionalizare diversă şi cercetarea lor în reacţiile de ciclizare, regrupare şi funcţionaluzare cu heteroatomi.
Noutatea şi originalitatea ştiinţifică: În lucrarea prezentă a fost demonstrată influenţa majoră a grupelor funcţionale din scheletul terpenoidelor asupra reacţiilor de ciclizare/regrupare *in vitro*. Aceasta a permis de a elabora căi de sinteză foarte eficiente a terpenoidelor complexe. Completarea acestor metode cu reacţiile de funcţionalizare spaţială post-ciclizare lărgerste şi mai mult arsenalul de metode sintetice disponibile pentru generarea întregii diversităţi structurale a terpenoidelor, pregătind astfel terenul pentru studii profunde ale utilităţii compuşilor terpenici în ansamblu.
Rezultatele principial noi pentru ştiinţă şi practică obţinute: În cadrul tezei curente a fost demonstrată viabilitatea combinării succesive a diferitor procese biomimetice pentru sinteza compuşilor terpenici cu diverse structuri. Faptul complexităţii avansate a căilor biogenetice care conduc la diversitatea enormă a terpenoidelor a permis de a înainta ipoteza intercalării etapelor biosintetice în mod flexibil. Această abordare strategică a fost numită *Sinteză Biomimetică Aleatorie*. În urma verificării şi valorificării ipotezelor înaintate în cadrul îndeplinirii lucrării curente, au fost realizate sinteze ale reprezentanţilor a 15 diverse clase de compuşi terpenici.
Semnificaţia teoretică şi valoarea aplicativă a lucrării: Relevanţa teoretică primordială a lucrării se bazează pe lansarea principiului *Sintezei Biomimetice Aleatorii* în planificarea sintezelor compuşilor naturali cu structură complexă. De asemenea, studiul profund al compuşilor naturali a condus la identificarea unei noi super-familii de terpenoide ciclice cu grupe prenil terminale pendante. Implementarea rezultatelor ştiinţifice menţionate mai sus s-a exprimat în sintezele a 7 compuşi naturali sau precursori apropiaţi. De asemenea, iniţierea studilor reacţiilor de degradare ozonolitică în medii apoase a condus la brevetarea unei metode eficiente de obţinere a sclareoloxidului – compus important, utilizat în caltate de component al compoziţiilor de aromatizare.

ANNOTATION

First name, Last name: Veaceslav KULCIŢKI.
Thesis title: Synthesis of Terpenic Compounds with Advanced Functionalization via Biomimetic Methods
Academic degree: doctor habilitate in chemistry / **Place:** Chisinau, Moldova / **Year of presentation:** 2016 / **Thesis structure:** introduction, 5 chapters, the first representing literature review and the next 4 chapters integrating the results of own investigations on the thesis subject, followed by general conclusions and recommendations, bibliography – 266 references, 219 pages of the main text, 121 Figures and 7 tables / **Number of publications:** research results have been published in 42 scientific works. / **Key words:** Organic chemistry, organic synthesis, terpenoids, cyclization, rearrangement, functionalization, biomimetic, prenylation / **Field of research:** Organic chemistry.
The aim and objectives of the thesis: Due to the fact that the majority of terpenic compounds which represent practical interest have complex carbon backbones and advanced functionalization with heteroatoms, the main aim of the current work was elaboration of synthesis methods for diverse classes of terpenic compounds by a flexible combination of major biomimetic processes, including oligomerization, cyclization, rearrangement and selective functionalization. The specific objectives of the work included the synthesis of terpenic compounds of different oligomeric series, having diverse functionalization pattern and their investigation in cyclization, rearrangement and heteroatom functionalization reactions. **Scientific novelty and originality of the research:** A major influence of the functionalization pattern in the terpenoid skeletons on the cyclization/rearrangement reactions *in vitro* has been demonstrated in the present work. Addition of post-cyclization functionalization reactions to these synthetic transformations enlarge even more the arsenal of available synthetic tools for the generation of the entire structural diversity of terpenoids, preparing the ground for advanced studies on terpenic compounds utility in general. **Conceptually novel scientific results for basic and applied science achieved:** The current thesis has demonstrated the viability of the successive combination of different biomimetic processes for the synthesis of terpenic compounds with diverse structures. The relevant complexity of biogenetic paths which lead to the enormous structural diversity of terpenoids has prompted us to launch the hypothesis of the flexible combination of biosynthetic steps within biomimetic synthesis strategies. This approach has been defined as *Random Biomimetic Synthesis*. As a result of verification and valorization of thesis hypothesis, the synthesis of representatives from 15 different classes of terpenic compounds has been realized. **Theoretical and application value of the research:** The main theoretical relevance of the work is based on the coining the *Random Biomimetic Synthesis* principle in planning the synthesis of complex natural product. The deep study of natural products with some specific structural features, basing on the same biogenetical root, has led to the identification of a super-family of cyclic terpenoids with terminal pendant prenyl groups. Implementation of the above mentioned scientific results has been expressed in the synthesis of 7 natural products or close precursors. In addition, initiation of research on ozonolytic cleavage of terpenoids in aqueous solvents has led to patenting of an efficient method for the production of sclareoloxide – an important compound with a broad use as component of aromatization compositions.

АННОТАЦИЯ

Фамилия, имя автора: Вячеслав КУЛЬЧИЦКИЙ
Название диссертации: Синтез Высоко-Функционализированых Терпеновых Соединений Биомиметическими Методами / **Соискание ученой степени:** доктора хабилитат химических наук / **Место защиты:** г. Кишинёв / **Год представления диссертации:** 2016 / **Структура диссертации:** введение, 5 глав, из которых первая является обзором литературы, а последующие 4 включают результаты собственых иследований на тему диссертации, а также общие выводы и рекомендации, библиография - 266 источников, 219 страниц основного текста, 121 рисунков и 7 таблиц / **Количество публикаций по теме:** результаты опубликованы в 42 научных работах / **Ключевые слова:** органическая химия, органический синтез, терпеноиды, циклизация, перегрупировки, функционализация, биомиметика, пренилирование / **Цель и задачи исследования:** Исходя из того что большинство терпеновых соединений которые представляют практический интерес имеют сложные структуры и высокую степень функционализации гетероатомами, главная цель настоящей работы была разработка методов синтеза различных классов терпеноидных соединений путем гибкого комбинирования биомиметических процессов олигомеризации, циклизации, перегрупировки и целенаправленой функционализации. Задачи исследования включили синтез терпеноидов из разных олигомерных серий с различной функционализацией и их иследование в реакциях циклизации, перегрупировки и дальнейшего функционализирования гетероатомами. **Научная новизна и оригинальность исследования:** В рамках настоящей работы было выявлено особое влияние функциональных групп на ход реакций циклизации/перегрупировки *in vitro*. Это позволило разработать высоко-эфективные пути синтеза сложных терпеноидов. Дополнение этого подхода методами пост-циклизационной пространственной функционализации, намного расширяет арсенал доступных синтетических приемов для генерации более широкого структурного разнообразия терпеноидов, приготавливая таким образом почву для применеия терпеновых соединений вообще. **Принципиально новые результаты полученые для науки и практики:** В настоящей работе была доказана возможность последовательного комбинирования различных биомиметических процессов для синтеза терпеновых соединений различной структуры. Факт повышеной сложности биогенетических путей которые приводят к огромному разнообразию структур природных терпеноидов, привел к выдвижению гипотеза интеркаляции биосинтетических этапов гибким способом. Данный стратегический подход был назван *Алеаторным Биомиметическим Синтезом*. В ходе проверки и применении гипотез выдвинутых в настоящей работе, были выполнены синтезы представителей 15 различных структурных групп терпеновых соединений. **Теоретическое и практическое значение работы:** Основная теоретическая значимость работы основывается на выдвижении принципа *Алеаторного Биомиметического Синтеза* в планировании синтеза природных соединений с сложной структурой. Также в ходе глубокого исследования природных терпеноидов с специфическими структурными особенностями привело к выявлению нового сверх-семейства циклических терпеноидов с пендантными терминальными пренильными групами. Внедрение вышеуказаных результатов выразилось в синтезе 7 природных соединений или их близких аналогов. Кроме того, начало иследований озонолитического расчепления в водных средах позволило запатентировать эфективный метод синтеза склареолоксида – важного соединения применяемого в качестве компонента ароматических композиций.

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	2,2-azobis(2-methylpropionitrile)
9-BBN	9-Borabicyclo[3.3.1]nonane
bmim	buthylmethylimidazole
Bn	benzyl
Bu	n-butyl
t-Bu	tert-butyl
Bz	benzoyl
CAN	ammonium cerium(IV) nitrate
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
m-CPBA	meta-chloroperoxybenzoic acid
CPTS	collidinium p-toluenesulfonate
DBU	1,8-diazabiciclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethylazodicarboxylate
DET	diethyl tartrate
DHP	3,4-dihydro-2H-pyran
DIBAH	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMA-OPP	dimethylallylpyrophosphate
DME	ethylene glycol dimethyl ether
DMEU	1,3-Dimethyl-2-imidazolidinone
DMF	N,N-dimethylformamide
DMM	desktop molecular modelling
DMP	Dess–Martin periodinane
DMAP	4-dimethylaminopyridine
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino) ferrocene
dppp	1,3-Bis(diphenylphosphino) propane
EDCI	1-Ethyl-3-(3-dimethylamino-propyl)carbodiimide
Et	ethyl
EVE	ethylvinyl ether
EVK	ethylvinyl ketone
HETCOR	heteronuclear correlation
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HREIMS	high resolution electron impact mass spectrometry
HRESIMS	high resolution electrospray ionization mass spectrometry
HSQC	heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
IP-OPP	isopentenyl pyrophosphate
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LTA	lead tetraacetate
Mand	mandelate
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
MEP	methylerythritol phosphate
MP	mevalonate pathway
4A MS	4Å molecular sieves
Ms	methanesulfonyl
MSH	mesitylsulfonyl hydroxylamine
MVK	methylvinyl ketone
NBS	N-bromosuccinimide
NMO	4-methylmorpholine N-oxide;
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PDC	pyridinium dichromate

Pd(dppp)	palladium(1,3-bis(diphenylphosphino)) propane	TBHP	tert-butyl hydroperoxide
		TBS	tert-butyldimethylsilyl
Ph	phenyl	TES	triethylsilyl
PhH	benzene	Tf	trifluoromethylsulfonyl
PhMe	toluene	TFA	trifluoroacetyl
Ph_3P	triphenylphosphine	THF	tetrahydrofuran
o-PPA	ortho-perphthalic acid	THP	tetrahydropyranyl
PPTS	pyridinium p-toluenesulfonate	TIPS	triisopropylnaphtalenesulfonyl
i-Pr	iso-propyl	TMS	trimethylsilyl
Py	pyridine	TPAP	tetrapropylammonium perruthenate
Ra-Ni	Raney nickel		
L-Selectride	lithium tri-sec-butyl(hydrido) borate	TPP	tetraphenylporphyrin
		p-TSA	*p*-toluenesulfonic acid
TBAF	tetra-n-butylammonium fluoride	*p*-TsCl	*p*-toluenesulfonyl chloride
TBAI	tetra-n-butylammonium iodide	$VO(acac)_2$	vanadyl acetylacetonate
TBDPS	tert-butyldiphenylsilyl		

INTRODUCTION

Organic chemistry represents one of the basic areas of modern science. When we make an outline of the reasons which define the special place of this area of human knowledge, its two general aspects come into mind: cognitive and creative power. Both these aspects are quite clear. First of all, we strive in our endeavors to explain all the processes which surround us. Chemists see the life through the prism of chemical reactions: reactions that occur in our own bodies, reactions that occur in the invisible micro-world, reactions that permanently affect our environment and finally reactions that take place in the outer space. This cognitive function inevitably leads to our desire to create new matter, to produce materials and substances that we might consider useful for our lives. And the pivotal role of organic synthesis in this process is generally acknowledged. It is due to the practically infinite range of compounds which can be built on the basis of organic carbon chains. But what is the strategy which leads the chemists into this creative Odisea?

Again, two distinct approaches are valid: we create something that we think it might be interesting and we create what we see in the nature. The second approach in fact reflects one of the basic psychological features of humans as social beings: we build our lives by mimicking our environment. For organic chemists this means identifying natural targets and their reproduction. Following the same strategy, we try to hypothesize the *in vivo* biochemical pathways leading to the targets and then to reproduce similar synthetic sequences *in vitro*. This is called a **biomimetic strategy**.

A careful examination of the chemicals that have firmly entered our lives will make us conclude that most of them are mimics of natural matter: from low molecular weight bio-regulators (pheromones, drugs, agrochemicals) to polymers and supramolecular aggregates (textiles, rubber and plastics). A comprehensive study of the examples illustrating this reality would certainly do not fit the range of a bunch of books. The purpose of the current work is to provide just a single example of biomimetic approach in developing synthetic strategies [1],[2],[3],[4]. This is the example of terpenes – a very large and fascinating group of natural compounds.

Terpenes represent a large family of natural products with an impressive diversity of carbon skeletons and functionalization pattern. It is believed that this diversity is due to the latter steps of terpene biosynthesis [5]. This opinion has been confirmed by numerous biosynthetic studies which proved that common precursors of all terpenic families are only several open chain oligomers of

dimethylallylpyrophosphate (DMA-OPP): geranylpyrophosphate, farnesylpyrophosphate, geranylgeranylpyrophosphate and some other superior oligomers. The biosynthetic pathways to these basic building blocks include two steps. The first one is the synthesis of DMA-OPP either by mevalonate (MP) or methylerythritol phosphate (MEP) pathways, which along with its precursor isopentenyl pyrophosphate (IP-OPP) represent the elementary C_5 terpene units.

The second step of biosynthesis is the coupling of C_5 fragments leading to the corresponding open chain mono-, sesqui-, di- and polyisoprenoids. DMA-OPP and IP-OPP combine in an oligomerization process to form C_{10}, C_{15}, C_{20} and higher aliphatic chains lake geraniol (C_{10}), farnesol (C_{15}), geranylgeraniol (C_{20}) and higher polyprenols.

Both these steps are similar in all producing cells and living organisms and they bring no structural diversity. On the contrary, the next two steps of terpene biosynthesis play the crucial role in the tremendous expansion of possible terpene structures. These steps are cyclizations/isomerizations and selective functionalizations/degradations mainly by oxygenated functionalities. The enzymes responsible for these transformations are terpene cyclises and oxidases.

From the mechanistic point of view, the terpene cyclases represent an interesting subject, since their action is accompanied by a huge variety of other transformations, which besides cyclizations may include hydride shifts, Wagner-Meerwein and other skeleton rearrangements. Carbonium ion intermediates are the species that ensures reaction sequences leading to carbon skeleton diversity.

To date, there are two basic mechanisms of terpene cyclisations [6]. The first mechanism is given by the ability of the double bond to act as a nucleophile and to interact in a S_N2 fashion with the α-terminus of the chain, leading to elimination of the –OPP group and formation of a new C-C bond. The second mechanism includes a cascade of reactions initiated by a selective protonation of the double bond, followed by an electrophilic attack of the formed carbonium ions to the other double bonds of the aliphatic chain. Both mechanisms involve formation of intermediate carbonium ions, which can stabilize either by proton elimination, skeletal rearrangements or addition of other nucleophiles.

Finally, the other important process which defines the structural diversity is based on the selective functionalization of terpenes by different enzymes, which introduce additional heteroatoms, basically by an oxidative process. Intercalation of cyclisations, isomerisations and functionalization provides practically infinite opportunities for structural modification of the terpenes in living organisms.

All the enumerated biosynthetic processes have inspired organic chemists to devise synthetic methods which selectively transform the substrates exactly in the same way as enzymes do, that is to mimic the biosynthesis. Surprisingly, but for some instances chemical processes have been discovered long before the identification of corresponding enzymes. Baiyer-Williger oxidation of ketones and Diels-Alder cycloadditions are relevant examples. The most difficult component of this approach relates first of all to biosynthesis mechanisms, which can be hardly elucidated for the whole plethora of processes happening in living cells. The final proof of a certain biosynthetic pathway represents isolation of individual enzymes responsible for the specific transformations and this is a quite a challenging task. Even more than that, successive biosynthetic steps like olygomerization, cyclization and functionalization of terpenes can intercalate in the living systems in a random order, that bring even more complexity to the whole process. In order to tackle this hypothesis, the current work has aimed a flexible alternation of terpene functionalization with cyclization/olygomerization reactions, once it is not clear what is the real order of biochemical events in the cells. This strategy that mimics the biosynthetic steps in a random order possess a relevant potential for the synthesis of new classes of terpenic compounds with complex structure and broad spectrum of properties.

The scope and objectives of the thesis

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

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

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

Scientific novelty and originality

During the realization of the current work the viability of diverse biomimetic processes flexible combination has been demonstrated as a tool for the synthesis of terpenic compounds with diverse structures. The fact of advanced complexity of biogenetic pathways that lead to the enormous terpenoid diversity led to a proposed hypothesis of a flexible intercalation of biosynthetic steps. When translated to the biomimetic synthesis principle, this concept has been called **random biomimetic synthesis**. Application of this approach to the superacidic cyclization of terpenic substrates functionalized either at the extremities or in the middle of open chain allowed to control the selectivity of cyclization process: a functional group attached to the ω-extremity of the chain allowed to selectively initiate the cyclization process from an internal double bond, inhibiting in such a way the terminal one. On the other hand, the placement of a functional group in the chain interior allowed a selective suspension of the cyclization cascade. In both cases the reaction products were partially cyclic terpenoids with prenyl moieties pendant to the (poly-) cyclic skeleton.

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

And last, bat not least, the feasibility of using radical processes for post-cyclization functionalization of tetracyclic sesterterpenoids was demonstrated: in was shown for the first time that functionalization of scalaranic compounds can be made selectively in cycle B by substitution of

nonactivated hydrogens for chlorine, followed by successive elimination of hydrochloric acid and other transformations of the formed double bond.

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

Thesis overview

The presented thesis includes 5 chapters, divided in sections. The first chapter entitled "**Methods for the synthesis of some classes of terpenic compounds which incorporate condensed and partially opened cyclic systems**" comprises 3 sections and represents a literature review connected to the organic synthesis of three major families of natural terpenoids. The entire complexity of synthetic targets is addressed by a plethora of strategies and represents a combination of processes that mimic all the steps in terpene biosynthesis: oligomerization, cyclization, rearrangement and functionalization with heteroatoms.

Section 1.1 "Synthetic methods for cyclic terpenoids with pendant terminal prenyl groups" puts into discussion a superfamily of unusually cyclized terpenoids which are formed in nature by a specific cyclization involving a selective protonation of the internal double bond of the open chain terpenic substrate. As a result, cyclic compounds with terminal pendant prenylation are formed. Such compounds have been isolated from different natural sources, including only marine organisms and lower plants.

Section 1.2 "Synthetic methods towards cheilanthanic sesterterpenoids" relates on a unique family of sesterterpenic compounds with partially cyclic structure. Unlike the examples discussed in section 1.1, the biosynthesis of these compounds involves an enzymatic cyclization initiated at the terminal isoprenic residue of the open chain precursor, but suspended to a tricyclic product. As a result, the structure of natural cheilanthanes represents a tricyclic system with the head prenyl unit pendant.

Section 1.3 "Methods for the synthesis scalaranic sesterterpenoids" relates on sesterterpenes of totally condensed structure, with no pendant prenyl units, belonging to the scalarane family. The challenges connected to these compounds synthesis are connected to the building of tetracyclic skeleton and selective introduction of heteroatomic functional groups.

Section 1.4 presents the concluding remarks related to literature review and formulation of basic thesis goals.

The following four chapters represent the results of author's original research. They are presented under the title "**Methods for the synthesis of terpenic compounds basing on the random biomimetic principle**".

Chapter 2 "Synthesis of terpenic compounds with multiple functionalization via oligomerization or direct functionalization" includes 4 sections.

Section 2.1 "Direct functionalization of open chain terpenoids" relates on the elaborated procedures for the synthesis of open chain mono-, sesqui- and diterpenoids with additional functional groups at both head and terminal extremities (α,ω-bifunctionalized). Only direct oxidative procedures have been considered.

Section 2.2 "Oligomerization approach in the synthesis of terpenes with multiple functionalization" relates to both the synthesis of α,ω-bifunctionalized linear terpenoids, as well as higher terpenoids with functional groups intercalated into the linear chain. Only procedures based on the olygomerization protocols are addressed.

Section 2.3 "Synthesis of terpenic compounds with multiple functionalization via oligomerization or direct functionalization. Experimental methods and procedures" presents detailed experimental procedures discussed in chapter 2.

Section 2.4 presents the concluding remarks related to chapter 2.

Chapter 3 "**Synthesis of cyclic terpenic compounds by selective cyclization sequences**" includes 5 sections.

Section 3.1 "Synthesis of partially cyclized terpenic compounds by a selective biomimetic initiation of the cyclization cascade" relates to the methods used for the synthesis of cyclic terpenoids with terminal pendant prenylation by a biomimetic cyclization involving selective protonation of an internal double bond of open chain substrates.

Section 3.2 "Synthesis of partially cyclized terpenic compounds by a selective biomimetic suspension of cyclization cascade" relates to the methods used for the synthesis of cyclic terpenoids with the head unit pendant to a condensed cyclic system by a biomimetic suspension of the cyclization cascade.

Section 3.3 "Synthesis of cyclic terpenic compounds in non-conventional media. Superacidic cyclization in ionic liquids" includes the first examples of using ionic liquids as nonconventional media for biomimetic superacidic induced cyclizations.

Section 3.4 "Synthesis of cyclic terpenic compounds by selective cyclization sequences. Experimental methods and procedures" presents detailed experimental procedures discussed in chapter 3.

Section 3.5 presents the concluding remarks related to chapter 3.

Chapter 4 "**Application of the rearrangement biomimetic processes for the synthesis of some terpenic families**" includes 4 sections.

Section 4.1 "Rearangement processes involving ring contractions. Synthesis of austrodoric acid and austrodoral" relates to the elaborated synthesis of two natural products isolated from marine organisms with a perhidrindanic skeleton basing on a ring contraction strategy applied to drimanic and homodrimanic compounds.

Section 4.2 "Rearangement processes involving functional group migrations" relates to the elaborated biomimetic synthesis of several compounds belonging to the *ent*-halimane series, as well as to an unique rearrangement process discovered for a bicyclic triterpenic compound, leading to congeners of neopolypodatetraenes. The synthetic strategy was based on hydride and methyl shifts.

Section 4.3 "Application of the rearrangement biomimetic processes for the synthesis of some terpenic families. Experimental methods and procedures" presents detailed experimental procedures discussed in chapter 4.

Section 4.4 presents the concluding remarks related to chapter 4.

Chapter 5 "**Application of the oxidative - degradation biomimetic processes for the synthesis of specifically functionalized terpenes. Remote C-H functionalizations**" relates to the chemical transformations which bring about structural diversity of terpenoids through different heteroatomic functional groups following a post-cyclization scenario. It includes 5 sections.

Section 5.1 "Synthesis of the perhydroindanic fragment of norrisolide" relates to the elaborated synthesis of perhydrindanic unit of norrisolide - a natural product of marine origin with relevant biological activity. Synthetic strategy was based on an oxidative degradation approach.

Section 5.2 "Biomimetic degradation processes based on ozonolysis" includes the results of unusual ozonolysis of a terpenic diene, leading to heterocyclization into functionalized tetrahydrofuranic derivatives. It was an attempt to elaborate a model for functionalization of brevenal

– a polyetheric compound with unusual biological activity isolated from marine dinoflagellate *Carenia Brevis.* An efficient catalytic method for ozonolytic cleavage of diterpenic sclareol into sclareoloxide – a compound with relevant industrial relevance was also demonstrated. The ozonolytic process was performed in an aqueous solvent system which allowed the use of an inorganic catalyst for efficient degradation of the substrate into target compound.

Section 5.3 "Terpene modification by functionalization of inactivated C-H bonds. Radical relay remote functionalization of scalaranic compounds" includes the functionalization of the B-cycle of the scalaranic framework making use of the Radical Relay Halogenation procedure. Following functional group transformations, including allylic oxidation, allowed for the synthesis of several scalaranic derivatives possessing oxygenated functional groups in cycle B.

Section 5.4 "Application of the oxidative - degradation biomimetic processes for the synthesis of specifically functionalized terpenes. Remote C-H functionalizations. Experimental methods and procedures" presents detailed experimental procedures discussed in chapter 5.

Section 5.5 presents the concluding remarks related to chapter 5.

After the basic thesis content, overall conclusions are presented, followed by the list of cited references and annexes.

Theoretical significance

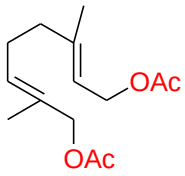
The first theoretical relevance of the current work is based on the hypothesis of random biomimetic synthesis, which can be successfully applied in the planning of synthetic schemes towards natural products with complex structure. Additionally, application of a new biomimetic mechanism for cyclization of linear terpenic compounds by selective protonation of an internal double bond and in-depth study of compounds formed in nature via such a mechanistic pathway has led to the identification of a supra-family of cyclic terpenic compounds with pendant terminal prenyl groups. [7],[8].

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

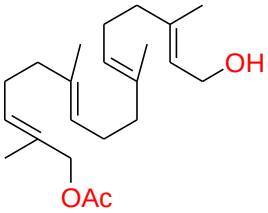
Applied value of the work

Verification and implementation of the hypotheses made in this work has led to the synthesis of the representatives of the following classes of terpenic compounds, which include secondary metabolites isolated from terrestrial and marine sources, pheromones, precursors of compounds with relevant biological activity and also substances known for their use as aroma constituents in perfumery and cosmetic industry:

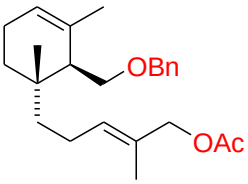
Compounds with geraniol skeleton



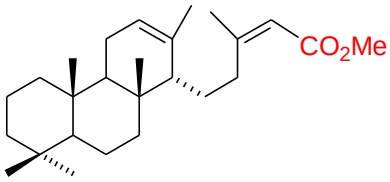
Compounds with geranylgeraniol skeleton



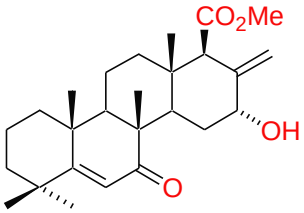
Compounds with seco-eudesmanic skeleton



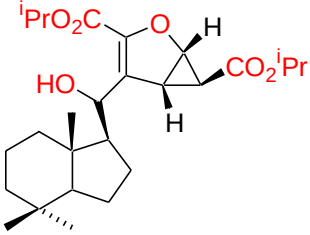
Compounds with cheilanthanic skeleton



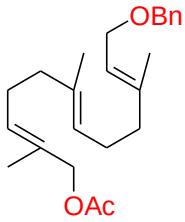
Compounds with scalaranic skeleton



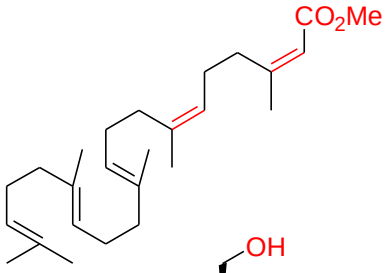
Compounds with rearranged spongianic skeleton



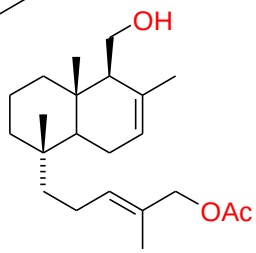
Compounds with farnesol skeleton



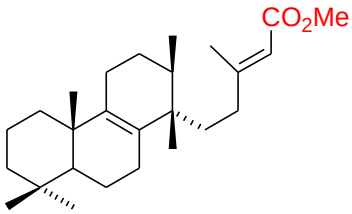
Compounds with geranylfarnesol skeleton



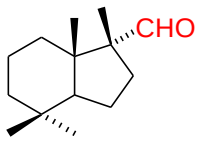
Compounds with sacculatanic skeleton



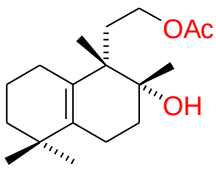
Compounds with rearranged cheilanthanic skeleton



Compounds with austrodoranic skeleton



Compounds with halimanic skeleton



And finally, initiation of a program directed to the use of unconventional media for biomimetic transformations has let patenting of an efficient method for the synthesis of sclareoloxide [9] – an important compound which found implementation in tobacco industry [10],[11].

Approval of scientific results

Approval of scientific results of the current work has been ensured by a broad participation to the international scientific meetings with presentations of the most important achievements on the thesis subject in the form of posters and oral communications. The following can be mentioned: International Symposium "Chemistry & Biology of Marine Organisms", Kolympari, Creta, Greece (**2003**), the series of international conferences "Achievements and perspectives of modern chemistry", Chisinau (**2003**, **2007**, **2009**, **2014**), the Ukrainian conference on organic chemistry, Odessa (**2004**), the XI-lea MaNaPro congress, Sorrento, Italy (**2004**), international symposium "Advanced Science in Organic Chemistry", Sudak/Miskhor, Ukraine (**2006**, **2010**), the series of international conferences of the Chemical Society of Romania, Rmn. Vâlcea (**2006**, **2010**), international conference "Netzwerktagung der Alexander von Humboldt-Stiftung", Darmstadt, Germany (**2008**), international conference Humboldt-kolleg „Cooperation and Networking of Universities and Research Institutes – study by doing research" NANO-2011, Chisinau (**2011**), the XXIII-rd session of scientific communications "Progresses in the science of organic and macromolecular compounds" within the framework of Iaşi Academic Days, Iaşi (**2011**), The International Simposium-Conference "Ecological Chemistry 2012", Chişinău (**2012**), the Phytochemical Society of Europe conference "Phytochemicals in Medicine and Pharmacognosy", Piatra Neamţ (**2014**). Additionally, a series of presentations related to the implementation of the random biomimetic synthesis concept has been performed on the invitation of international collaboration partners, including Institute of Biomolecular Chemistry, Naples, Italy (**2004**, **2012**), Institute of Organic Chemistry, Regensburg University, Germany (**2008**), Fraunhofer Research Center, Straubing, Germany (**2009**), Center for Marine Science of the University of North Carolina, Wilmington, USA (**2005**, **2015**).

1. ORGANIC SYNTHESIS METHODS TOWARDS SOME CLASSES OF TERPENIC COMPOUNDS WHICH INCORPORATE CONDENSED AND PARTIALLY OPPENED CYCLIC SYSTEMS

1.1. Synthesis of cyclic terpenoids with pendant terminal prenyl groups

The distribution of isoprenoids derived from different biosynthetic cyclization pathways in natural sources is quite even, and the enzymes responsible for specific steps are quite well studied. But there are still some exceptions. A careful examination of the whole range of terpenic compounds derived from lower plants like briophites or some marine organisms has revealed a very interesting group of terpenes with a cyclic structure formed presumably by an electrophilic cyclization initiated on a double bond other than the terminal one (Figure 1.1). As a result of such a biosynthetic scenario the terminal prenyl unit (ω-unit) is not involved in the carbocyclization sequence but remains attached pendant to the formed carbocyclic fragment. This prenyl unit can transform further, basically by oxidative processes and additional functional groups, including heterocycles, span the structural diversity of the known representatives.

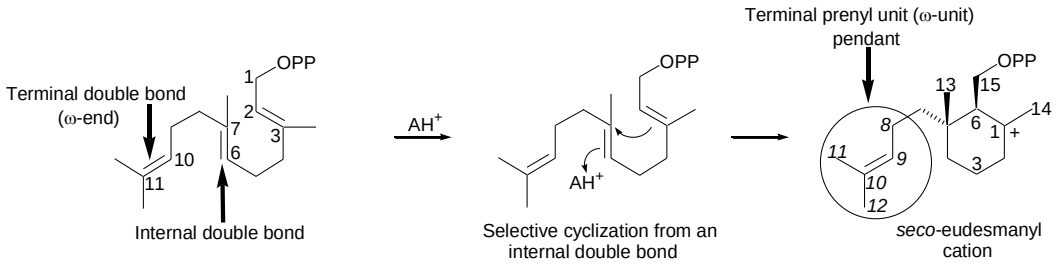
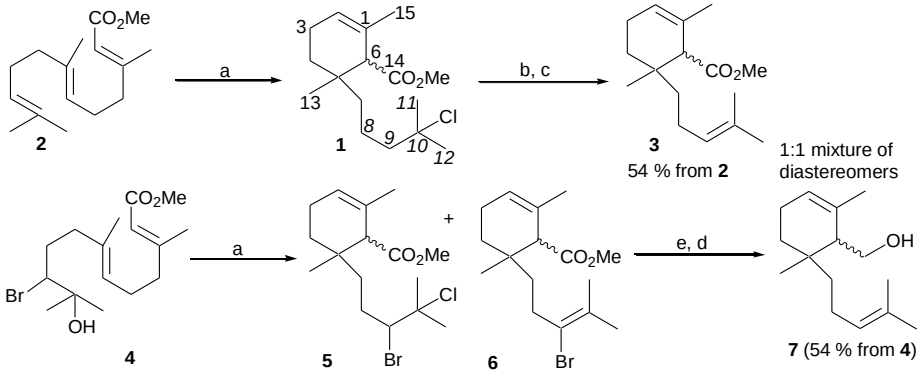


Figure 1.1. The biogenesis of cyclic terpenoids with terminal pendant prenyl moieties.

The enzymatic machinery of such specific cyclizations still represents a "white spot" in terpenoid biosynthesis and it was the effort of natural product chemists who hypothesized the biogenesis of this intriguing group of terpenoids. "Unusually" cyclized terpenoids have been sporadically reported from different natural sources, starting basically from the mid 70-th of the last century. Initially, there were compounds of sacculatane family, isolated from liverworts of different origin. The last 10 years witnessed an increasing number of examples and more cyclic compounds with the pendant ω-terminus are isolated both from terrestrial and marine sources.

The current section attempts to summarize the known-to-date reported synthesis of terpenic representatives with such an unusual prenylation pattern. The information on their occurrence in natural sources and biological activity can be found in the published review paper [7].

From the point of view of synthetic organic chemistry, elaboration of cyclic terpenoids containing terminal pendant prenylation can be achieved via two basic approaches. One is based on a biomimetic cyclization of an open chain terpenic substrate, which can be selectively manipulated in order to leave the terminal prenyl unit inactive in the cyclization sequence. This approach has been addressed in the synthesis of the *seco*-eudesmanic compound **1** on cyclization of the readily available methylfarnesoate **2** under the action of the Lucas reagent, followed by dehydrochlorination to ester **3** [12].

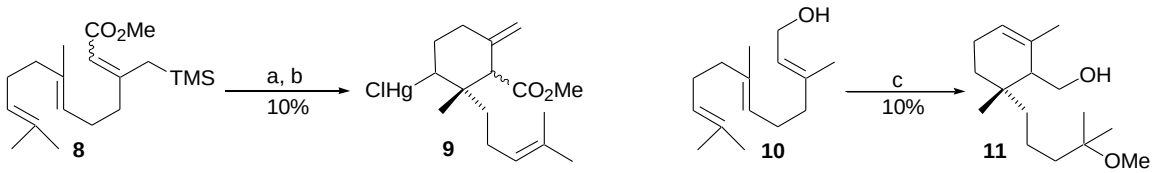


Reagents and conditions: (a) $ZnCl_2$/HCl; (b) $ZnCl_2/H_2O$; (c) $ZnCl_2$/PhH; (d) LAH; (e) Zn/AcOH.

Figure 1.2. Synthesis of the *seco*-eudesmanes on cyclization of farnesoates with Lucas reagent [12].

This procedure was quite efficient, providing a *seco*-eudesmanic framework in one single step with an acceptable yield (Figure 1.2). An alternative procedure for the generation of the *seco*-eudesmanic skeleton proved to be the cyclization of bromohydrin **4** with the same reagent. The obtained monocyclic compounds **5** and **6** were not investigated as substrates for eudesmanes, but reduced to the alcohol **7** of the same *seco*-eudesmanic structure. In both cases, the cyclisation event was preceded by the selective saturation of the terminal double bond either by chlorination or by bromohydrine formation. Under these circumstances, initiation of the reaction from the internal double bond was the most favorite cyclisation route.

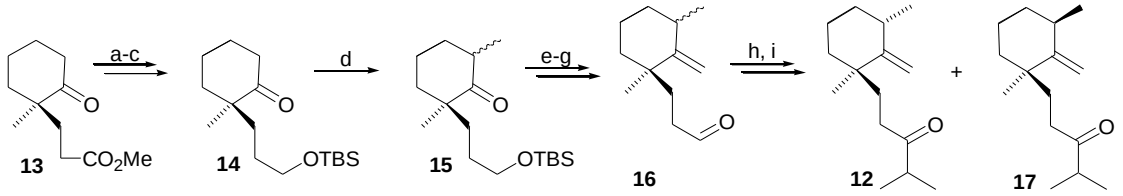
Farnesol derivatives have been also shown to cyclize into *seco*-eudesmanic compounds under the action of other cyclization agents. Mercuric trifluoroacetate has induced cyclization of the silylated methylfarnesoates **8** (Figure 1.3) to the corresponding monocyclic mercurated esters **9** [13].



Reagents and conditions: (a) $Hg(OTFA)_2$, $MeNO_2$; (b) NaCl, H_2O; (c) FSO_3H, SO_2FCl then MeOH.

Figure 1.3. Cyclization of silylated methylfarnesoates with mercury triflate [13].

Farnesol **10** under the action of FSO_3H in SO_2FCl at -110 ^oC and MeOH quenching also cyclized to the corresponding monocyclic compound **11** [14]. But in both cases, the yields of **9** and **11** were cca. 10%, the major reaction products being bicyclic compounds of drimane series.



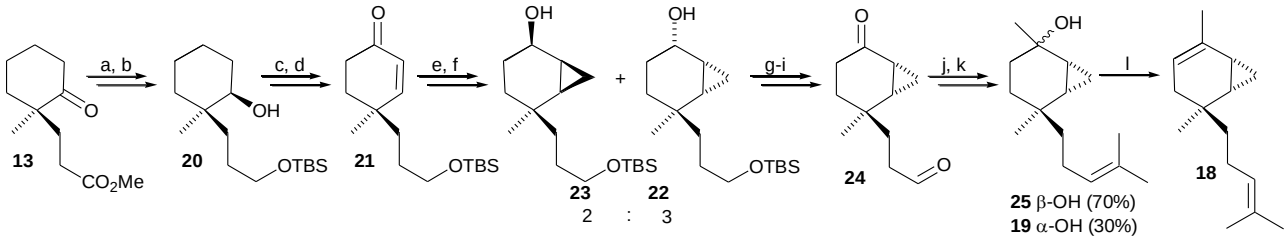
Reagents and conditions: (a) LAH, Et_2O; (b) TBSCl, Et_3N, DMAP; (c) PDC, DCM; (d) LDA, MeI; (e) Ph_3PMeBr, BuLi; (f) Bu_4NF; (g) $(COCl)_2$, DMSO, Et_3N; (h) MeCH(Me)MgBr, Et_2O; (i) Jones.

Figure 1.4. Synthesis of *ent*-tridensone **12** [15].

The second approach for the construction of terminal pendant prenylation represents a totally different strategy. It assumes the use of a cyclic building block possessing a functional group at a gem-dimethyl position, which can serve as a handle for attachment of prenyl units. Such a strategy was demonstrated by Asakawa and collaborators in the synthesis of *ent*-tridensone **12** [15] as outlined in Figure 1.4.

The starting monocyclic building block **13** was prepared in optically active form on the base of a very efficient enantioselective procedure [16], including 1,4-addition of the enamines of the chiral amine auxiliary. Applying this methodology and using (S)-(-)-phenylethylamine [17] allowed **13** in 80% yield. A standard functional group manipulation sequence led to the TBS-protected ketol **14**, which was deprotonated with LDA and methylated with methyl iodide to a mixture of diastereomeric ketones **15** (3:2). The Wittig olefination was used to introduce the exomethylenic double bond, while deprotected primary hydroxyl under oxidation gave aldehyde **16**. Treatment of **16** with the corresponding Grignard reagent and oxidation of the secondary alcoholic group led to the mixture of **12** and **17**, readily separated by column chromatography on silver nitrate impregnated silicagel. The overall synthetic sequence included nine steps from ketone **13**.

Ketone **13** was a good starting point for the synthesis of chenopodene **18** and chenopodanol **19** [18]. The corresponding synthetic sequence is shown in Figure 1.5. In this case, for the introduction of the cyclopropane fragment, a Simmons-Smith cyclopropanation was used after reduction of ketone **21**, which gave disappointing results on cyclopropanation under several conditions.



Reagents and conditions: (a) LAH, Et_2O (quant.); (b) TBSCl, NEt_3, DMAP (97%); (c) $POCl_3$, Py, 4A MS (66%); (d) PDC, PhH, t-BuOOH, Celite (72%); (e) DIBAH, THF (81%); (f) Et_2Zn, CH_2I_2 (36% **22** and 20% **23**); (g) **22**, PDC, DCM (96%); (h) TBAF, THF (81%); (i) PDC, DCM, 4A MS (56%); (j) Ph_3PCHMe_2I, BuLi, Et_2O (20%); (k) MeLi, Et_2O (34%); (l) **25**, $POCl_3$, Py, 4A MS (36%).

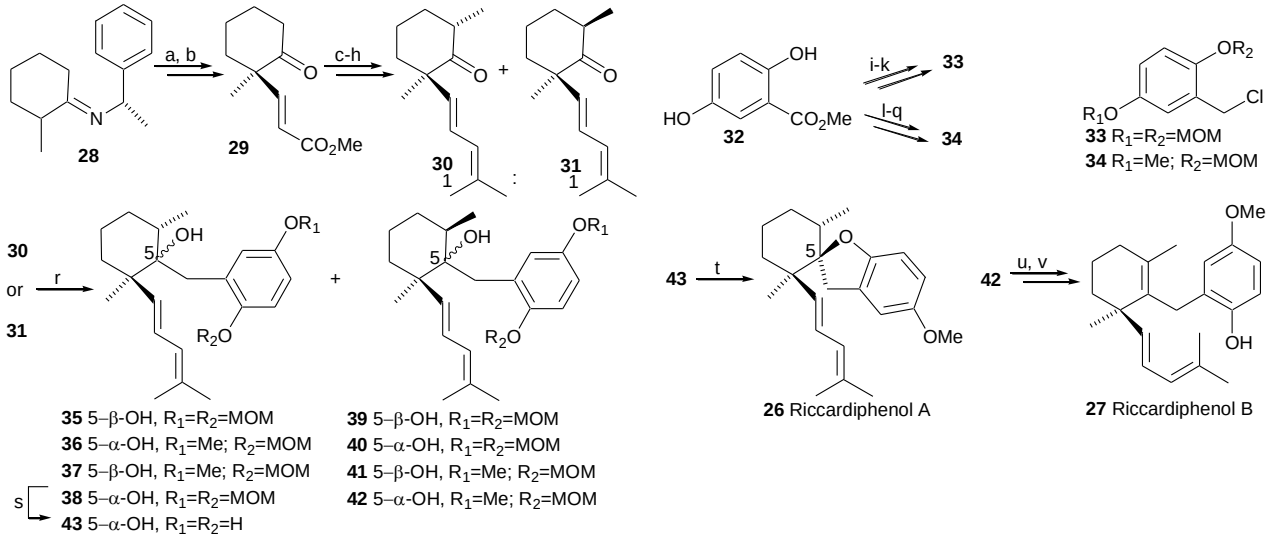
Figure 1.5. Synthesis of chenopodene **18** and chenopodanol **19** [18].

The cyclopropanation occurred with moderate selectivity, and the major alcohol **22** had the relative stereochemistry matching that of **18** and **19**. Assembling the pendant prenyl group was achieved by the selective Wittig olefination of the keto-aldehyde **24** with the phosphorane generated from isopropyltriphenylphosphonium iodide under the action of butyl lithium in diethyl ether at room temperature. Following treatment with MeLi gave chenapodanol **19** as a minor diastereomer. The major alcohol **25** was dehydrated to chenapodene **18**.

The same strategy was applied for the synthesis of riccardiphenols A **26** and B **27** (Figure 1.6) [19]. Since the pendant prenyl chain in riccardiphenols contains an additional unsaturation, the synthesis of the monocyclic terpenic fragment in optically active form was performed on the Michael addition of the imine of 2-methylcyclohexanone of (S)-(-)-phenylethylamine **28** to methylpropiolate. The resulting α,β-unsaturated ester **29** was obtained with a good yield and ee. Further elaboration of the pendant prenyl unit required six steps, and the isopropilidene fragment was introduced by an oxidation-Wittig olefination sequence. The introduction of the methyl group in the α- position to the ketone functionality was performed according to a similar protocol as applied in the synthesis of tridensone precursor **15**. Unfortunately, there was no selectivity for this step and dienes **30** and **31** were separated by HPLC.

Gentisic acid methyl ester **32** was converted to the aromatic fragments **33** and **34** that comprised different protection patterns of phenolic groups. Coupling of C15 and aromatic fragments was performed using the Grignard reagents derived from both **33** and **34**. In order to modulate reaction

diastereoselectivity, diastereomers **30** and **31** have been coupled with both aromatic fragments.

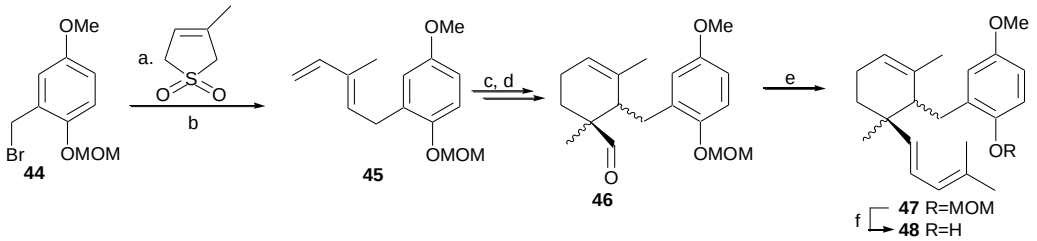


Reagents and conditions: (a) Methylpropyolate; (b) AcOH, H_2O (79% over steps a, b, 80% ee); (c) $HOCH_2CH_2OH$, *p*-TSA (85%); (d) LAH, Et_2O (quant.); (e) $(COCl)_2$, DMSO, Et_3N; (f) Ph_3PCHMe_2I, BuLi, Et_2O (52% over steps e, f); (g) *p*-TSA, H_2O, $(CH_3)_2O$ (74%); (h) LDA, MeI then HPLC; (i) MOMCl, NaH (quant.); (j) LAH, Et_2O; (k) Ph_3P, CCl_4 (59% over steps i, j); (l) DHP, PPTS, DCM (99%); (m) MOMCl, NaH; (n) MeOH, PPTS (57% over steps m, n); (o) MeI, K_2CO_3 (92%); (p) LAH, Et_2O; (q) Ph_3P, CCl_4 (73% over steps p, q); (r) **33** or 34, Mg, THF (18% **38** or 41% **42**); (s) HCl, THF (79%); (t) *p*-TSA, PhH (4% **26**); (u) $SOCl_2$, Py (33%); (v) HCl, THF (32%).

Figure 1.6. Synthesis of riccardiphenols A **26** and B **27** [19].

The reaction yield and selectivity were good, but the epimer used for the synthesis of riccardiphenols A was minor. Removal of MOM protection from **38** and cyclization with *p*-TSA gave riccardiphenol A **26**. Its yield was low, due to competing cyclization from the less hindered α-face of **43** to give the riccardiphenol A epimer. Riccardiphenol B major precursor **42** was dehydrated and cyclized with *p*-TSA to give the target **27** in two steps. Other diastereomers obtained on coupling experiments after a proper removal of protecting groups and dehydration have been also investigated as substrates towards **26** and **27**, but all showed different reaction pathways.

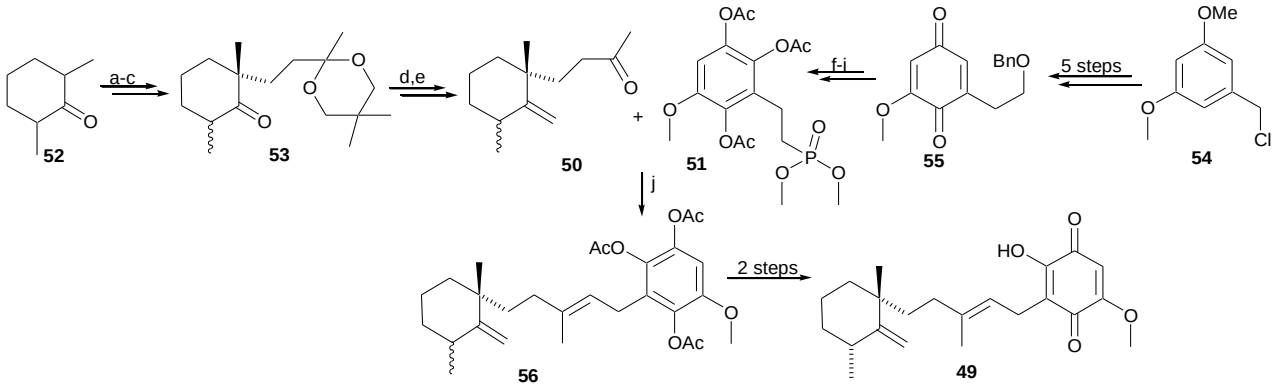
More recently, the synthesis of riccardiphenol B isomers in racemic form has been reported [20]. The synthetic strategy was based on sequential prenylation of benzylbromide **44** (Figure 1.7), prepared in four steps from *p*-hydroxyanisol. The first prenyl unit was attached by the interaction of **44** with the lithiated 3-methyl-3-sulfolene, followed by SO_2 elimination on refluxing in pyridine. The Diels-Alder reaction of the resulting diene **45** with acrolein and methylation of the resulting aldehyde was used to construct the other cyclic unit in **46**. No diastereomeric ratio for these steps has been reported.



Reagents and conditions: (a) LiHMDS, HMPA, THF (70%); (b) Py, (86%); (c) acroleine, PhMe (78%); (d) NaH, MeI, THF (55%); (e) prenyl phosphonate, THF (19%); (f) HCl, THF (30%).

Figure 1.7. Synthesis of racemic riccardiphenol B isomers **48** [20].

And finally, the pendant prenyl unit was attached making use of a HWE olefination with prenyl-diethylphosphonate, prepared by the Arbuzov reaction from prenylbromide. Removal of the MOM protecting group in **47** resulted in the diastereomeric mixture of riccardiphenol B isomer **48**. The yields of the reported synthetic transformations were in general good to excellent, except for the last three steps. It can be explained by the relevant steric hindrances around the neopentyl fragment, as well as by a complementary reactivity of the pendant polienic chain during the acid induced removal of the MOM protection in **47**.



Reagents and conditions: (a) Et_3N, TMSCl, NaI-MeCN (82%); (b) MVK, $MeNO_2$, $BF_3{\cdot}Et_2O$, menthol (85%); (c) $OHCH_2C(CH_3)_2CH_2OH$, *p*-TSA, PhH (95%); (d) *t*-BuOK, PhH, $MePPh_3Br$ (80%); (e) PPTS, PhMe (90%); (f) Ac_2O, H_2SO_4 (65%); (g) H_2, Pd/C, EtOAc (85%); (h) CBr_4, Ph_3P, DCM (80%); (i) $(MeO)_3P$, DME (56%); (j) BuLi, THF then **50** (60%).

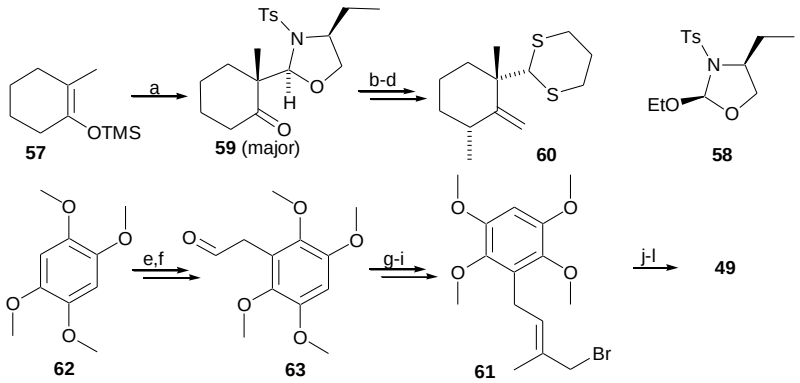
Figure 1.8. Synthesis of metachromin A **49** [21],[22].

The synthesis of metachromin A **49** – a pendant prenylated sesquiterpene with the quinone functional group attached to the lateral chain, was realized according to a convergent strategy [21], [22]. Connection of the terpenic and aromatic fragments was based on a HWE olefination of the monocyclic ketone **50** with the aromatic phosphonate **51** (Figure 1.8). In order to attach the lateral chain in the monocyclic fragment of **50**, the Michael addition of trimethylsilylenolether derived from 2,5-dimethylcyclohexanone **52** to methylvinylketone was applied. The selectively protected adduct

53 was submitted to the Wittig olefination in order to install the exomethylenic double bond, providing the HWE substrate **50**.

The aromatic coupling partner **51** was prepared from commercial benzylchloride **54** in nine steps with the total yield of 19%. Cyanide-homologation of **54**, followed by several standard transformations, led to benzoquinone **55**. The introduction of the remaining oxygenated functionality in the aromatic ring was achieved by the Thiele acetoxylation procedure, and the resulting triacetate was routinely transformed to phosphonate **51**.

Deprotonation of **51** was better achieved with buthyllithium, and olefination of **50** occurred with a 60% yield (3:1 E-Z ratio). Reduction of **56** with LAH and re-oxidation with $FeCl_3$ furnished metachromine A **49**. The elaborated synthetic scheme involved twelve steps in its longest sequence and sixteen steps overall. It also allowed preparation of the enantio-enriched natural product by asymmetric deprotonation of **52** with a chiral base [23].



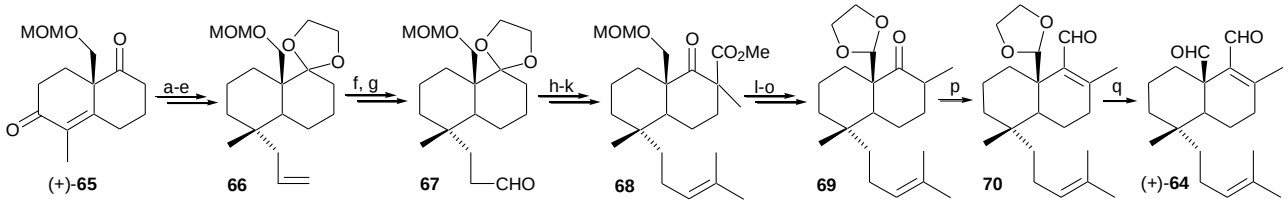
Reagents and conditions: (a) $TiCl_4$, then **58** (79%, dr=81:19); (b) *t*-BuOK, 18-crown-6, THF, MeI (86%, dr=96:4); (c) Me_3Ph_3Br, *t*-BuOK, PhMe (93%); (d) $CH_2(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, DCM (93%); (e) BuLi, LiCl, THF, then ethyleneoxide (80%); (f) $(COCl)_2$, DMSO, Et_3N, DCM (79%); (g) $Ph_3P{=}C(CH_3)CO_2Et$, DCM (92%, *E/Z*=98/2); (h) DIBAH, DCM (92%); (i) MsCl, Et_3N, DCM then LiBr, THF (89%); (j) **60**, *t*-BuLi, HMPA, THF then **61** (85%); (k) Bu_3SnH, AIBN (95%); (l) CAN, $MeCN/H_2O$ (37% **49**).

Figure 1.9. Enantioselective synthesis of metachromin A **49** [24].

Enantioselective synthesis of **49** was also reported by Hoppe and collaborators [24] who applied an alternative strategy for the construction of the monocyclic chiral part. That was based on adding a chiral C1 synthon **58** to the cyclic enolether **57** (Figure 1.9). Under $TiCl_4$ chelating conditions, addition of **58** to **57** occurred with an excellent selectivity to provide a diastereomeric mixture easily resolved by flash chromatography. The major epimer **59** was diastereoselectively methylated with MeI on deprotonation with t-BuOK in the presence of a crown ether. Then, the Wittig olefination and removal of chiral auxiliary occurred smoothly and the resulting thioketal **60** represented the coupling partner for the prenylated aromatic fragment **61**. The latter was obtained from 1,2,4,5-tetramethoxybenzene

62, on ortholithiation and treatment with ethyleneoxide. Addition of other three carbons of the prenyl unit of **61** included the Swern oxidation to aldehyde **63**, the Wittig olefination, reduction and substitution of the allylic hydroxyl for bromine.

Coupling of both parts included a standard lithiation procedure. The following reductive desulfurisation and CAN oxidation concluded the synthetic scheme to metachromine A **49**. The enantiomer of **49** was similarly obtained starting from *ent*-**58**. Both **49** and *ent*-**49** showed absolute values of optical rotations slightly higher than reported for natural product. The overall performance of this scheme was very good, including eight steps in the longest linear sequence. The global yield was diminished only by the last step of CAN oxidation, which occurred with a modest 37% yield.



Reagents and conditions: (a) D-CSA, ethylene glycol-2-methyl-2-ethyl-1,3-dioxolane, (70%); (b) Li, liq. NH_3, CH_2=$CHCH_2Br$, H_2O (92%); (c) LAH, Et_2O (97%); (d) BuLi, THF, CS_2, MeI (quant.); (e) Bu_3SnH, AIBN, PhMe (82%); (f) BH_3, THF then NaOH, H_2O_2 (75%); (g) PDC, 4A MS, DCM (88%); (h) Ph_3P=$C(Me)_2$, Et_2O (68%); (i) PPTS, aq. $(Me)_2CO$ (quant.); (j) NaH, $(MeO)_2CO$, 15-crown-5, THF (95%); (k) NaH, MeI, HMPA (97%); (l) LiCI, HMPA (92%); (m) H_2SO_4, aq. EtOH (88%); (n) $(COCl)_2$, DMSO, Et_3N, DCM (91%); (o) $(CH_2OSiMe_3)_2$, $Me_3SiO_3SCF_3$, DCM (86%); (p) LDA, DCM then $LiClO_4$, $CaCO_3$, HMPA (64%); (q) PPTS, aq. acetone (78%).

Figure 1.10. Synthesis of perrottetianal A **64** [25],[26].

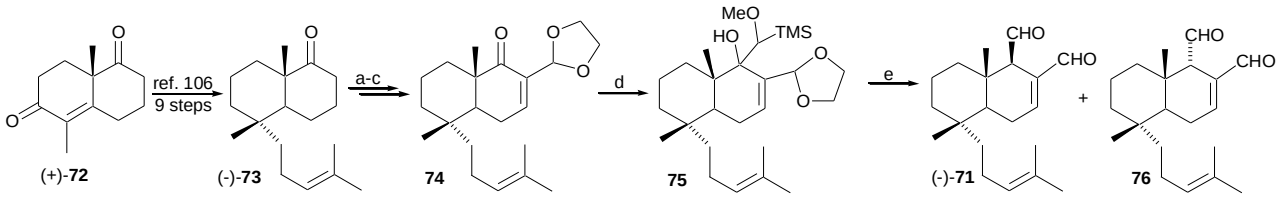
The synthesis of perrottetianal A **64** was reported [25],[26] basing on a Wieland-Miescher ketone analogue **65** [27]. After a selective protection of one keto-group (Figure 1.10), the introduction of the pendant prenyl unit was performed stepwise. A reductive allylation with vinyl bromide was followed by reduction of the remaining unprotected keto-group and deoxygenation of C-3 by the Barton-McCombie procedure. Hydroboration-oxidation sequence of **66** provided aldehyde **67**, which was olefinated with the corresponding phosphorane. Elaboration of the B-cycle of **64** required addition of two carbons. Removal of acetal protection liberated the free carbonyl ready for enolization. Since direct methylation was not successful, introduction of the methyl group was performed via a methoxycarbonylation-methylation leading to **68**, which was easily decarboxylated. In continuation of the synthetic sequence, the carbonyl group at the ring junction was installed and selectively protected, making use of standard procedures.

Introduction of the remaining carbonyl group in **69** was achieved by the Nozaki-Yamamoto homologation procedure, involving dichloromethyllithium addition and hydrochloric acid elimination from the corresponding α-chloroaldehyde. Final removal of acetal protection from the angular

carbonyl of **70** led to the natural product **64**.

The integral synthetic scheme included 17 steps and most of these occurred with very good yields. The least performing step was the Nozaki-Hiyama homologation to aldehyde **70**, which was produced with a still acceptable 64% yield.

The synthesis of (-)-sacculatal **71** (Figure 1.11) [28] was also based on the very well explored Wieland-Miescher ketone **72**, which was prenylated in the A-cycle according to the methodology devised for the synthesis of perrottetianal A **64**. The resulting prenylated bycyclic building block **73** on formylation of the α - position to the keto-group and oxidation with DDQ was transformed to the α,β-unsaturated aldo-ketone, selectively protected as an ethylene acetal **74**. Addition of the remaining C1 synthon was based on the use of methoxy(trimethylsilyl)methyllithium, which added to the ketone functionality and formed the adduct **75**. The final removal of protection groups led to a mixture of sacculatal **71** (26%) and isosacculatal **76** (16%).

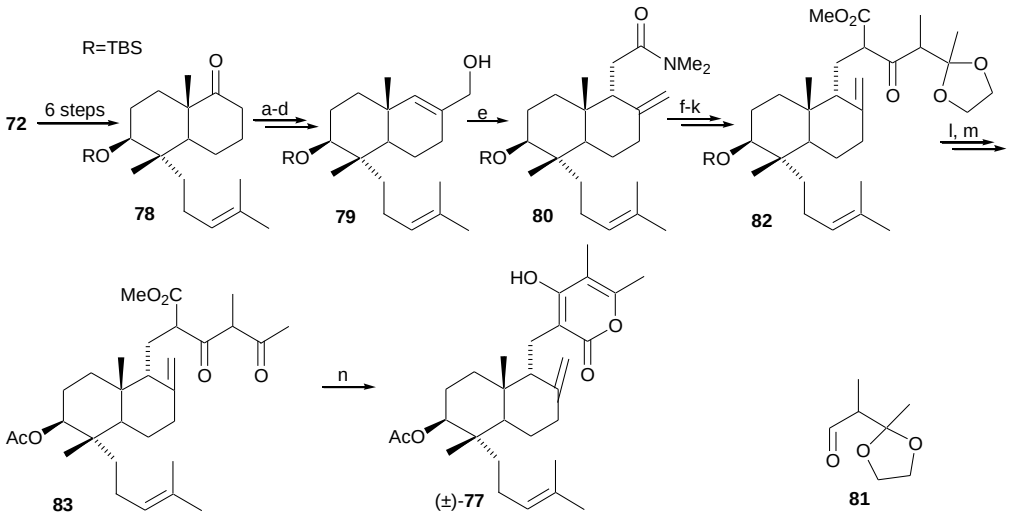


Reagents and conditions: (a) NaH, HCO_2Et, PhH; (b) DDQ, dioxane; (c) Ethylene glycol, cat. *p*-TSA, PhH (69% over steps a-c); (d) $TMSCH_2OMe$, *s*-BuLi, THF; (e) HF, Et_2O.

Figure 1.11. Synthesis of (-)-sacculatal **71** [28].

The total synthesis of some diterpenic bicyclic pendant prenylated pyrones has been also reported. The first example of these series was the synthesis of racemic sesquicillin **77** by Zhang and Danishefsky [29]. The synthetic strategy was based on the reductive alkylation of the known racemic Wieland-Mischer protected ketone and attachment of the second lateral chain, containing the α-pyrone group by an elegant amide acetal version of the Claisen rearrangement. In fact, this transformation represented the key step of the synthesis. The synthetic sequence leading to **77** is outlined in Figure 1.12.

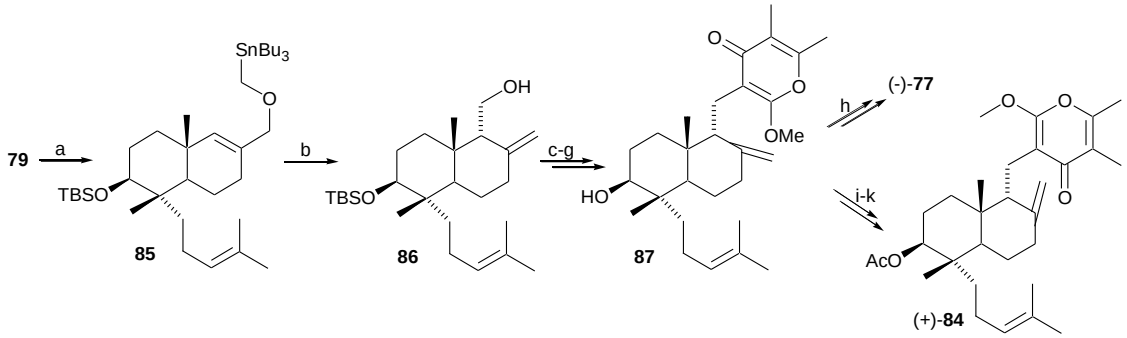
Transformation of the starting ketone **72** to the prenylated bicyclic ketone **78** has been performed in six steps, making use of the same strategy as discussed for the synthesis of sacculatanes. Formylation of **78** and trapping of the less hindered enolic form, making use of a mixed enol acetalization protocol, was followed by the reduction of ketone functionality and acidic treatment, which caused enol deprotection, isomerisation to the corresponding aldehyde and dehydration to the unsaturated aldehyde, precursor of alcohol **79**.



Reagents and conditions: (a) NaH, THF, HCO_2Et; (b) Ethylvinyl ether, H_3PO_4 (cat.); (c) $NaBH_4$, EtOH then HCl (0.5N), THF-H_2O (80% over steps a-c); (d) $NaBH_4$, EtOH (100%); (e) N,N-dimethylacetamide dimethyl acetal, m-xylene (87%); (f) superhydride, THF (99%); (g) MsCl, Et_3N, DCM then NaCN, DMF (100%); (h) DIBAH, hexanes; (i) $NaClO_2$ then $TMSCHN_3$, MeOH, PhH (50% over steps h-i); (j) LDA, **293**, THF (62%); (k) DMP, DCM (100%); (l) HF, MeCN then Ac_2O, Et_3N, DMAP, DCM (83%); (m) $[Pd(MeCN)_2]Cl_2$, Me_2CO (97%); (n) DBU, PhH (61%).

Figure 1.12. Synthesis of racemic sesquicillin **77** [29].

When **79** was treated with N,N-acetamide dimethylacetal, a Claisen-like sigmatropic rearrangement occurred, and amide **80** was generated with a good yield and diastereoselectivity. Direct hydrolysis of **80** was unsuccessful and C1 homologation to the corresponding methyl ester was achieved by a sequence of functional group manipulations. Deprotonation with LDA and condensation with aldehyde **81** led to ester **82**. The following removal of protecting groups and acetylation of the C-3 hydroxyl provided ester **83**, which under DBU treatment gave racemic sesquiciline.



Reagents and conditions: (a) Bu_3SnCH_2I, KH, 18-crown-6, THF (98%); (b) BuLi, hexane (92%); (c) DMP, DCM (quant.); (d) 3-bromo-2-methoxy-5,6-dimethyl-4H-pyran-4-one, BuLi, THF (87%); (e) $NaN(SiMe_3)_2$, CS_2, MeI, THF; (f) Bu_3SnH, AIBN, toluene (82% over steps e, f); (g) $BF_3{\cdot}Et_2O$, MeCN (95%); (h) Ac_2O, DMAP, Py (86%); (i) 1M NaOH, MeOH; (j) Ac_2O, Et_3N, DMAP (70% over steps i,j); (k) 1M NaOH, THF (88%).

Figure 1.13. Synthesis of the optically active sesquiciline **77** and nalanthalide **84** [30],[31].

An alternative approach to optically active sesquiciline **77** and also to nalanthalide **84** was

published by Katoh and collaborators [30],[31]. It was based partially on the first synthesis of racemic **77** discussed above. The same sequence of transformations was used to get the bicyclic alcohol **79**, and slight modifications contributed to better yields. However, the subsequent transformation of **79** to **77** and **84** was different (fugure 1.13) from the Danishefsky's synthesis.

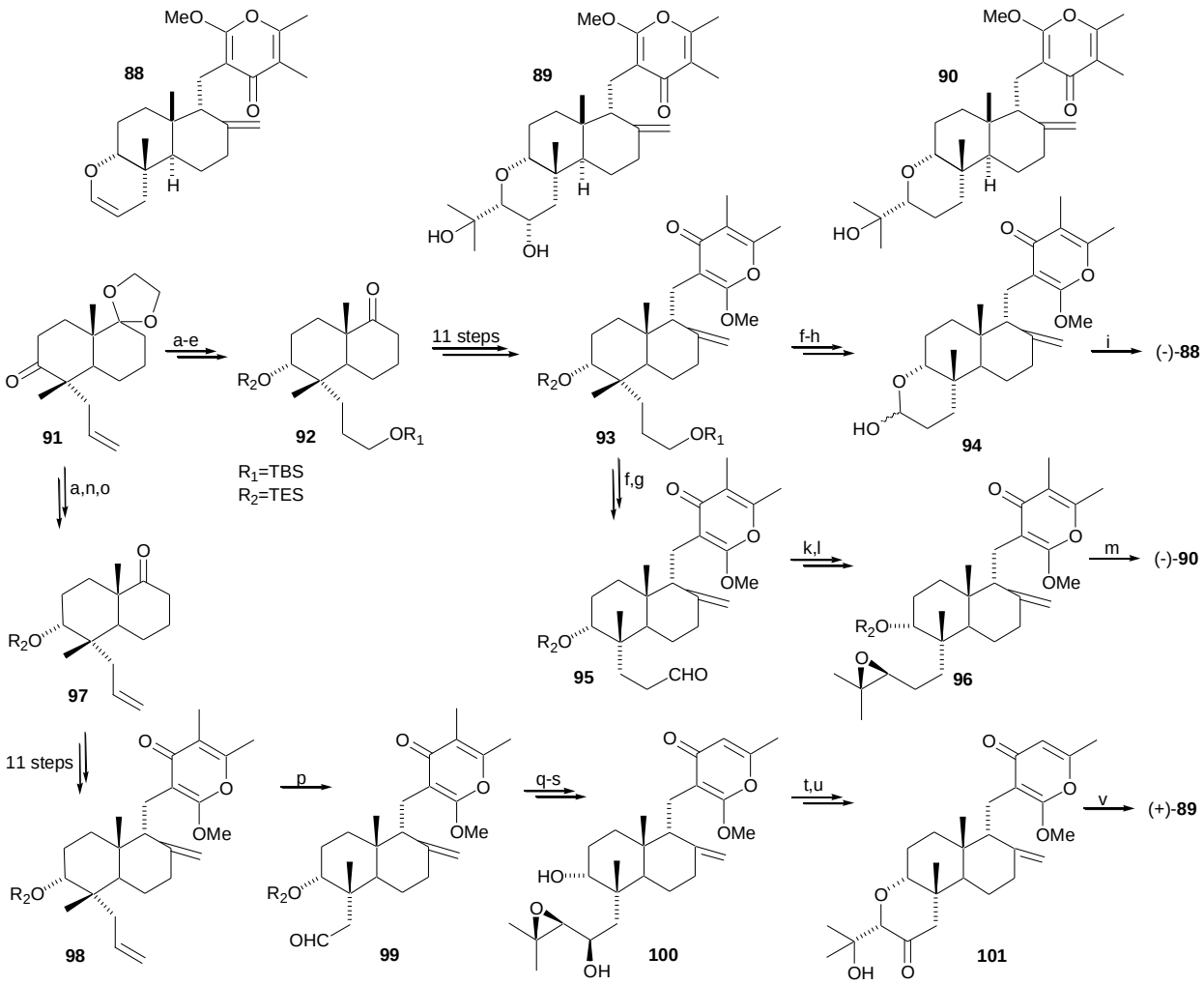
The key step in the building of an additional lateral chain in **79** was the [2,3]-Wittig rearrangement of the related stannylmethyl ether **85** to alcohol **86**. A careful selection of reaction conditions resulted in an excellent selectivity for this crucial step. Further elaboration of both natural products was straightforward and included addition of the lithiated 3-bromo-2-methoxy-5,6-dimethyl-4H-pyran-4-one to the aldehyde derived from DMP oxidation of **86**. The coupling product was deoxygenated according to the Barton-McCombie protocol and subsequent protecting group manipulations delivered both sesquiciline A **77** and nalanthalide **84** through the common intermediate **87**. The optical rotation values for both compounds have confirmed their previously reported absolute stereochemistry.

This synthetic strategy based on the Wittig rearrangement has been also employed for the synthesis of candelalides **88**-**90** [32],[33]. The difference was due only to the fact that terminal pendant prenyl chain in candelalides is hydroxylated or degraded and the oxygen at C-3 is α-configured. Therefore, the known [34] intermediate **91** was transformed to the differently protected keto-diol derivative **92** (Figure 1.14). The first reduction step required the use of L-selectride in order to get the required configuration of the C-3 hydroxy-group.

The following steps for the introduction of the γ-pyrone moiety have been performed according to the sequence employed for the synthesis of nalanthalide **84** discussed above. The resulting *bis*-protected diol **93** was selectively deprotected on the primary hydroxyl group and after oxidation resulted in the cyclic hemiacetal **94**. Its dehydration led to candelalide A **88**.

The pathway to candelalide C required building of a specifically functionalized prenyl chain, therefore aldehyde **95**, the precursor of the discussed hemiacetal **94**, was olefinated according to the Wittig protocol so as to put the prenyl unit in its place. Epoxidation with *m*-CPBA gave a mixture of epoxides (1:1), and the one with the right stereochemistry **96** on the removal of TES protection from the C-3 hydroxyl gave candelalide C **90**.

Candelalide B required more efforts on elaboration of the prenyl chain, since it contained an aditional hydroxy-group there. Its introduction was envisaged via a Grignard reagent addition to an aldehyde similar to **95**. This required degradation of the lateral chain in **91** by one carbon.



Reagents and conditions: (a) L-Selectride, THF (91%); (b) BH_3·THF, THF, H_2O_2, NaOH (96%); (c) 5% aq. HCl, THF, (91%); (d) TBSCl, imidazole, DMF, (93%); (e) TESOTf, 2,6-lutidine, DCM, (82%); (f) AcOH/THF/H_2O 3:2:2, (84%); (g) DMP, $NaHCO_3$, DCM, (96%); (h) TBAF, THF (99%); (i) MsCl, Et_3N, THF (87%); (k) Ph_3PCHMe_2I, BuLi, THF (82%); (l) *m*-CPBA, $NaHCO_3$, DCM (98%, d.r.= 1:1); (m) TBAF, THF (43%); (n) PPTS, Me_2CO, H_2O; (o) TESOTf, *i*Pr_2NEt, DCM (97% over steps n,o); (p) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O (85%); (q) Me_2C=CHMgBr, THF, (42%); (r) $VO(acac)_2$, TBHP, benzene, (84%); (s) TBAF, THF, (100%); (t) PPTS, DCM (79%); (u) TPAP, NMO, DCM (82%); (v) $NaBH_4$, THF, H_2O (88%).

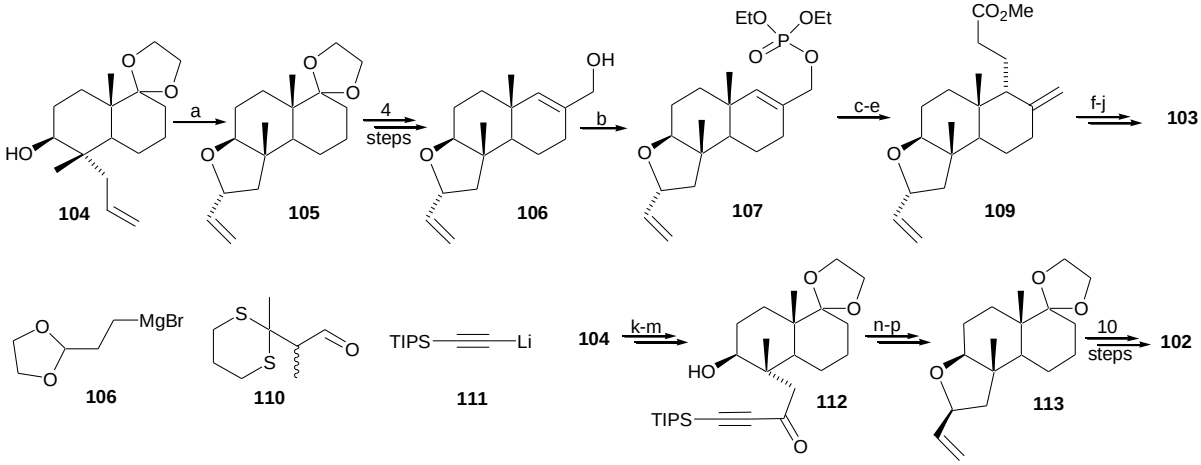
Figure 1.14. Synthesis of candelalides **88**-**90** [32],[33].

To this end, **91** was modified to allow attachment of γ-pyrone in the presence of the pendant allylic chain. Several standard transformations of **91** delivered ketone **97**, which underwent the same sequence of transformations as those used to add the γ-pyrone in other similar compounds.

Removal of one carbon in **98** was done by osmilation-periodate cleavage to nor-aldehyde **99**. It was treated with a Grignard reagent and after standard manipulation gave epoxide **100**. The latter was easily cyclized and final adjustment of its stereochemistry was achieved on borohydride reduction of ketone **101** to produce optically active candelalide B **89**.

A special chapter in the opera of pyrone- containing pendant prenylated diterpenes synthesis has been contributed by the works of Hong and collaborators on the synthesis of subglutinols A **102** and B **103** [35],[36]. These works include several original solutions for attachment of both lateral fragments in target structures of subglutinols. First of all, in addition to the amide acetal Claisen rearrangement devised by Danishefsky and the Wittig sigmatropic rearrangement introduced by Katoh, the alternative solution implemented in the work of Hong [35] was a Cu(I)-catalyzed intermolecular S_N2' reaction of the phosphates derived from alcohols of type **79** leading to the attachment of a C3 synthon for the following elaboration of the pyrone fragment.

Other specific new approaches are related to the need of controlling the stereochemistry of the lateral chain connected to the tetrahydrofuranic fragment in subglutinols, which, in fact, represents the structural difference between **102** and **103**. It was a Lewis acid-promoted deoxygenation of a cyclic hemiketal followed by stereoselective reduction of the resulting oxocarbenium ion intermediate that afforded the tetrahydrofuranic group with the lateral chain having a more sterically demanding configuration, corresponding to subglutinol A **102**. And finally, a cross metathesis - S_N2' tandem was applied on a olefin of type **97** (R_2=H) in order to get a tetrahydrofuran with the α-configured lateral chain.



Reagents and conditions: (a) allyl chloride, Grubbs' II catalyst, DCM (76%); (b) $ClP(O)(OEt)_2$, Et_3N, DMAP, DCM (97%); (c) **314**, $CuI \cdot 2LiCl$, Et_2O, THF (80%); (d) Jones, Me_2CO; (e) MeI, K_2CO_3, DMF, then NaOMe, MeOH (57% for steps d,e); (f) 2-methylpropene, Grubbs' II catalyst, DCM, (85%); (g) LDA, THF, then **316**, (91%); (h) DMP, $NaHCO_3$, DCM, (92%); (i) MeI, $CaCO_3$, MeCN, H_2O; (j) DBU, PhH (54% for steps i,j); (k) O_3, EtOAc, then Ph_3P (100%); (l) **317**, THF (89%); (m) MnO_2, DCM (95%); (n) $BF_3 \cdot OEt_2$, Et_3SiH, DCM (91%); (o) TBAF, THF (97%); (p) H_2, Lindlar's catalyst, EtOAc, Py (99%).

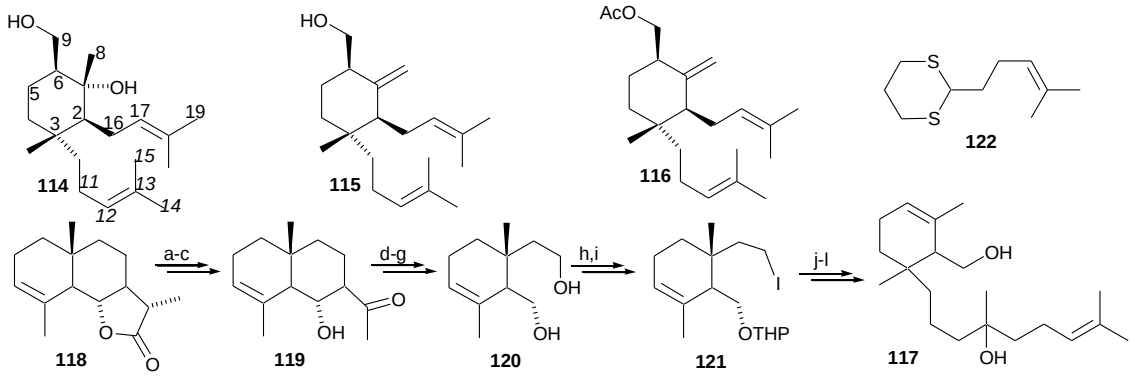
Figure 1.15. Synthesis of subglutinols A **102** and B **103** [35],[36].

The synthesis of both **102** and **103** started from the alcohol **104** (Figure 1.15). Its treatment with allyl chloride and a Grubbs second-generation catalyst allowed for a tandem cross metathesis-S_N2'

sequence to occur and the vinylated tetrahydrofuran **105** was obtained. The configuration of the vinyl lateral chain in **105** was controlled by the steric hindrance of the adjacent methyl group. The following transformation of **105** to alcohol **106** included the sequence established for the synthesis of similar alcohol **79** (Figure 1.12) by Danishefsky [29] and Katoh [31].

The phosphate **107**, derived from **106** was a good substrate for an S_N2' reaction with the protected synthon **108**. The corresponding adduct was routinely transformed to the ester **109 –** the similar substrate reported in Danishefsky's protocol for assembling the pyrone ring [29]. Setting-up of the terminal prenyl unit was achieved by a cross-metathesis involving the vinyl group of **109** and 2-methylpropene. Use of protected aldehyde **110** instead of **81** allowed for better yields of the aldol condensation products, which were transformed to **103** according to the known sequence of transformations.

For the synthesis of subglutinol A **102**, it was necessary to apply a different protocol, in order to build the vinylated tetrahydrofuran fragment with the opposite configuration. This required removal of one carbon in **104** by ozonolysis and following addition of the lithiated alkyne **111**. Oxydation of the secondary alcohol led to **112 -** a suitable substrate for reductive ketalisation. As expected, reduction was selective and oriented the acetylenic chain in β-configuration. The presence of the bulky TIPS-protection was required in order to avoid the 1,4-reduction product. Following TIPS-removal and hydrogenation of the triple bond installed the required functionalized tetrahydrofuran **113**. Its transformation followed the identical sequence that led **105** to subglutinol B **103** in order for the synthesis of subglutinol A **102** to be completed.



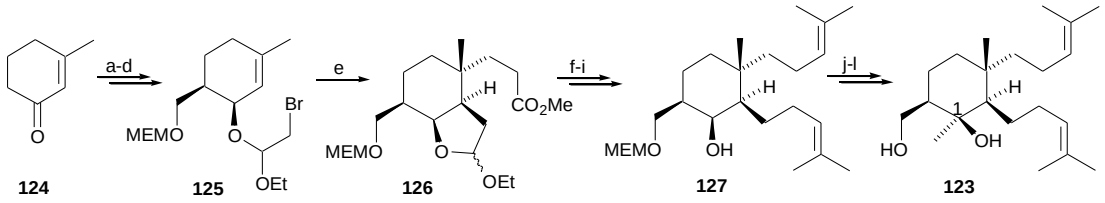
Reagents and conditions: (a) LDA, then MoO_5, Py, HMPT (75%); (b) LAH, THF (75%); (c) $NaIO_4$, THF-H_2O (98%); (d) *o*-MSH then basic alumina (50%); (e) LAH, THF (80%); (f) $NaIO_4$, THF-H_2O; (g) $NaBH_4$; (h) p-TsCl, Py then NaI, Me_2CO (18% over steps d-h); (i) DHP, *p*-TSA (quant.); (j) **324**, BuLi then **323** (52%); (k) $CuCl_2$-CuO, Me_2CO (40%); (l) $Ph_3P{=}CH_2$ (30%).

Figure 1.16. Synthesis of *iso*-magydardienediol **117** [37].

The last diterpenic compounds we intend to discuss are magydardienediol **114**, magydartrienol

115 and its acetate **116**. As we mentioned above, the biogenetical origin of these compounds is very interesting, since two monoterpenic units are connected in the tail-to-tail fashion, followed by a specific cyclization to a monocyclic fragment with two pendant prenyl units. Initial report on the isolation of **114** related on an alternative structure **117**, and the group of Nagano suggested structural revision, based on their synthesis of **117** [37]. This pioneering work was based on a degradation approach applied on an optically active substrate. The outline of the synthetic transformations leading to a pendant prenylated monocyclic diterpenoid **117** (*iso*-magydardienediol) is represented in Figure 1.16.

The starting lactone **118**, prepared from α-santonine, was hydroxylated by LDA deprotonation and MoO_3 oxidation and after LAH reduction was submitted to periodate cleavage. The resulting ketone **119** was further cleaved, making use of a Beckmann rearrangement procedure, followed by a similar reduction-periodate cleavage sequence to deliver a labile dialdehyde, reduced to the corresponding diol **120**. It was selectively tosylated and after several standard manipulations led to the protected iodide **121** – the coupling partner for the bishomoprenyldithiane **122**. The coupled product was transformed easily to **117** by oxidative removal of dithiane group and the Wittig olefination.



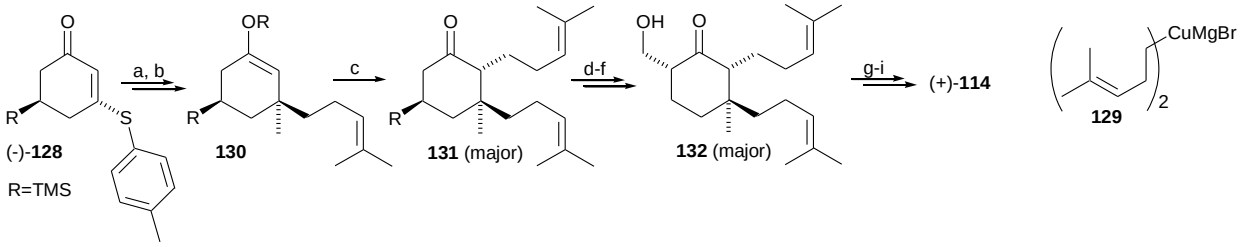
Reagents and conditions: (a) LDA, $H_2C{=}O$, (65%); (b) MEM-Cl, DIPEA, (87%); (c) L-Selectride, (61%, 94% d.r.); (d) NBS, $EtOCH{=}CH_2$, (56%); (e) AIBN, $NaBH_3CN$, Bu_3SnCl, $CH_2{=}CHCO_2Me$, *t*-BuOH, (56%, 80% d.r.); (f) DIBAH, PhMe, (77%); (g) Ph_3PCHMe_2Br, BuLi, (69%); (h) aq. AcOH, (86%); (i) Ph_3PCHMe_2Br, BuLi, (72%); (j) $CrO_3{\cdot}2Py$, (96%); (k) MeLi, (71%); (l) 1% HCl-Me_2CO, (51%).

Figure 1.17. Synthesis of racemic 1-*epi*-magydardienediol **123** [39].

The synthesis of corrected structures **114**-**116** have been reported in both racemic [38],[39], and optically active [40] forms. In the synthesis of racemic 1-*epi*-magydardienediol **123** [39], the same research group of Nagano employed a homolytic alkylation procedure as a key step, basing on the enone **124** (Figure 1.17). On the first step, the formylation of the enolate generated from **124** was used to introduce the β-hydroxymethylene group, which was protected as a MOM-ether. Following reduction of the carbonyl group with L-selectride resulted in the *cis*-product with an excellent diastereoselectivity. Introduction of the side arm as a prerequisite for radical alkylation was achieved on prolonged treatment with NBS in a large excess of ethylvinyl ether. The resulting bromoacetal **125**

was submitted to radical alkylation conditions in the presence of a large excess of methyl acrylate. The alkylated product **126** was formed with an acceptable yield and good diastereoselectivity. The building of the first prenyl unit required partial reduction of the esteric group, followed by the Wittig olefination. The second prenyl unit was installed according to the same olefination protocol after hydrolysis of ethylacetal moiety. The *bis*-prenylated compound **127** required three additional steps in order to be transformed into the 1-*epi*-magydardienediol **123.** Contrary to the expectations, the methylation of the ketone derived from oxidation of **127** occurred exclusively from the α-side, not allowing the direct synthesis of the natural product **114**. The reported synthesis of (±)-**123** represented a formal total synthesis of (±)-magydardienediol **114**, (±)-magydartrienol **115**, (±)-magydartrienol acetate **116**.

The synthesis of **114-116** in optically active form (Figure 1.18) was also achieved [40], basing on a chiral building block **128**, available from anisole in five steps. Conjugate addition of *bis*-homoprenylcuprate reagent **129** to **128** allowed monoprenylation, which was followed by methylation in the presence of TMSCl, in order to trap the enolate **130** as a single diastereomer. The second prenylation with prenyliodide was less selective and the required **131** was isolated in a slight excess over the diastereomer with the β-oriented prenyl chain. Elimination of the TMS group in **131** was performed involving a desilylbromination protocol, and selective reduction of the resulting olefinic bond was followed by formylation to ketoalcohol **132** with an excellent diastereoselectivity. The remaining transformations to the natural product included olefination of the ketone with the Lombardo reagent, selective epoxidation and reduction, to assure the required stereochemistry of the arising tertiary alcohol.

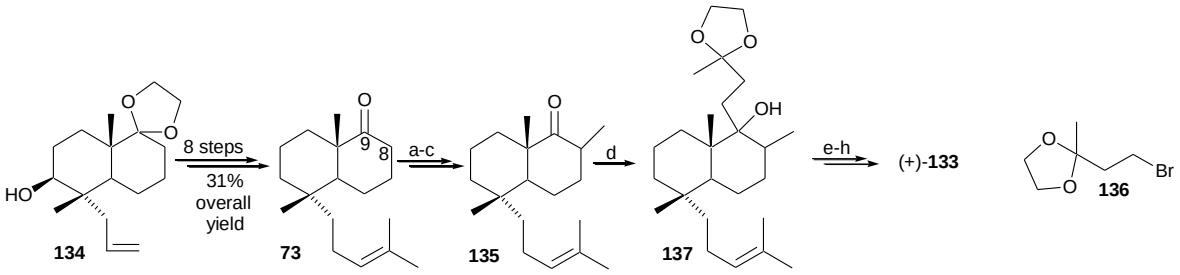


Reagents and conditions: (a) Addition of **129** (77%); (b) MeMgI, cat. CuBr, TMSCl (quant.); (c) MeLi, prenyl-I (66%, d.r. 1.2/1); (d) LDA, TMSCl then NBS, then TBAF (86%); (e) L-selectride (95%); (f) LDA, HCHO (77%); (g) $TiCl_4$-Zn-CH_2Br_2 (45%); (h) *t*-BuOOH, $VO(acac)_2$ (79%); (i) LAH (74%).

Figure 1.18. Synthesis of magydardienediol **114** in optically active form [40].

The first synthesis of a pendant prenylated sesterterpenic compound refers to disideapalaunic acid **133** [41],[42]. Its structural feature resembles the framework of sacculatanes but, unlike

sacculatanes, **133** has the head terpenic unit also pendant to the other part of the bicyclic fragment. This is due to a specific cyclization internally initiated and suspended to a bicyclic carbocycle, as it is also known in other examples discussed above. To the best of our knowledge, all pendant prenylated sesterterpenes have this bicyclic double-prenylated structure. Taking into consideration this structural similarity with sacculatanes, the synthesis of disideapalaunic acid **133** was based on the elaborations reported for sacculatanes synthesis. The starting material was the known [43] protected ketone **134 (**Figure 1.19**)**. Setting up the terminal prenyl chain was performed according to a sequence similar to the synthesis of perrottetianal A **64 (**Figure 1.10**)** and sacculatal **71 (**Figure 1.11**)**. The resulting prenylated bicyclic ketone **73** required addition of a methyl at C-8 and a homoprenyl unit at C-9. To avoid over methylation, a methoxycarbonylation-methylation protocol was applied, and the decarboxylated methylketone **135** was treated with the Grignard reagent derived from **136**. The resulting carbinol **137** was dehydrated and a HWE olefination completed the second prenyl chain. Hydrolysis of the ester group in the HWE adduct furnished the natural disideapalaunic acid **133**.



Reagents and conditions: (a) NaH, $(MeO)_2CO$, THF (87%); (b) NaH, MeI, THF (77%); (c) LiCl, HMPA (72%); (d) **336**, Mg, THF (82%); (e) $SOCl_2$, Py (86%); (f) *p*-TSA, Me_2CO, H_2O (quant.); (g) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (quant.); (h) NaOH, H_2O, EtOH (67%).

Figure 1.19. Synthesis of disideapalaunic acid **133** [41],[42].

Finally, we are at the point to discuss the endeavors concerning the synthesis of dysidiolide **138**. This compound was explored broadly as a synthetic target and a lot of investigations have been reported on its total or formal synthesis. A sharp interest towards **138** is due to several synthetic challenges, which required elaboration of novel and original approaches.

First of all, it is a bicyclic rearranged skeleton that is extremely rare in available natural product scaffolds and needs elaboration from more available precursors. Besides, appendage of two prenyl units at opposite sides of a bicyclic framework requires challenging stereochemical control, as well as overall chiral complexity of dysidiolide, due to its 5 fixed chiral centers. Therefore, the chemical community had a very convenient area to prove the power of modern synthetic techniques and strategy on dealing with this interesting secondary metabolite. A review including the dysidiolide synthesis

has been recently published by Hog, Webster and Trauner [44], therefore we will outline only principal strategic approaches implemented in order to synthetically produce the quite complex dysidiolide molecule.

The first report on the synthesis of optically active **138** was the work of Corey and Roberts [45]. The synthetic strategy was based on a biomimetic rearrangement of a suitable functionalized Wieland-Miescher ketone analogue **91** (Figure 1.20) and it is in line with the most of the approaches implemented for other discussed here pendant prenylated compounds. But due to the rearranged dysidiolide skeleton, use of **91** required incorporation of a TMS-group at the C-1 for a regioselective double bond formation. Therefore, the key transformation represented dehydration of carbinol **139**, which was accompanied by methyl migration and TMS-elimination to generate the double bond at the ring junction position in resulting **140**. Besides, the use of bulky α-oriented substituents at C-1 and C-4 installed methyl at C-3 in the required configuration by a diastereoselective hydrogenation of the olefinic precursor.

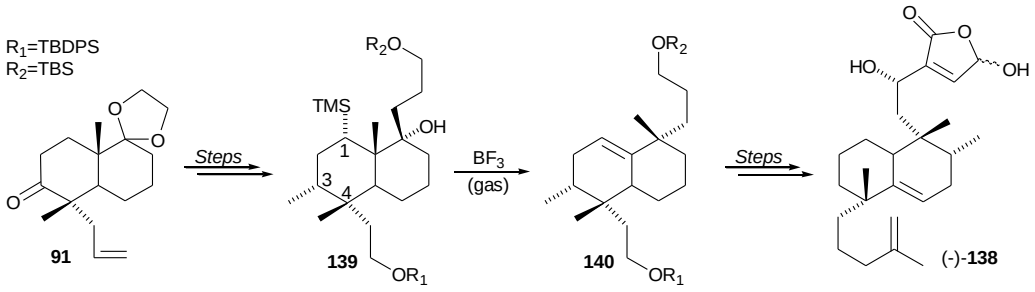


Figure 1.20. Synthesis of optically active dysidiolide **138** [45].

Another approach was demonstrated by Boukouvalas and Danishefsky, who contemporaneously published results on the synthesis of **138** in racemic form [46] and of optically active *ent*-**138** [47]. The starting materials for both syntheses were similar methylcyclohexanone derivatives **140** and **13** (Figure 1.21). The racemic prenylated ketone **140** was obtained in two steps from commercially available compounds; the optically active keto-ester **13** has been previously reported for the synthesis of other pendant prenylated terpenes as stated above. The key transformation in this case was a Diels-Alder 2+4 - cycloaddition for assembling the bicyclic backbone of **138**. The dienic components **141** and **142** were derived from **140** or **13**, respectively; dienophyles **143** and **144** have been carefully designed in order to provide a good selectivity for the crucial cycloaddition step. The corresponding adducts **145** and **146** have been converted to the natural product after standard manipulations.

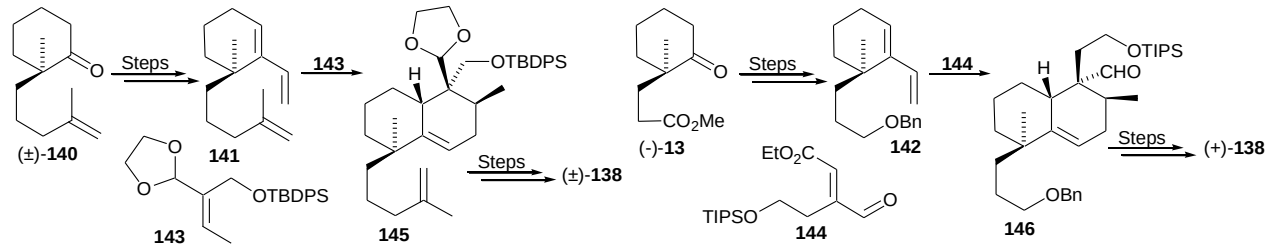


Figure 1.21. Synthesis of dysidiolide **138** in racemic form [46] and of optically active *ent*-**138** [47].

The third approach suggested by Forsith and collaborators [48],[49] included a sequential building of monocyclic, then bicyclic fragments of dysidiolide, followed by appendage of lateral chains. This flexible path comprised several key-transformations and allowed development of alternative synthetic schemes oriented to generation of dysidiolide analogues for SAR studies.

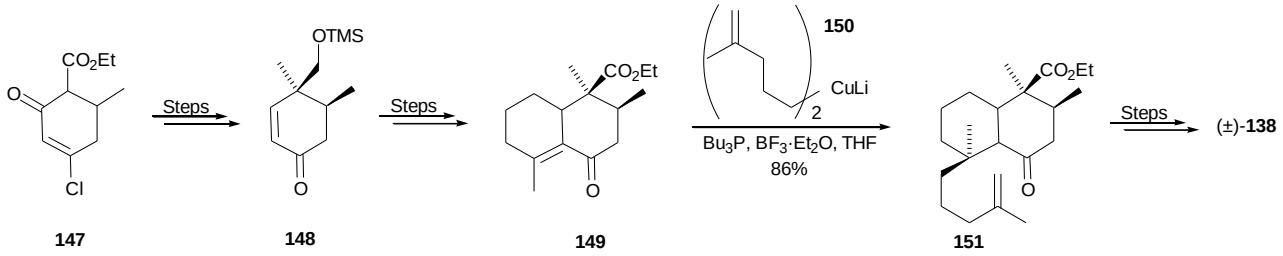


Figure 1.22. Synthesis of racemic dysidiolide **138** [48],[49].

The B-cycle of **138** was generated on condensation of ethylacetoacetate with ethylmetacrylate to deliver, after chlorination, ketoester **147** (Figure 1.22). It was efficiently methylated with methyl iodide on deprotonation with sodium hydride, and the resulting adduct had the required *anti*-configuration of methyl groups as shown by structure **148**. Conjugate addition to **148** of a C5 synthon derived from levulinic acid furnished a lateral chain comprising the methylketone functionality, which condensed intramolecularly into the bicyclic ester **149**. The next step was the most challenging from stereochemical point of view, since it allowed attachment of the homoprenyl chain to a sterically demanding position. After multiple experimentations, it became possible to devise a procedure for a direct 1,4-addition of homoprenylcuprate **150** to the α,β-unsaturated ketone **149**.

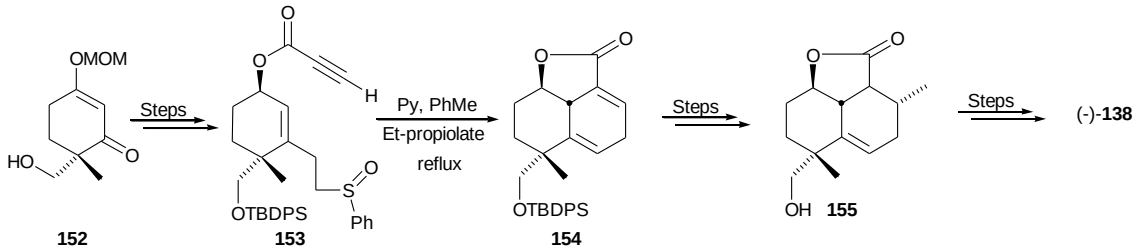
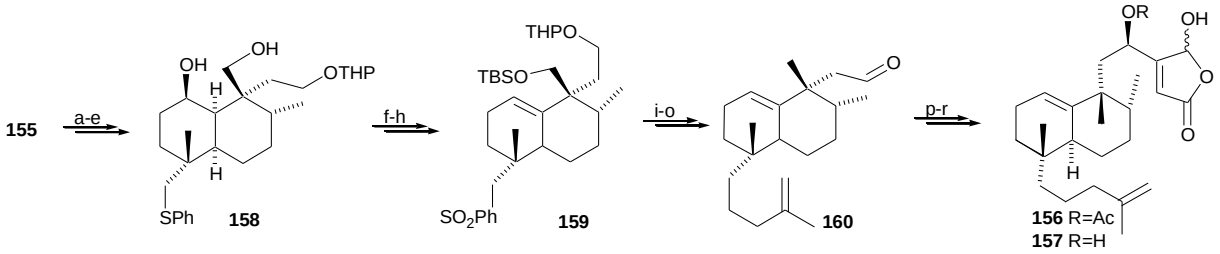


Figure 1.23. Synthesis of both racemic [50] and optically active [51] dysidiolide **138**.

The resulting prenylated ester **151** was converted to racemic dysidiolide in several steps of standard manipulations.

A very interesting intramolecular version of the Diels-Alder strategy has been devised by Yamada and collaborators in order to produce both racemic [50] and optically active [51] dysidiolide (Figure 1.23). In particular, the optically active cyclohexenone **152** has been used as a convenient starting material. The key substrate **153** for the intramolecular Diels-Alder cycloaddition was prepared in a short sequence of transformations, oriented to the protection of primary alcoholic function, vinylation and subsequent protection of the vinyl moiety as a sulfoxide and reduction of ketogroup, followed by esterification with propiolic acid. The tricyclic product **154** was subjected to conjugate addition of the methyl group, and the removal of the protection group from the primary alcohol delivered hydroxilactone **155**. It was converted to the optically active dysidiolide in a linear sequence of transformations, including second alkylation of the lactone functionality, lactone reduction, deoxygenation and final adjusting of both pendant chains.

The intermediate hydroxilactone **155** was also used to synthesize cladocorans A **156** and B **157**, which allowed for the structure of these compounds to be revised [52]. In order to get cladocorans, which are in fact dysidiolide isomers, **155** was hydrogenated and converted to a phenylsulfide - the prerequisite of sulfone-coupling chemistry (Figure 1.24).



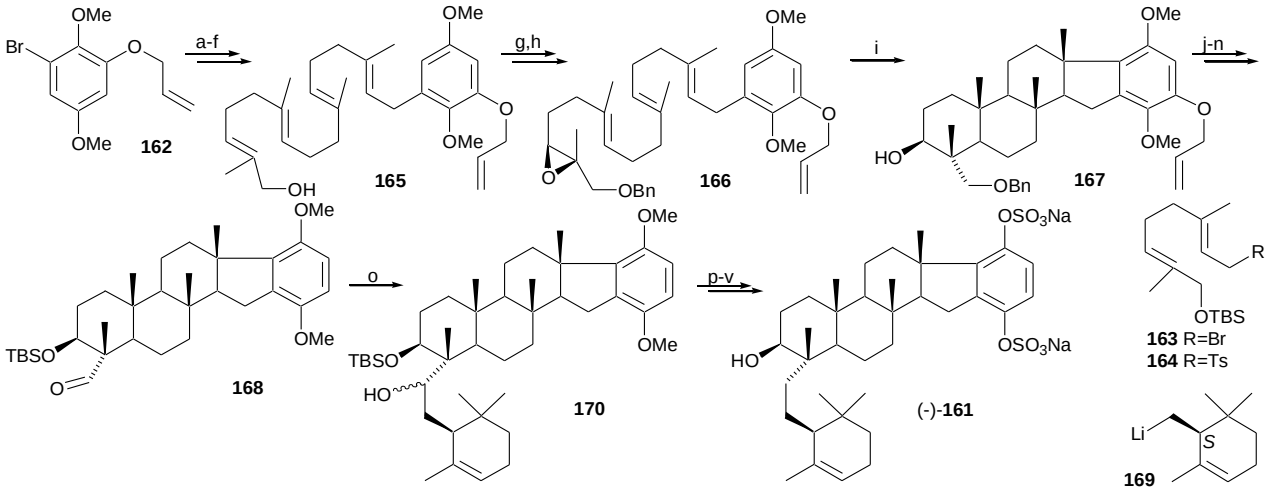
Reagents and conditions: (a) H_2, PtO_2, AcOH, (89%); (b) N-phenylthiosuccinimide, Bu_3P, Py (86%); (c) LDA, HMPA, $THPOCH_2CH_2I$, THF (94%); (d) DIBALH, PhMe; (e) $LiBH_4$, THF (91% over steps d,e); (f) TBSCl, imidazole, DMF; (g) $SOCl_2$, Py (93%); (h) TPAP, NMO, DCM (98%); (i) BuLi, 4-iodo-2-methyl-1-butene, THF (89%); (j) Na-Hg, Na_2HPO_4, MeOH (91%); (k) TBAF, THF (85%); (l) TPAP, NMO, DCM (82%); (m) H_2NNH_2, KOH, diethylene glycol (70%); (n) PPTS, MeOH (94%); (o) TPAP, NMO, DCM (80%); (p) 3-bromofuran, BuLi, THF (95%); (q) Ac_2O, Py (quant.); (r) O_2, hν, Rose Bengal, DIPEA, DCM (83%).

Figure 1.24. Synthesis of cladocorans A **156** and B **157** [52].

The following alkylation with the C_2 THP-protected iodide installed the missing lateral chain, which after reduction delivered diol **158**. After its selective protection and dehydration, the required double bond in the A-cycle was installed and oxidation of the phenyl sulfide resulted in sulfone **159**. Its alkylation with isopentenyl iodide delivered the first pendant chain and installation of the second was straightforward. Deoxygenation of the TBS-protected primary hydroxyl was achieved by

selective deprotection-oxydation and the Kishner-Wolff protocol. Sequential removal of THP-protection and oxidation led to aldehyde **160** – the coupling partner for 3-lithiofuran. Final fotosensitized oxygenation furnished the target cladocoran A **156**. Cladocoran B **157** was also obtained on direct photooxygenation of furan-coupling secondary alcohol.

In the triterpenic series there was basically the family of adociasulfates to show terminal pendant prenylation. As demonstrated in previous chapter, the structural diversity of adociasulfates is broad and only one of 12 representatives of these series is a fully condensed polycyclic compound. The chemical synthesis has been reported only for adociasulfate-1 **161** [53]. This synthesis is an eloquent example of the implementation of a biomimetic approach for the generation of a cascade of cyclizations of an open chain terpenic substrate to deliver in one step an extremely challenging structural complexity, including a policyclic backbone and multiple chiral centers. The creative beauty of this example is also complemented by the fact that an aromatic ring was carefully designed in order to assure its sufficient nucleophilicity as a terminator of the cyclization sequence, and the ω-terminus of the terpenic chain served as a convenient handle to introduce chirality and also to connect the monoterpenic pendant element.



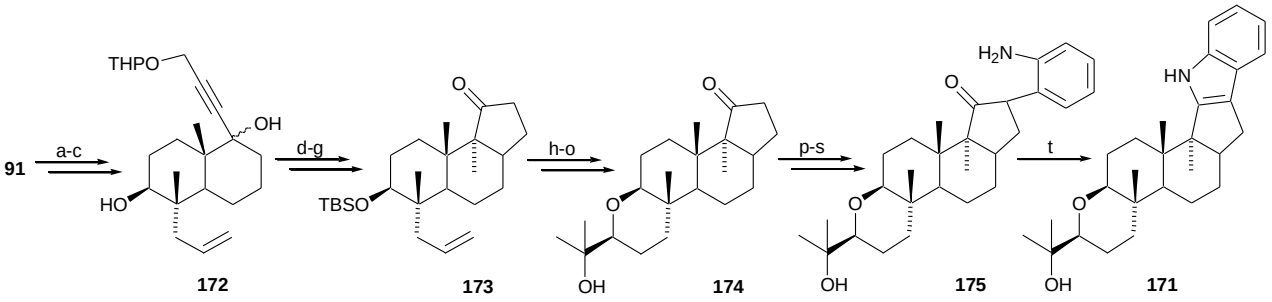
Reagents and conditions: (a) *t*-BuLi, Li_2CuCl_4, THF, **163** (74%); (b) TBAF (80%); (c) MsCl, LiBr (95%); (d) *t*-BuOK, THF-DMF, **164**; (e) Pd(dppp), $LiEt_3BH$ (64% over steps d,e); (f) allyl bromide, K_2CO_3, then *p*-TSA, MeOH (75%); (g) (+)-DET, *t*-BuOOH, Ti(*i*-PrO)$_4$ (95%, 95% e.e.); (h) BnBr, NaH (90%); (i) $Sc(OTf)_3$, DCM (15%); (j) TBSOTf, lutidine; (k) $Pd(PPh_3)_4$, pyrrolidine; $PhNTf_2$, Cs_2CO_3; (l) Pd(dppp), $(n\text{-}Bu)_3N$, HCO_2H (66% over steps j-l); (m) H_2, Pd/C (83%); (n) DMP; (o) **169** (79% over steps n,o); (p) BuLi, CS_2, MeI; (q) AIBN, $(n\text{-}Bu)_3SnH$ (100 equiv., 78% over steps p,q); (r) Bu_4NF (85%); (s) Ac_2O, DMAP (100%); (t) CAN, $Na_2S_2O_4$ (90%); (u) $SO_3{\cdot}Py$; (v) NaOH, MeOH, H_2O (67% over steps u,v).

Figure 1.25. Synthesis of adociasulfate-1 **161** [53].

The starting material was the known 3-bromo-2,5-dimethoxyphenol, which was allylated with allylbromide, and the resulting aromatic bromide **162** was lithiated, then coupled with the known

bifunctional derivative of geraniol **163** (Figure 1.25). An iteration of this prenylation procedure, making use of the corresponding tolylsulfone **164**, allowed assembling of the geranylgeraniol fragment. Desulfurization was accomplished successfully with $LiEt_3BH$ and Pd(dppp) at 0 °C to avoid isomerizations of the allylic substrate, observed with other reducing agents. The resulting TBS-protected substrate was deprotected to **165**, and epoxidation of the terminal double bond was carried out by the Sharpless method. The Bn-protected epoxi-alcohol **166** represented the optimal cyclization substrate, which, on treatment with scandium triflate, led to the required pentacyclic alcohol **167**. Use of the allylether in the aromatic ring assured a sufficient nucleophilicity, in order to efficiently terminate the cyclization sequence to a pentacyclic product. The following transformations required some protecting group manipulations and oxidation to aldehyde **168**. It was coupled with *S*-cyclogeranyllithium **169** to deliver adociasulphate carbon backbone. Deoxygenation of the secondary alcohol **170** required forced conditions, and adociasulfate-1 **161** was obtained after several standard transformations.

The structural complexity of diterpenic indoles has hampered the enthusiasm of synthetic community and there were only a couple of research groups to report progress in this area. In fact, total synthesis of several diterpenic indoles has been accomplished only by Smith and his collaborators. This contribution represents a brilliant example of assiduity and devotion, including a line of original synthetic solutions, designed to achieve the challenging structure of these remarkable fungal metabolites.

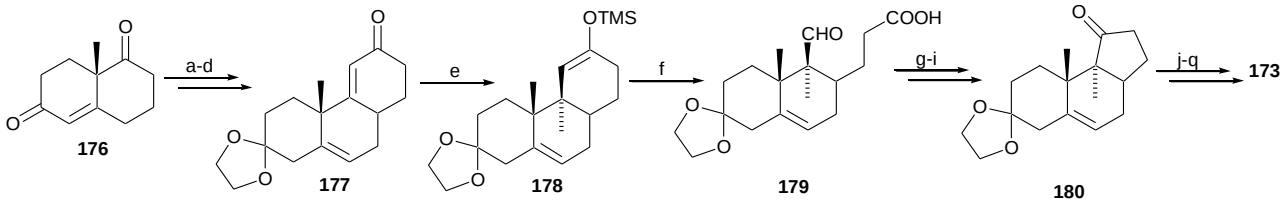


Reagents and conditions: (a) $NaBH_4$; (b) 3N HCl, THF (90 % over two steps); c)LiC≡CCH$_2$OTHP (85%); (d) MeOH, dil. H_2SO_4 (85%); (e) conc. H_2SO_4, MeOH (25%); (f) TBDSCl, imidazole/DMF (85%); (g) Li-NH_3, CH_3I, HMPA, NH_3 (50%); (h) dithexylborane, then H_2O_2 (73%); (i) PCC, DCM (94%); (j) Ph_3P=CHMe, THF (81%); (k) aq. HF, MeCN (98%); (l) *m*-CPBA, DCM; (m) PCC, DCM; (n) Base (81% over 3 steps); (o) MeMgCl, Et_2O (80%); (p) LDA/THF, HMPA/Me_2S_2 (92%); (q) N-chloraniline, DCM, -78 ^{o}C; (r) Et_3N, DCM; (s) Ra-Ni (48% over 3 steps); (t) PTSA, DCM (83%).

Figure 1.26. Synthesis of (-)-paspaline **171** [54].

The synthesis of (-)-paspaline **171** was the first work in this area reported in 1985 by the American research group [54]. Total synthetic sequence included 21 linear steps, starting from the

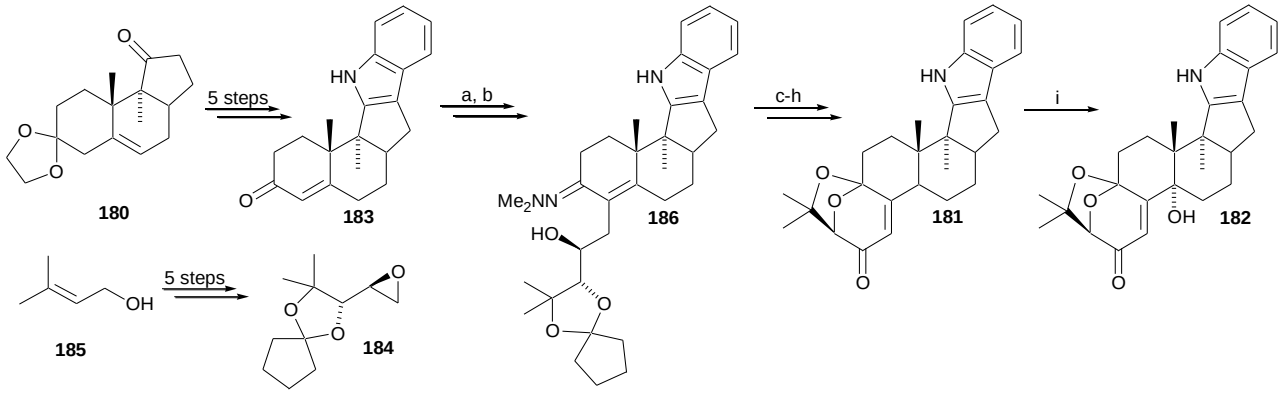
ketone **91** (Figure 1.26) [55]. It was reduced, and following removal of acetal protection allowed a C-3 homologation to the acetilenic monoprotected triol **172**. Removal of THP-protection and acidic treatment let to cyclization to an α,β-unsaturated enone, methylated from the less hindered α-face to generate the tricyclic ketone **173**. A sequential elaboration of the terminal pendant prenyl unit included a hydroboration-oxidation sequence and Wittig olefination. Epoxidation of the resulting olefin was accompanied by a heterocyclization to the pyranyl ring system, and an additional methyl was introduced by a Grignard C_1 unit. With the tetracyclic ketol **174** in hands, elaboration of the indole ring system was achieved efficiently basing on enolate addition of dimethyldisulfide to **174** and following interaction with N-chloroaniline. Treatment with triethylamine and Ra-Ni reduction resulted in a [2,3]-sigmatropic rearrangement, rearomatization and reductive removal of thiomethyl unit to provide the coupled aniline **175**. Its dehydration afforded (-)-paspaline **171**.



Reagents and conditions: (a) CPTS, PhH, ethyleneglycol; (b) CPTS, PhH (77% over 2 steps); (c) $PhCH_2N_2$, PhH, TsOH, then EtOH and MVK (87%); (d) NaH, PhH (82%); (e) $ZnMe_2$, cat. $Ni(acac)_2$, Et_2O then TMSCl, Et_3N; (f) O_3, DCM then Me_2S (44% over 2 steps); (g) EVE, *p*-TSA (79%); (h) $LiN(SiMe_3)_2$, THF (75%); (i) Swern, then H_3O^+ (60%); (j) 70% $HClO_4$, DCM (83%); (k) PhSH, Et_3N then HCHO, EtOH (82%); (l) $Li/NH_3/H_2O$, THF, allyl bromide (50%); (m) TMSCl, Et_3N (95%); (n) $NaBH_4$, EtOH (95%, 6:1 mixture of epimers); (o) TBSOTf, Py, DCM (92%); (p) Citric acid, MeOH (91%); (q) PCC, DCM (85%).

Figure 1.27. An unified strategy for paspaline synthesis [56].

An alternative scheme for paspaline synthesis has been also reported [56], which aimed on an unified strategy, amendable for the synthesis of other indole diterpenes. The Wieland-Miescher ketone **176** was selectively protected and transformed to the tricyclic enone **177** making use of the Robinson annulations procedure (Figure 1.27). A diastereoselective methylation of **177** was performed, and the resulting enolether **178** was oxidatively cleaved to the aldo-acid **179**. Its cyclization and decarboxylation led to the key intermediate **180**, which was envisioned as a potential precursor for other diterpenic indoles of these series. Transformation of **180** to **173** included a linear sequence of protecting group manipulations and reductive alkylation to conclude the alternative formal synthesis of (-)-paspaline.



Reagents and conditions: (a) H_2NNMe_2, EtOH, AcOH (96%); (b) LDA, THF then **378** then BzOH, DCM (50%); (c) Ac_2O, Py, DMAP (84%); (d) MeI, HCO_2Na, $MeO(CH_2)_2OH$ (59%); (e) 70% $HClO_4$, DCM (76%); (f) K_2CO_3, MeOH (95%); (g) DCC, TFA, Py, DMSO, PhH (80%); (h) $RhCl_3$, EtOH, PhH (70%); (i) SeO_2, dioxane (44%).

Figure 1.28. Synthesis of paspalicine **181** and paspalinine **182** [57], [58].

Basing on the elaborated building block **180**, the synthesis of paspalicine **181** and paspalinine **182** has been reported [57], [58]. Unlike the synthesis of **173**, the strategy here was different and included building of the indole part basing on **180** and addition of the terminal pendant prenyl unit and heterocyclization in the end of synthetic sequence (Figure 1.28). The indole **183**, was generated from **180** in the same manner as described for the synthesis of **173**. Addition of the homoprenyl unit to **183** included generation of a dimethylhydrazone and its alkylation following a metalloenamine protocol. The coupling partner **184** was obtained in 6 steps from dimethylallyl alcohol **185**. After proper protecting group manipulation in the coupled product **186**, the heterocyclization has occurred and oxidation of the secondary alcohol provided natural paspalicine **181**. Selenium dioxide oxidation of **181** led to natural paspalinine **182**.

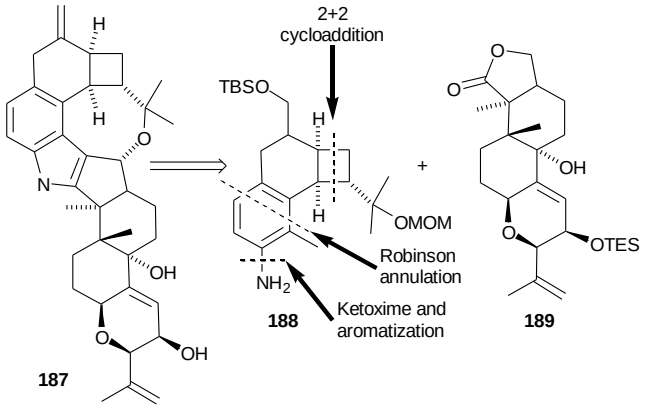
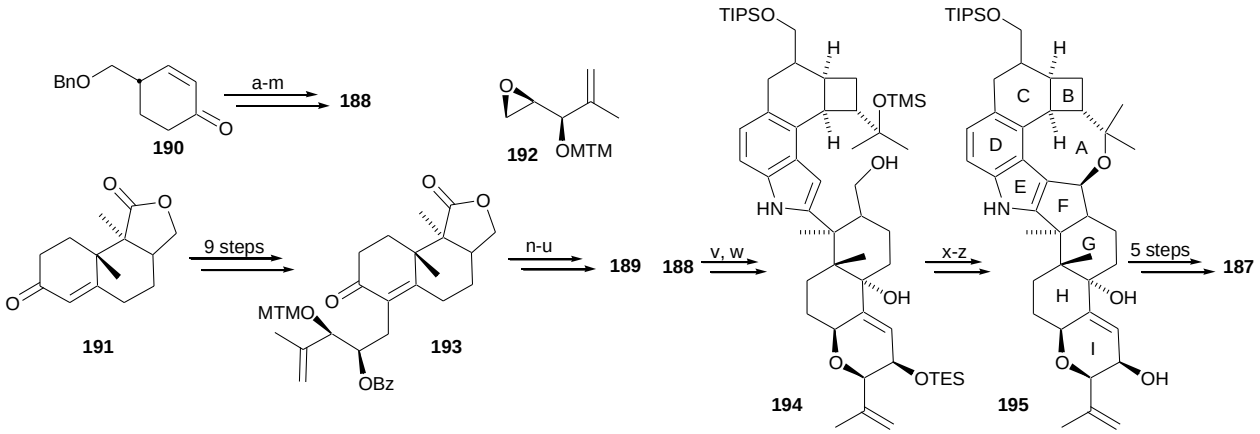


Figure 1.29. Retrosynthetic analysis of penitrem D **187**.

Penitrem D **187**, another fungal indole diterpenoid obtained synthetically [59],[60] required more efforts in order to face the multiple challenges of its extremely complex structure. Unlike the

examples reported above, **187** includes two additional isoprene units attached to the benzene ring of indole fragment, cyclized into a condensed C_6-C_4 bicycle. This structural feature required additional operations in order to assemble the western unit of **187** (C_{10}-indole) and a following convergent strategy included a union of both western **188** and eastern (diterpenic) fragments **189** by an original procedure of indole synthesis from o-toluidines and esters or lactones (Figure 1.29). The western unit **188** was assembled from optically active enone **190** and included 13 linear steps (Figure 1.30). Key transformations were a photochemical 2+2 cycloaddition for introduction of the cyclobutane unit, a modification of the Robinson annulations for introduction of the benzene ring precursor and finally a ketoxime formation, followed by aromatization to the suitable protected fragment of the western unit of **187**.

The eastern unit was generated from the known lactone **191**, which was alkylated with the homoprenyl building block **192** to ketone **193** according to the metalloenamine protocol, similar to that applied for the synthesis of **181** and **182**. Assembling the pyranic ring was achieved basing on a reductive cyclization protocol, involving hemiacetal formation, followed by reduction. An allylic autooxidation facilitated the introduction of the tertiary hydroxyl with the required stereochemistry in order to generate the eastern fragment **189**.



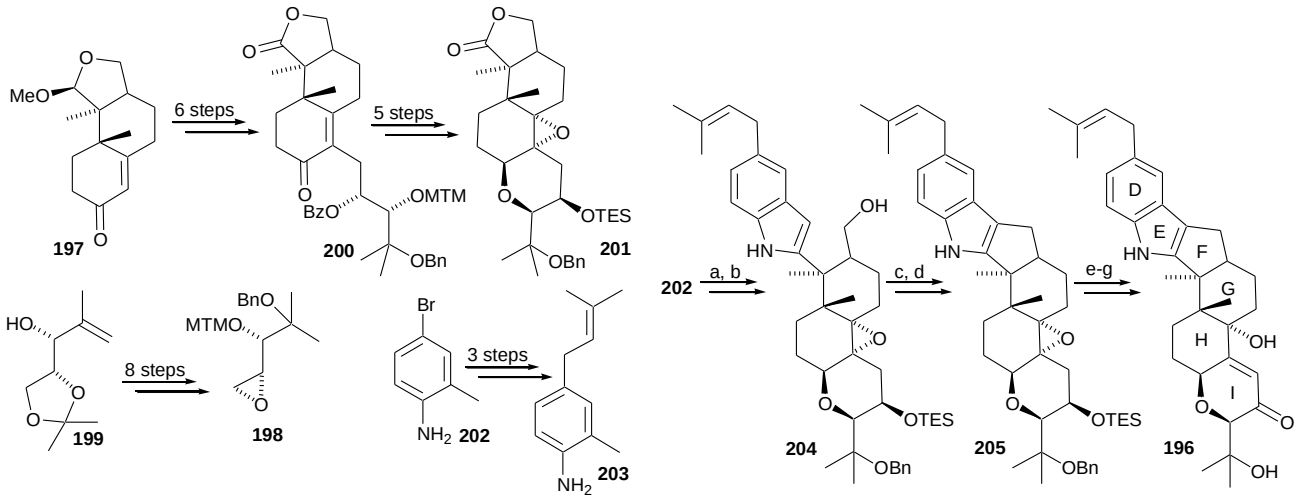
Reagents and conditions: (a) Methyl acrylate, DCM, hν (b) $(MeO)_3CH$, Amberlist-15; (c) MeMgBr, PhH; (d) PPTS, Me_2CO; (e) MOMCl, DIPEA, DCM (82%); (f) NaH, THF, EtOCHO; (g) EVK, Et_3N; (h) KOH, MeOH-H_2O (86% over 3 steps); (i) NH_2OH HCl, NaOAc, MeOH (85%); (j) Bz_2O, xylene; (k) NaOH, EtOH-H_2O (67% over 2 steps); (l) H_2, $Pd(OH)_2$/C, EtOH (98%); (m) TBSCl, DMAP, DIPEA, DCM (88%); (n) TfOH, Et_3SiH, PhMe (60%); (o) K_2CO_3, MeOH-H_2O; (p) EDCl, DMAP, DCM (90% over 2 steps); (q) DMP, DCM; (r) Si-gel, air, EtOAc (65% over 2 steps); (s) PPh_3, PhH (93%); (t) L-Selectride, THF; (u) TESOTf, 2,6-lutidine, DCM (76% over 2 steps); (v) BuLi, TMSCl, Et_2O then *s*-BuLi and 0.1 equiv. **189**, THF-Et_2O; (w) Si-gel, $CHCl_3$ (81% from **189**); (x) SO_3 Py, DMSO-Et_3N; (y) 1 N HCl, THF-H_2O (76% over 2 steps); (z) $Sc(OTf)_3$, PhH (62%).

Figure 1.30. Synthesis of penitrem D **187** [59],[60].

Connection of both western and eastern units included protection of the free amine in **188** by

silylation, lithiation and treatment with **189**. The primary hydroxyl group in the coupled product **194** was oxidized to the aldehyde and the tandem A, F ring system assembly in **195** was achieved by $Sc(OTf)_3$ treatment. Additional 5 steps (protecting groups manipulations and generation of the exomethylenic double bond) were required to obtain penitrem D **187**.

The synthetic strategy applied for the synthesis of penitrem D **187** was adopted with some modifications for the synthesis [61],[62] of another representative of fungal diterpenic indoles – (-)-21-isopentenylpaxilline **196** (Figure 1.31). The starting material was the mixed acetal **197** derived from the known lactone **191**. A similar metalloenamine acylation protocol reported above have been used to couple the dimethylhidrazone derived from **197** and the homoprenyl epoxide **198**. The latter was made available from optically active fragment **199** in 8 steps. The coupling product **200** after protecting group manipulations has been submitted to the reductive ketalization protocol reported in the synthesis of **187** to form the required pyranic ring. But unlike the synthesis of **187**, introduction of the tertiary hydroxyl in the E-ring was not achieved by autooxidation. In alternative, it was envisioned on fragmentation of an epoxyketone functionality via ketone enolization. Therefore, epoxidation was necessary in order to prepare the eastern (diterpenic) part of molecule **201**.



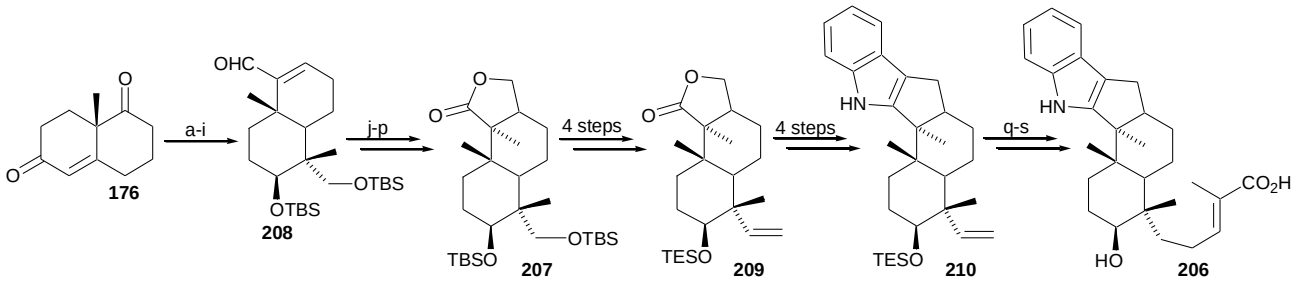
Reagents and conditions: (a) MeLi, Et_2O, TMSCl then *s*-BuLi and quench with 0.05 equiv. of **394**; (b) PhH, 110 ^oC (76% over 2 steps); (c) MsCl, DMAP, DCM (90%); (d) *t*-BuMgCl, PhH, 110 ^oC (73%); (e) TBAF, THF (93%); (f) Ph_3BiCO_3, PhH (69%); (g) 10% Pd/C, 1-methyl-1,4-cyclohexadiene, MeOH (70%).

Figure 1.31. Synthesis (-)-21-isopentenylpaxilline **196** [61],[62].

The western part of **196** is much more simple than that of **187** and contains only a single prenyl residue connected to the indole ring. In order to apply the same method of indole preparation from o-toluidines, prenylation of bromide **202** was performed to give the western coupling partner **203** in

three steps. Coupling of both fragments delivered the primary alcohol **204**, which cyclized after mesylation under the action of *t*-BuMgCl into the hexacyclic intermediate **205**. Additional 3 steps (protecting groups manipulations and oxidation of the secondary hydroxyl, accompanied by epoxide fragmentation) were required to obtain (-)-21-isopentenylpaxilline **196**.

Nodulosporic acid F **206** has been also obtained synthetically by the same research group of Smith [63],[64] and it included some modifications to the strategies reported above (Figure 1.32). The use of the general approach based on the common precursor **180** was not feasible, since the biosynthetic origin of **206** does not include the oxidative removal of the angular methyl from the E ring of the pentacyclic architecture. Therefore, the lactone **207** has been elaborated [65] to include both angular methyl group and an oxygenated functionality for the following finishing the pendant prenyl unit. The starting Wieland Miescher ketone **176** was selectively protected and submitted to (phenylthio)methylation, followed by reductive alkylation utilizing aqueous formaldehyde and $Sc(OTf)_3$ as a water tolerant Lewis acid. After the reduction of the ketone functionality, both primary and secondary hydroxyls have been protected as TBS- derivatives and the protection group from the remaining ketone functionality has been removed. The resulting ketone was converted to the corresponding enol-triflate and formylated under Pd(0) catalysis to furnish the nor-drimanic aldehyde **208**. It required other 8 steps in order to be converted to the desired tricyclic lactone **207**.



Reagents and conditions: (a) TsOH, 2-ethyl-2-methyl-1,3-dioxolane, ethylene glycol; (b) PhSH, aq. HCHO, Et_3N, EtOH (79% over 2 steps); (c) Li / NH_3, THF, *t*-BuOH; TMSCl, Et_3N; (d) $Sc(OTf)_3$, aq. HCHO, THF (75% over 2 steps); (e) $Me_4NBH(OAc)_3$, MeCN-AcOH (40%); (f) 2N HCl, THF (94%); (g) TBSOTf, 2,6-lutidine, DCM (90%); (h) LHMDS, THF, N-(5-chloro-2-pyridyl)triflimide (90%); (i) $Pd(PPh_3)_4$, CO, Bu_3SnH, THF, LiCl (95%); (j) L-tert-leucine tertbutyl ester, 4A MS, PhH (94%); (k) $CH_2CHMgBr$, THF then MeI, HMPA then 10% citric acid (59%); (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H2O; (m) $TMSCHN_2$, MeOH-PhH (87% over 2 steps); (n) O_3, DCM, Me_2S; (o) DBU, THF (70% over 2 steps); (p) $NaBH_4$, MeOH (80%); TsOH, PhH (81%); (q) 9-BBN dimer, PhMe then methyl-(E)-3-bromo-2-methylpropenoate, $Pd(dppf)Cl_2$, K_3PO_4, DMF (69%); (r) LiOH (1 M), MeOH/THF; (s) *p*-TSA, MeOH (80% over 2 steps).

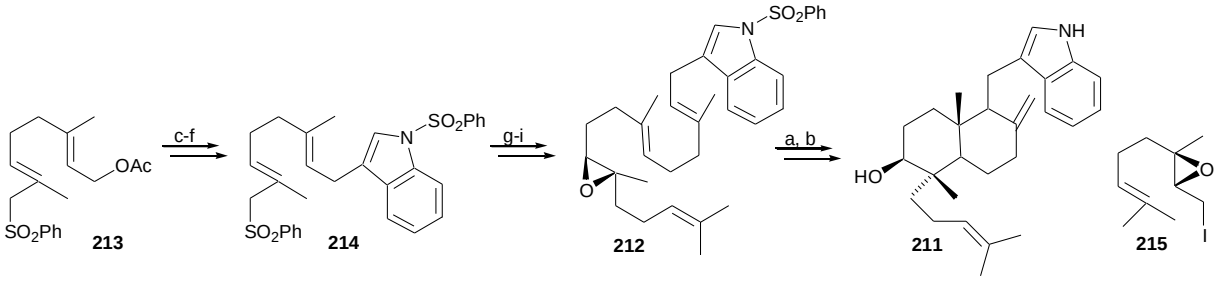
Figure 1.32. Synthesis of nodulosporic acid F **206** [63],[64].

The key step was a Koga three component conjugate addition-alkylation of an imine derived from **208**. The alkylated product was transformed to the lactone **207** by several functional group transformations, including ozonolytic degradation of the vinyl group, reduction and lactonization. The

lactone **207**, regarded as a common building block for the whole family of nodulosporic acids, has been transformed to nodulosporic acid F via additional 11 steps. These included addition of one carbon to the terminal pendant prenyl unit by a Wittig olefination, and attachment of the indole fragment to the resulting **209** via the above mentioned o-toluidine protocol. The end game included a Suzuki-Miyuara cross-coupling of the alkylborane generated from **210** and methyl-(E)-3-bromo-2-methylpropenoate, followed by protecting groups removal.

And the last example in the diterpenic indole series is the synthesis of emindole SA **211**. The beauty and splendor of the reported synthetic scheme resides into the biomimetic approach devised by authors more than one decade ago [66] and matching exactly the enzymatic machinery discovered only recently for this family of fungal metabolites [67].

The synthetic scheme is very simple, and is based on one single key transformation: biomimetic cyclization of the diterpenic indole **212** under the action of a Lewis acid. It was anticipated that epoxidation of the internal double bond of the geranylgeranyl chain will favor initiation of the cyclization process from the corresponding epoxy-group, leaving one prenyl unit pendant to the formed bicyclic fragment. Although the yield of this cascade reaction was modest, the efficiency of the whole synthetic scheme is relevant, since it includes a limited number of steps (Figure 1.33).



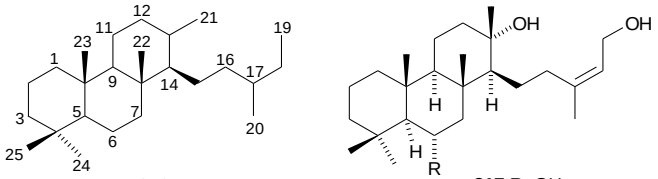
Reagents and conditions: (a) $BF_3 \cdot Et_2O$, DCM (20%); (b) Et_2NH, Li (75%); (c) Na_2CO_3, MeOH (80%); (d) NBS, DMS, DCM; (e) indole, EtMgBr, PhH (60% over 2 steps); (f) $PhSO_2Cl$, 50% KOH (aq.), $BuNHSO_4$, PhH (72%); (g) LDA, DMEU, THF, (-)-**215** (83%); (h) $EtNH_2$, Et_2O, Li, MeOH (63%); (i) $PhSO_2Cl$, 50% KOH (aq.), $BuNHSO_4$, PhH (95%).

Figure 1.33. Synthesis of emindole SA **211** [66].

The starting phenylsulfone **213** has derived from geraniol and was transformed to the prenylated indole by direct coupling. Protection of the indole nitrogen as a N-phenylsulfonyl derivative **214** was followed by lithiation and union with the optically active epoxy-iodide **215**, amendable from geraniol by Sharpless epoxidation. The coupled product was submitted to reductive desulfurization and re-protection of the indole nitrogen delivered the cyclization substrate **212**. Its treatment with boron trifluoride etherate led to the N-protected emindole SA, which was efficiently deprotected to the natural product **211** under reductive treatment.

1.2. Synthetic methods towards cheilanthanic sesterterpenoids

Cheilanthanes represent a relatively new class of tricyclic sesterterpenoids with a carbon skeleton of the hypothetic cheilanthane **216** (Figure 1.34). It represents a tricyclic condensed system with a free "head" prenyl unit. Such a molecular architecture suggests a biosynthetic pathway *via* a controlled enzymatic cyclization of the open chain precursor catalyzed by class II cyclases and selectively suspended to a tricyclic structure with the head isoprene unit remaining pendant.



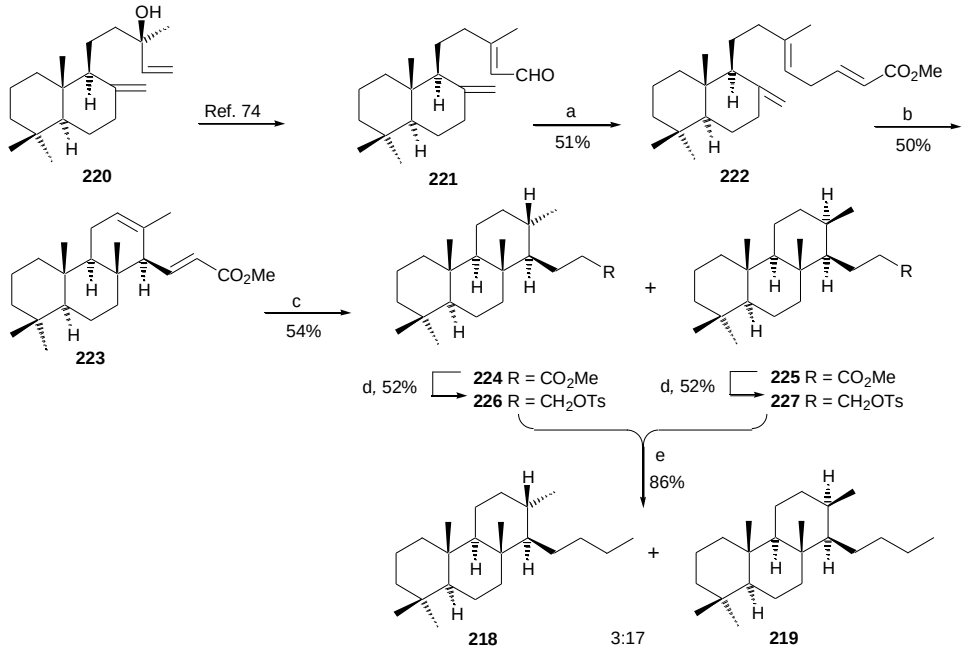
216 **217** R=OH **255** R=H

Figure 1.34. Representatives of cheilanthane sesterterpenoids.

The name "cheilanthane" is derived from the name of the fern *Cheilanthes farinosa* – the source of the first representative of this class of compounds, namely cheilanthatriol **217**, isolated in 1971 by Indian researchers [68]. Numerous cheilanthanic sesterterpenoids have been isolated later on from other plant sources, marine organisms and fossil sediments. Today, there are more than 50 known cheilanthanes. The majority of these compounds have been isolated in the 1990s, mostly from marine sources. The interest in these compounds is first of all due to their strong biological activity. This aspect has also inspired synthetic chemists to develop several synthetic routes to cheilanthane sesterterpenoids. An outline of the synthetic approaches implemented for the synthesis of cheilanthanic structures will be provided below. The information on their occurrence in natural sources and biological activity can be found in the published review paper [69].

The first reports on the synthesis of cheilanthanes go back 20 years and concern the bisnorcheilanthane hydrocarbons **218** and **219**, isolated from petroleum sediments [70],[71],[72]. These syntheses were targeted to molecular markers in petroleum sediments. Herz and collaborator were the first to prepare the hydrocarbons **218** and **219**, starting from manool **220** (Figure 1.35) [73]. Manool was oxidized to aldehyde **221** according to a reported procedure [74], followed by chain elongation by a Wittig-Horner reaction to provide the triene **222**. This triene was cyclized to the trisnorcheilanthanic ester **223**, followed by hydrogenation over PtO_2 to a mixture of esters **224** and

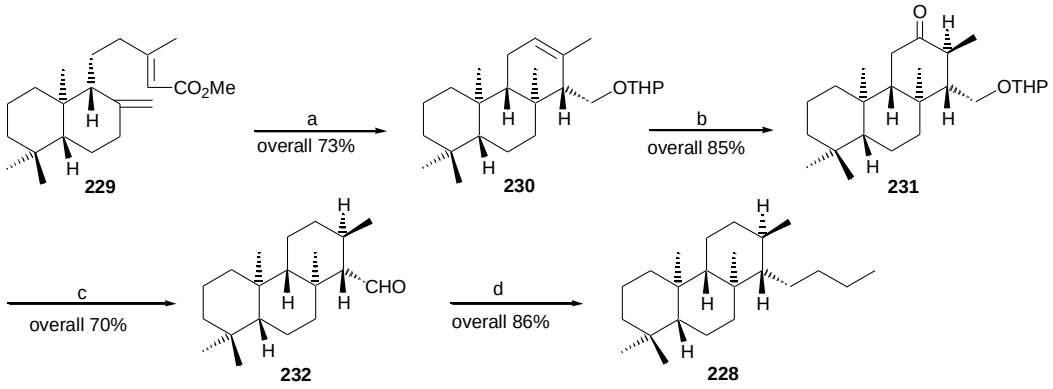
225 (~1:10), which was converted in two steps via tosylates **226** and **227** into a mixture of hydrocarbons **218** and **219** (~3:17).



Reagents and conditions: (a) $(MeO)_2P(O)CH_2CO_2Me$; NaH, DMSO, 60 ºC, 30 min; (b) BF_3 Et_2O, C_6H_6, 10 ^oC to rt, 72 h; (c) H_2, PtO_2, AcOH, rt, 6 h; (d) (1) $LiAlH_4$, Et_2O, rt; (2) *p*-TsCl, Py, rt; (e) MeMgCl, Li_2CuCl_4, THF.

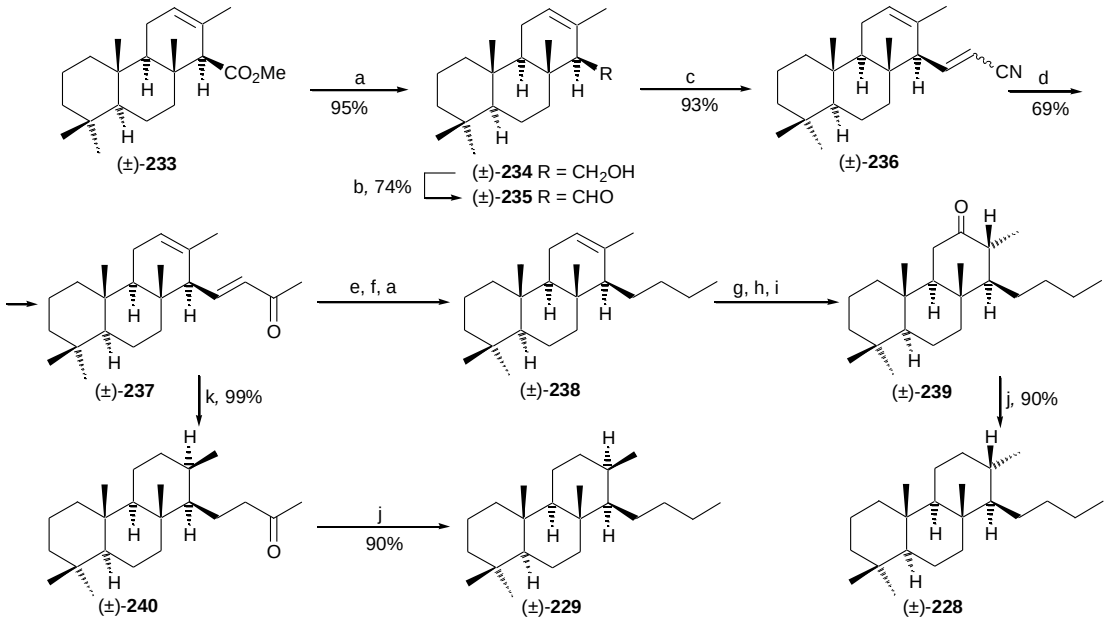
Figure 1.35. The first synthesis of cheilanthanes: hydrocarbons **218** and **219** [73].

The synthesis of bisnorcheilanthane **228**, the enantiomer of **218**, was reported starting from the methyl ester of copalic acid **229** (Figure 1.36) [75], which was transformed in three steps into the isocopalic THP-ether **230** in good yield. The later was converted in three steps into the ketoether **231**, and another three standard reactions provided the tricyclic saturated aldehyde **232**. Wittig olefination of **232** and hydrogenation then led to the hydrocarbon **228**.



Reagents and conditions: (a) (1) HCO_2H (98%), rt, 12 h; (2) $LiAlH_4$, Et_2O, reflux, 4 h; (3) DHP, CH_2Cl_2, CSA, rt (b) (1) BH_3 SMe_2, THF, 20 h; (2) H_2O_2, 3 M NaOH aq., EtOH, reflux, 1 h; (3) CrO_3 2Py, CH_2Cl_2, rt; (c) (1) N_2H_2 H_2O, *p*-TsOH, $(HOCH_2)_2$, 130 ºC, 4 h, then KOH, 210 ºC, 3 h; (2) 10% HCl (aq), MeOH, Hexane, (3) CrO_3 $_2$Py, CH_2Cl_2, rt; (d) (1) Ph_3P=CHEt, DMSO, (2) H_2, 10%Pd/C, MeOH-EtOAc.

Figure 1.36. Synthesis of bisnorcheilanthane **228** [75].



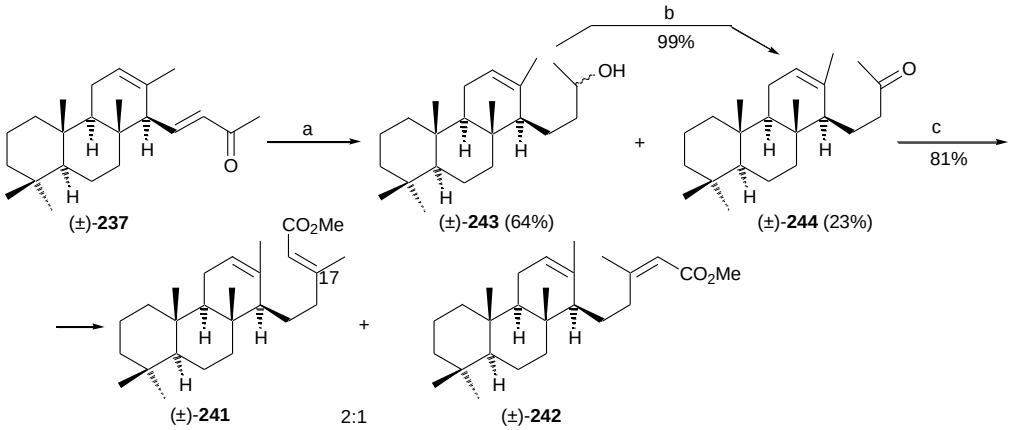
Reagents and conditions: (a) $LiAlH_4$, Et_2O, reflux, 2 h; (b) PCC-Al_2O_3, C_6H_6, rt, 3 h; (c) NaH, $(MeO)_2P(O)CH_2CN$, THF; (d) (1) MeLi, Et_2O, 0 ºC; (2) 1 N H_2SO_4-Me_2CO (1:9), 1 h; (e) Na/NH_3 (liq.), -69 ºC, 1 h; (f) *p*-TsCl, Py, CH_2Cl_2, rt, 15 h; (g) (1) BH_3 SMe_2, rt, 20 h; (2) H_2O_2, 3 M NaOH, 40 ºC, 1.5 h; (h) Jones reagent, Me_2CO, 0 ºC; 30 min; (i) MeONa, MeOH, rt, 30 min, overall yield after 6 steps ~40%; (j) (1) $(HSCH_2)_2$, BF_3 Et_2O, CH_2Cl_2, rt, 14 h; (2) Ra-Ni, EtOH, reflux, 4 h; (k) PtO_2, H_2 (3 atm), EtOAc, rt, 4 h.

Figure 1.37. Synthesis of the bisnorcheilanthanic hydrocarbons **228** and **229** [76].

Racemic methyl isocopalate **233** was used as starting material by Ruveda and collaborators [76] in the synthesis of the bisnorcheilanthanic hydrocarbons **228** and **229** (Figure 1.37). The side chain of the ester **233** was elongated in five steps. Initial reduction of the ester **233** to the corresponding alcohol **234** was followed by oxidation to the aldehyde **235**, olefinated with the corresponding phosphonate to the diene **236**. The latter was transformed to the α,β–unsaturated ketone **237**, which was converted into the individual bisnorcheilanthane hydrocarbons **228** and **229** by two different pathways. A three-step saturation-deoxygenated of the lateral chain in **237** provided the hydrocarbon **238**, which was transformed over other three steps to the tricyclic ketone **239**. Deoxygenation of **239** led to the hydrocarbon **228**. The hydrocarbon **229** was obtained in two steps from **237** via the tricyclic ketone **240**.

Ketodiene **237** was used in the synthesis of the racemic cheilanthane methyl esters **241** and **242** (Figure 1.38) [77]. Reduction of the double bond led also to reduction of the carbonyl group and a mixture of alcohol **243** and ketone **244** was obtained. Re-oxidation of the alcohol **243** with Jones reagent gave a quantitative yield of ketone **244**. A Wittig-Horner olefination led to the formation of a

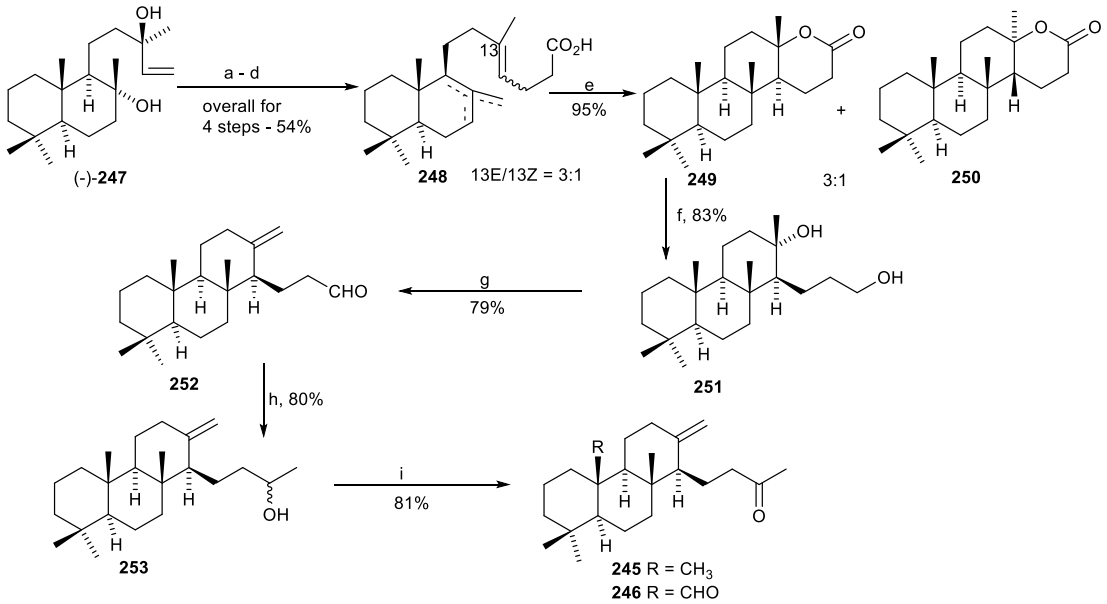
mixture of the cheilanthane esters **241** and **242**. Separation of this mixture was not reported, and the esters have been characterized as a mixture.



Reagents and conditions: (a) Na/NH_3 (liq.), -69 ºC, 1 h; (b) Jones reagent, Me_2CO, 0 ºC; 30 min; (c) $(MeO)_2P(O)CH_2CO_2Me$; C_6H_6, NaOMe, 70 ºC, 1 h.

Figure 1.38. Synthesis of racemic cheilanthane methyl esters **241** and **242** [77].

The synthesis of 23-deoxoluteone **245**, an analogue of the natural compound, luteon **246**, has been performed starting from (-)-sclareol **247** (Figure 1.39), which was converted in four steps into a mixture of the bishomolabdanic acids **248** [78]**.**

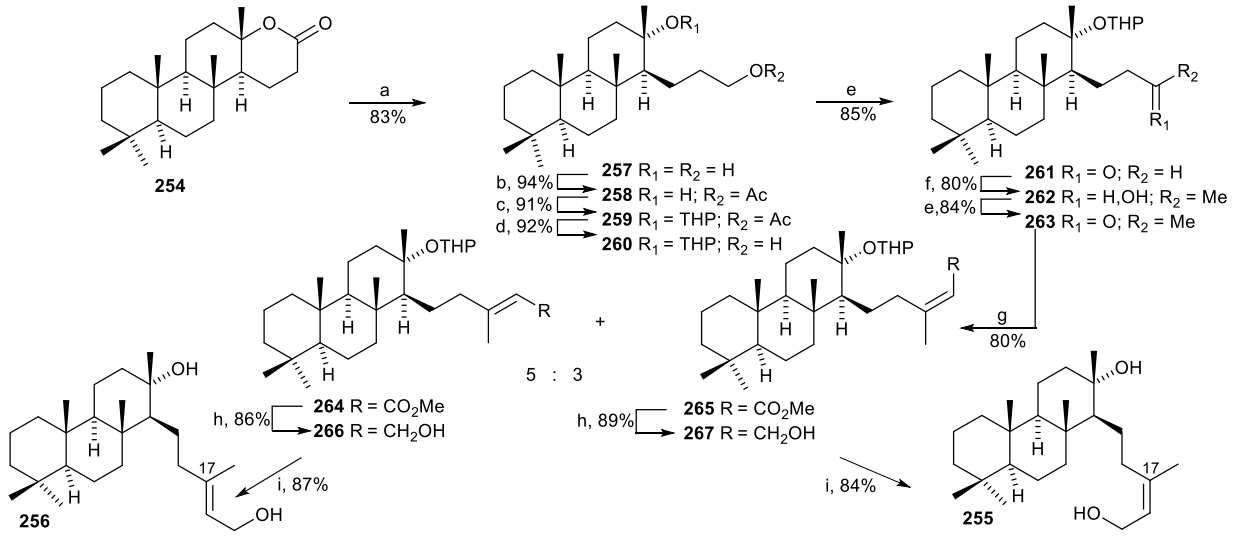


Reagents and conditions: (a) PBr_3/Et_2O, Py, 0 C, 12 h; (b) K_2CO_3, $CH_2(CO_2Et)_2$; DMF, Me_2CO, $Et_3BnN^+Cl^-$, 75 ^oC, 20 h, 77%; (c) NaCl/DMSO-H_2O, 155 ^oC, 26 h, 83%; (d) 10%KOH/EtOH, reflux, 5 h, 90%; (e) FSO_3H (11 eq), *i*-$PrNO_2$, -80 ^oC, 20 min, 95%; (f) $LiAlH_4$, THF, rt, 3.5 h, 83%; (g) $(COCl)_2$/DMSO, CH_2Cl_2, -60 ^oC, 45 min, then Et_3N, 79%; (h) MeMgI (2.5 eq), Et_2O, rt, 30 min, 80%; (i) PDC/CH_2Cl_2, rt, 4 h, 81%.

Figure 1.39. Synthesis of 23-deoxoluteone **245** [78].

This mixture was submitted to a low-temperature superacidic cyclisation to provide a mixture of the lactones **249** and **250** in excellent yield (95%). The prevailing lactone **249** was transformed into the corresponding diol **251**, which was oxidized with Swern reagent to the aldehyde **252**. It is noteworthy that the oxidation is accompanied by a selective dehydration process to the exocyclic isomer, matching exactly the structure of the natural compound. Subsequent transformation of compound **252** via alcohol **253** led to the bisnorcheilanthane ketone **245** in good yields.

Lactone **254** has served as starting material for the synthesis of the natural cheilanthadiol **255** and its 17*E*-isomer **256**. All subsequent transformations of lactone **254** are represented in Figure 1.40. Although the synthetic sequence in this approach is quite long, it is attractive, due to the high yields of all transformations [79]. Reduction of lactone **254** to the diol **257**, followed by the selective acetylation, led to the monoacetate **258**. Protection of the free hydroxyl-group as a THP-derivative **259** and following removal of acetyl protection produced the primary alcohol **260**. This was oxidized to the aldehyde **261**, which was methylated with methylmagnesium iodide. Further oxidation of the resulting secondary alcohol **262** provided the ketoether **263**.

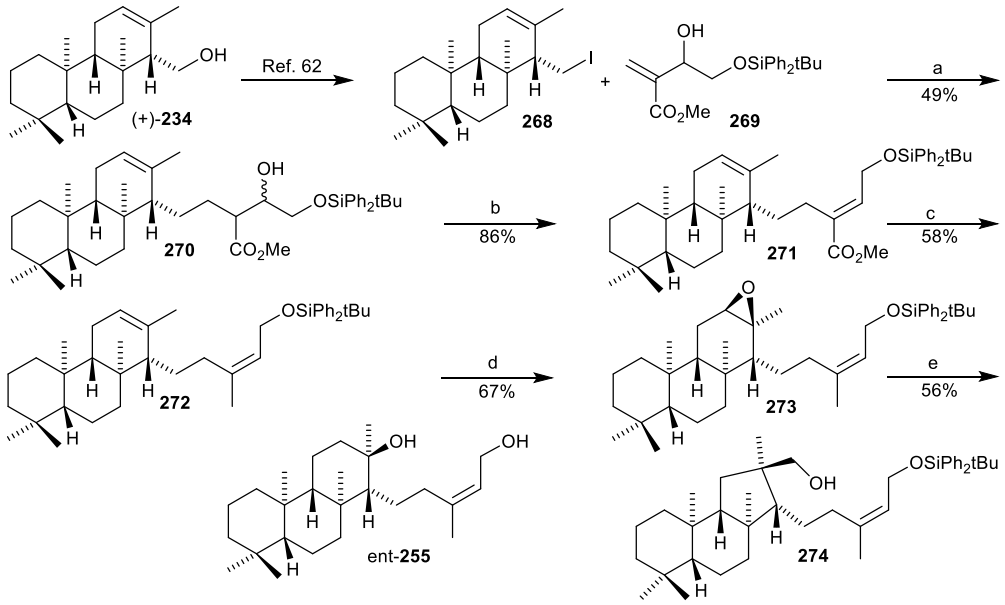


Reagents and conditions: (a) $LiAlH_4$, THF, rt, 3.5 h, (b) Ac_2O/Py, rt, 10 h; (c) DHP, C_6H_6, *p*-TsOH (cat), rt, 2 h; (d) 10% KOH/EtOH, rt, 3 h; (e) PDC/CH_2Cl_2, rt; (f) MeMgI (3 eq), Et_2O, rt, 45 min; (g) LDA,THF, -78 °C, $Me_3SiCH_2CO_2Me$, 40 min; (h) $LiAlH_4$ - $CeCl_3$/THF, rt, 20 min; (i) 0.02 N H_2SO_4/MeOH, rt, 40 min.

Figure 1.40. Synthesis of cheilanthadiol **255** [79].

Olefination of the ketogroup in **263** with methyl trimethylsilylacetate led to a mixture of esters **264** and **265**, which were separated chromatographically. Cerium-assisted reduction of the individual isomers provided the alcohols **266** and **267**, respectively. A final deprotection step gave the individual

cheilanthadiols (17*E*)- **256** and (17*Z*)- **255**. The overall synthetic sequence counted ten steps and provided the target cheilanthanes in 26% overall yield, starting from the readily available lactone **254**.



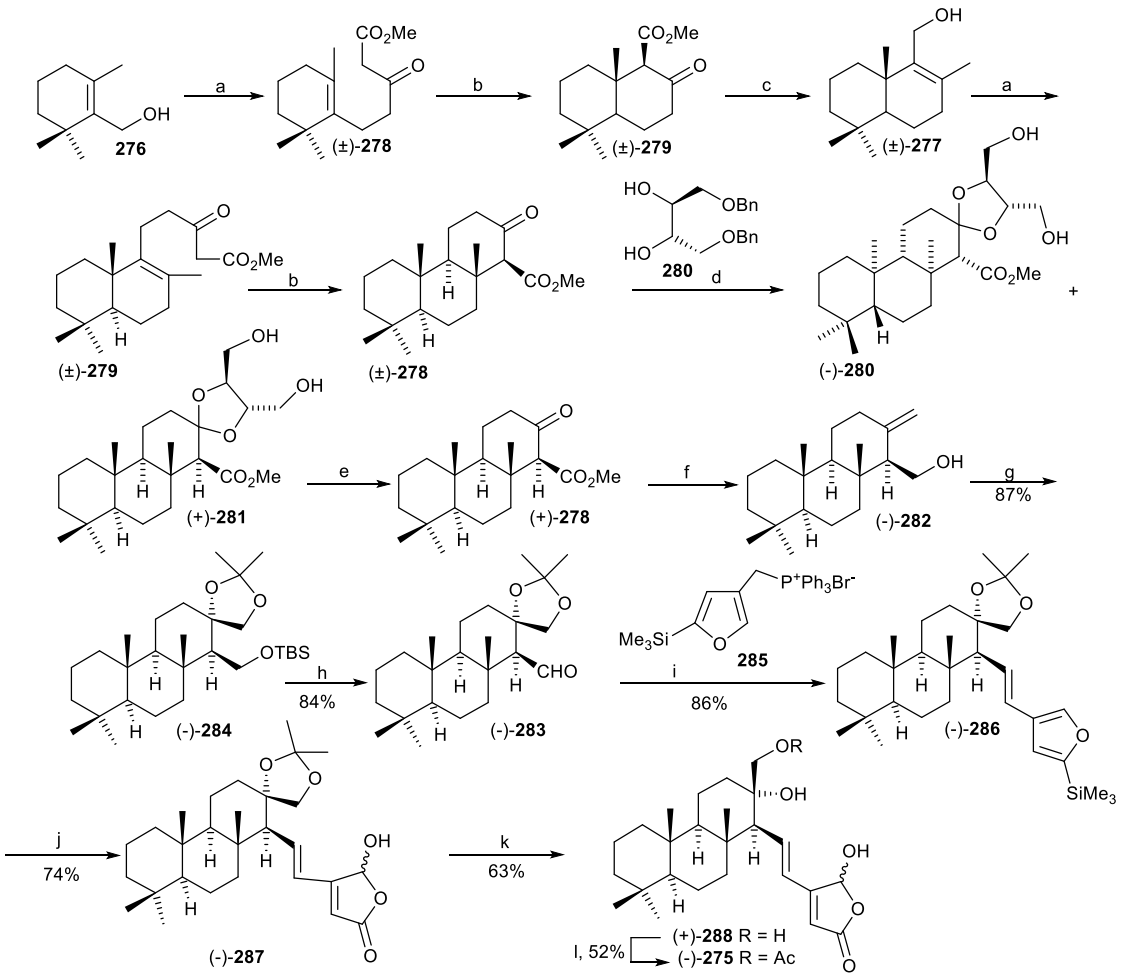
Reagents and conditions: (a) **269** (6 equiv.), Bu_3SnH (1.8 equiv), Et_2O, hν (200 W tungsten lamp), 5 h; (b) (1) MsCl, NEt_3, CH_2Cl_2, 0 ºC; (2) DBU, PhMe, reflux 4 h; (c) (1) *i*-Bu_2AlH, PhMe, -78 ºC; (2) CCl_4, PPh_3, reflux 3 d; (3) $LiBHEt_3$, THF, 30 min; (d) *m*-CPBA, CH_2Cl_2, -10 ºC, 1.25 h; (e) (1) $LiAlHiBu_2nBu$, DME, reflux, 3.5 h; (2) *n*-Bu_4NF, THF, rt, 7.5 h.

Figure 1.41. Synthesis of *ent*-cheilanthadiol **255** [80].

The synthesis of *ent*-cheilanthadiol **255** was realized by Heisler and collaborator [80]. The starting compound was isocopalic iodide **268**, obtained from isocopalic alcohol (+)-**234** by the same group (Figure 1.41) [81]. The key step in this synthesis was the radical-induced coupling of iodide **268** with compound **269**. This provided the cheilanthane skeleton **270**, which was transformed in two steps into compound **271** and another three steps provided the *ent*-cheilanthane derivative **272**. This was selectively epoxidised to **273** and reduction of this epoxide with a complex hydride in DME followed by removal of the protective group led to *ent*-cheilanthadiol **255**. It is noteworthy that this final reduction step, performed with the same reagent in toluene, led selectively to the rearranged product **274**.

A cascade method of (-)-spongianolide A **275** synthesis was developed starting from β-cyclogeraniol **276** (Figure 1.42) [82],[83]. The later was transformed into the racemic isodrimenol **277** via compounds **278** and **279**. After a similar reaction sequence, isodrimenol **277** was transformed via the ester **280** to the tricyclic ketoester **281**. It was coupled with the optically active 1,4-*O*-benzyl-L-threitol **282**, and the resulting mixture of diastereomers **283** and **284** was separated

chromatographically. After the hydrolysis of the ester **284** to the optically active keto-ester **285**, the tricyclic alcohol **286** was obtained over two additional steps.

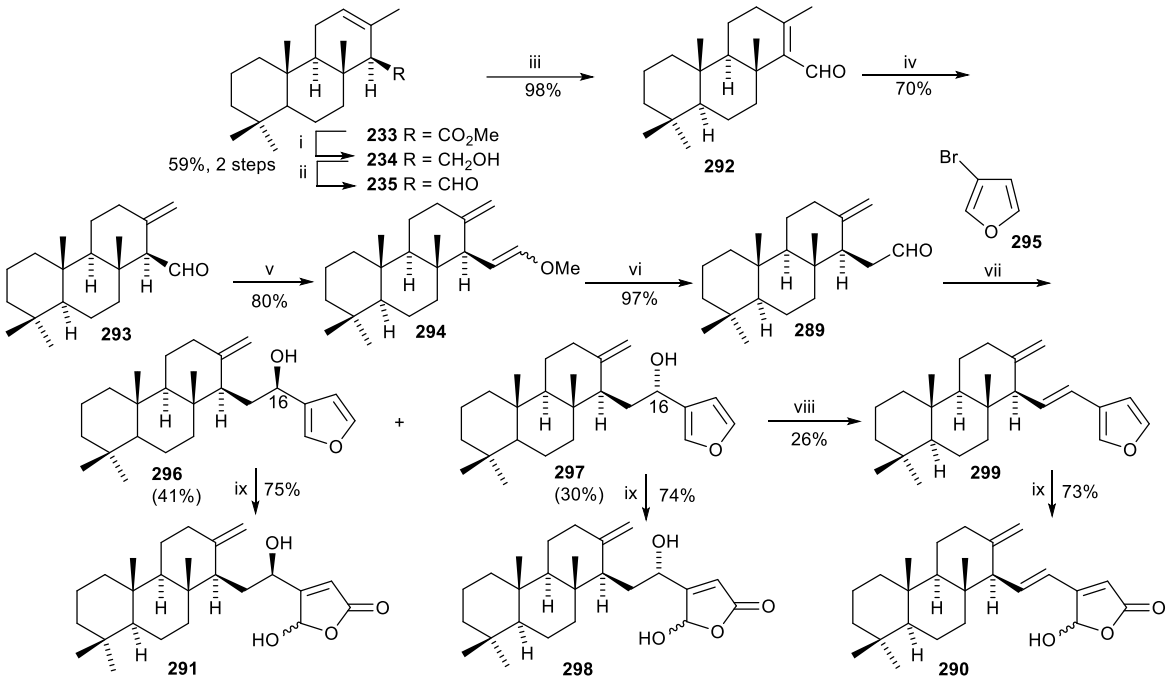


Reagents and conditions: (a) (1) PBr_3, Py, Et_2O; (2) NaH, THF, $MeC(O)CH_2CO_2Me$, 0 ºC, *n*-BuLi; (b) $SnCl_4$, CH_2Cl_2, -10 ºC (0.5 h), rt, (20 h); (c) (1) NaH, THF, 0 ºC, $ClP(O)(OEt)_2$, 0 ºC to rt, 10 min; (2) MeLi, CuI, Et_2O, -10 º to 0 ºC, 30 min; (3) $LiAlH_4$, Et_2O, rt, overnight; (d) (1) 280, *p*-TsOH, C_6H_6, 90 ºC, 2 h; (2) Pd/C, H_2, 68 atm, EtOAc, 23 ºC, overnight; (3) SiO_2 separation; (e) 2N H_2SO_4 -aq. MeOH, THF, 90 ºC, 2 d; (f) (1) $Ph_3P^+MeBr^-$, $NaNH_2$, THF, rt, 10 min; (2) $LiAlH_4$, THF, rt, 12 h; (g) (1) Et_3N, DMAP, TBDMSCl, DMF, 0 ºC, quant.; (2) OsO_4, Py, 4 h, then 2 M $NaHSO_3$ aq., 18 h, rt; (3) PPTS, $Me_2C(OMe)_2$, Me_2CO, rt; (h) (1) *n*-Bu_4NF, THF, 60 ºC, 3 h; quant; (2) $(COCl)_2$, DMSO, CH_2Cl_2, -78 ºC, 40 min, then Et_3N; (i) n-BuLi, 285, THF, then (-)-**283**, 0 ºC 1 h; (j) O_2, TPP, h , CH_2Cl_2, -78 ºC 30 min; (k) 2 N HCl aq, THF, 60 ºC, 2 days; (l) (1) Ac_2O, Py, 50 ºC 3 h; (2) $NaHCO_3$ aq, MeOH, rt, 30 min.

Figure 1.42. Synthesis of (-)-spongianolide A **275** by a cascade method [82],[83].

Transformation to the aldehyde **287** was achieved via compound **288**. Following coupling with the phosphorane **289** led to the sesterterpenic derivative **290** which was photolytically oxidized into the butenolide **291**. The last two steps included removal of acetonide protection to give the diol **292**, followed by acetylation to complete the synthesis of (-)-spongianolide A **275**.

Recently the synthesis of three biologically active cheilanthanes has been accomplished [84]. Aldehyde **289** was obtained in six steps from the optically active methyl *ent*-isocopalate **233** as a key synthon in the synthesis of natural cheilanthanes **290** and **291** (Figure 1.43). Accordingly, its tetrasubstituted isomer **292** was transformed over two steps into the aldehyde **293** containing the exocyclic double bond. Additional two steps provided the aldehyde **289**, via the ether **294**.

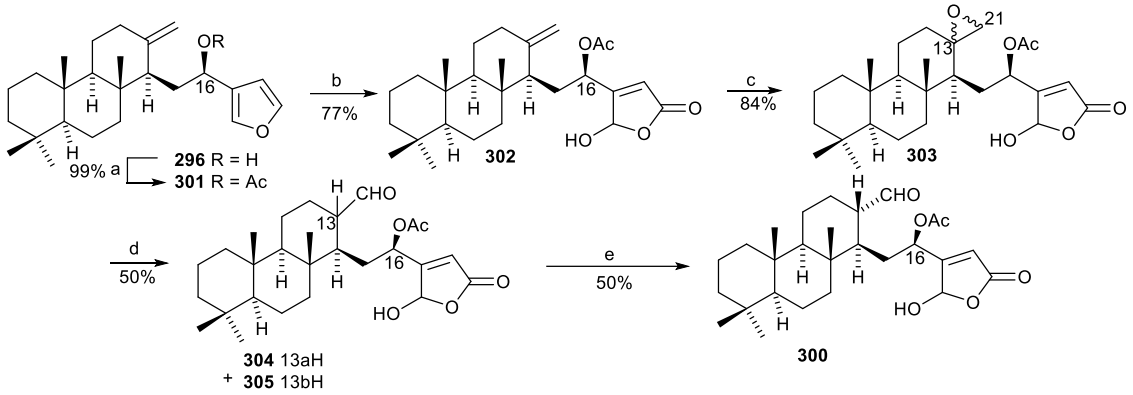


Reagents and conditions: (a) *i*-Bu_2AlH, CH_2Cl_2, -78 °C, 2 h; (b) TPAP, NMO, CH_2Cl_2, sieves 4 Å, rt, 1 h; (c) *p*-TsOH, C_6H_6, 80°C, 2 h; (d) (1) LDA, HMPA, THF, -78 °C, 20 min, (2) H_2O/THF 1:3; (f) $(MeOCH_2Ph_3)^+Cl^-$, NaHMDS, THF, -78°C, 1 h; (g) *p*-TsOH, acetone/H_2O 45:1, rt,12 h; (h) 3-bromofuran 148, *n*-BuLi, -78 °C, 1 h; (i) $POCl_3$, Py, 0°C to rt, 4 h; (j) $^1O_2$ hν , Rose Bengal, CH_2Cl_2, -78 °C, 3 h.

Figure 1.43. Synthesis of natural cheilanthanes **290** and **291** [84].

Aldehyde **289** was coupled with 3-bromofurane **295** to give the 16*R*- **296** and 16*S*- **297** epimeric alcohols, which were separated chromatographically. Photo-oxidation in the presence of Rose Bengal then led to the natural cheilanthane **291** [85] and its epimer **298**. Dehydration of the mixture of alcohols **296** and **297** with phosphorus oxychloride provided the diene **299** in a modest 26% yield. The later was converted into the natural cheilanthane **290** by photo-oxidation [85].

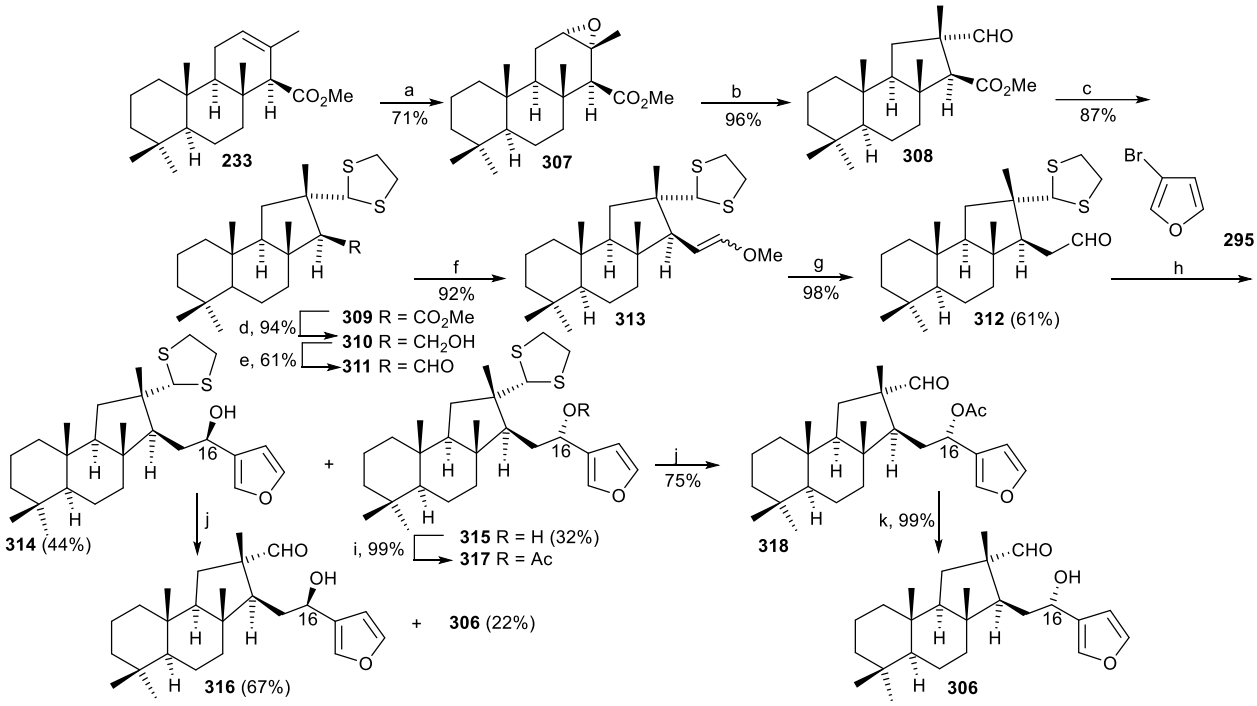
Luffolide **300** was obtained in a five steps sequence from the cheilanthanic furo-alcohol **296** (Figure 1.44) [86]. Initial protection of the secondary hydroxyl provided acetate **301**, transformed over three steps via compound **302** into a mixture of α– and β–epoxides **303**, which upon isomerization led to the natural compound **300**.



Reagents and conditions: (a) Ac_2O, Py, rt, 12 h; (b) $^1O_2$ hν, Rose Bengal, CH_2Cl_2, -78 °C, 3 h; (c) *m*-CPBA, CH_2Cl_2, rt, 1 h; (d) $BF_3{\cdot}Et_2O$, C_6H_6, 10 °C, 5 min; (e) *p*-TsOH, C_6H_6, rt, 12 h.

Figure 1.44. Synthesis of luffolide **300** [86].

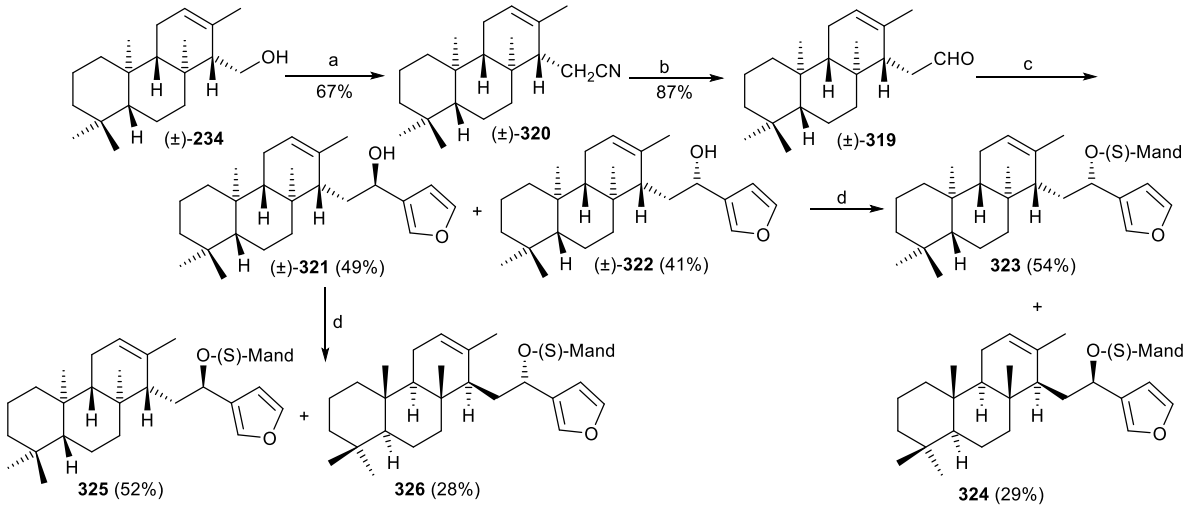
The synthesis of hyrtiosal **306** was realized independently via two different pathways. The first approach was developed by Urones and collaborators [87],[88], starting from the optically active methyl isocopalate **233** (Figure 1.45). Their synthetic strategy included a ring-contraction reaction of ring C, followed by side-chain elongation to hyrtiosal **306**.



Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 10°C, 12 h; (b) $BF_3{\cdot}Et_2O$, C_6H_6, 60°C, 1 h; (c) ethanedithiol, CH_2Cl_2, rt, 12 h; (d) *i*-Bu_2AlH, CH_2Cl_2, -78 °C, 1 h; (e) CrO_3, Py, rt, 0.25 h; (f) Ph_3P=CHOMe, NaHMDS, THF, -78 ºC, 1 h; (g) Me_2CO, *p*-TsOH, rt, 8 h; (h) *n*-BuLi, 3-bromofuran **295**, THF, -78 ºC, 1 h; (i) Ac_2O, Py, rt, overnight; (j) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt, 10 min; (k) 2% K_2CO_3/ MeOH, rt, 2 h.

Figure 1.45. Synthesis of hyrtiosal **306** [87],[88].

The starting methyl isocopalate **233** was epoxidised, followed by treatment of the epoxide **307** with boron trifluoride-etherate to provide the aldehyde **308**. The latter was transformed into thioketal **309**, sequentially reduced and oxidized into the alcohol **310** and aldehyde **311**. Homologation to the aldehyde **312** was performed via the ether **313**. Aldehyde **312**, was coupled with 3-bromofuran **295** to give the C16 epimeric mixture of alcohols **314** and **315**. Removal of the thioketal protecting group in the prevailing epimer **314**, led to the formation of 16-*epi*-hyrtiosal **316**, accompanied by a small amount (22%) of hyrtiosal **306**. Alcohol **315** with the desired configuration of the secondary hydroxyl group was protected by acetylation, and removal of the thioketal then gave the 16-acetoxyhyrtiosal **318**. Hydrolysis of the acetate group led to natural hyrtiosal **306**.



Reagents and conditions: (a) (1) MsCl/Py, rt, 15 h; (2) NaCN, Adogen 464®, PhMe:H_2O (10:1), 60 ºC, 36 h; (b) *i*-Bu_2AlH, PhMe, 0°C, 1.5 h; (c) *n*-BuLi, 3-bromofuran **295**, THF, -78 ºC, 1.5 h; (d) (S)-(+)-methyl mandelic acid, DCC, DMAP, CH_2Cl_2, rt, 2 h.

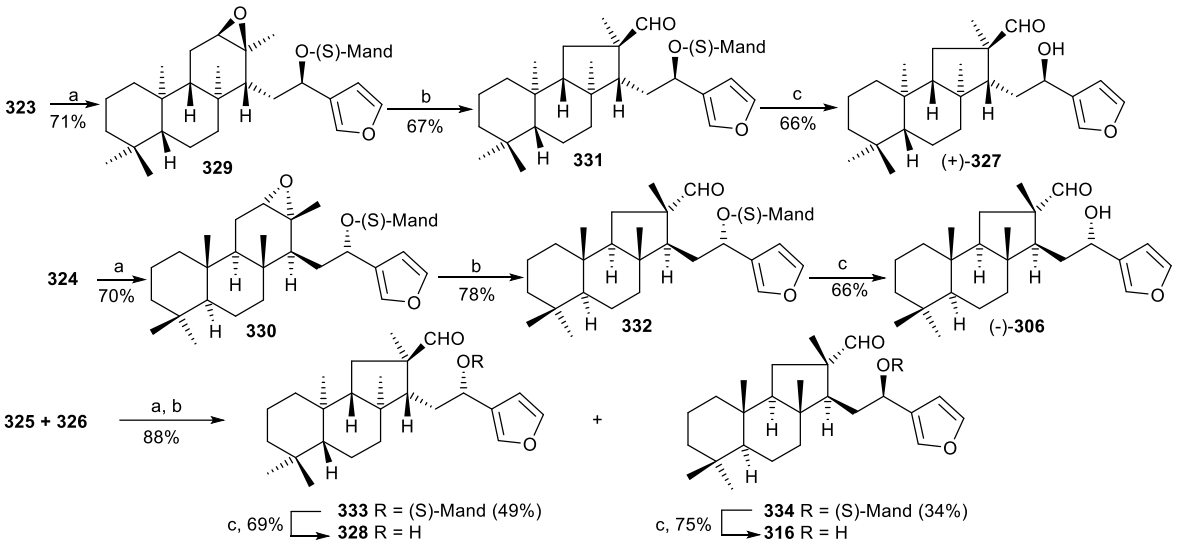
Figure 1.46. An alternative synthesis of hyrtiosal **306** [89].

An alternative synthetic solution for the synthesis of natural hyrtiosal **306** was published by Imamura and collaborators [89] starting from racemic isocopalic alcohol **234**, which was obtained by a known method [90]. The transformation of **234** into racemic homoaldehyde **319** via nitrile **320** is shown in Figure 1.46. The aldehyde **319** was transformed into furyl alcohols **321** and **322**. Separation of these compounds and coupling with (*S*)-(+)-methyl mandelic acid provided two pairs of diastereomers **323**, **324** and **325**, **326**, respectively, which were separated by chromatography.

The transformation of the obtained diastereomers **323**–**326** into hyrtiosal **306** and its diastereomers **316**, **327** and **328** is shown in Figure 1.47. Accordingly, **323** and **324** provided after epoxidation the corresponding epoxides **329** and **330**, which were isomerized with boron trifluoride-etherate into aldehydes **331** and **332**. The latter provided on basic hydrolysis the *ent*-hyrtiosal **327** and

natural hyrtiosal **306**. The diastereomeric mixture of **325** and **326** was epoxidized, followed by isomerization under acidic conditions to form the mixture of compounds **333** and **334**.

The rearrangement of cheilanthanes **323-325** into compounds with hyrtiosal skeleton is in accordance with the biogenetic scheme proposed previously by Iguchi and collaborators [91], and represents a biomimetic solution for the synthesis of cheilanthanes with a contracted C-ring.



Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, -40 °C, 1.5 h; (b) $BF_3{\cdot}Et_2O$, $MeNO_2$, -23 °C, 40 min; (c) K_2CO_3/MeOH:THF:H_2O (1:1:0.5), rt, 16 h.

Figure 1.47. End game in the synthesis of hyrtiosal **306** [89].

1.3. Methods for the synthesis of scalaranic sesterterpenoids

An increasing number of compounds of the relatively new family of the scalarane sesterterpenoids, which show structures based on the hypothetical scalarane skeleton **335** (Figure 1.48), have been isolated from different marine organisms [92],[93],[94],[95]. The first reported representative of this group, named scalarin **336**, was isolated in 1972 from the Mediteranean sponge *Cacospongia scalaris* [96].

Many scalarane compounds play important ecological roles and also possess interesting biological properties. For example, (-)-scalaradial **337** vas isolated from a marine sponge, a specimen of *Cacospongia mollor,* and shows not only antitumor and antiinflammatory but also fish antifeedant property (LD_{50} 0.77 μg mL^{-1} in *Artemia salina* shrimp bioassay) [97],[98]. (-)-Scalaradial **337** strongly inhibits the hydrolytic activity of the hydrolytic enzyme, phospholipase A_2 (PLA_2), as well as manoalide [99],[100].

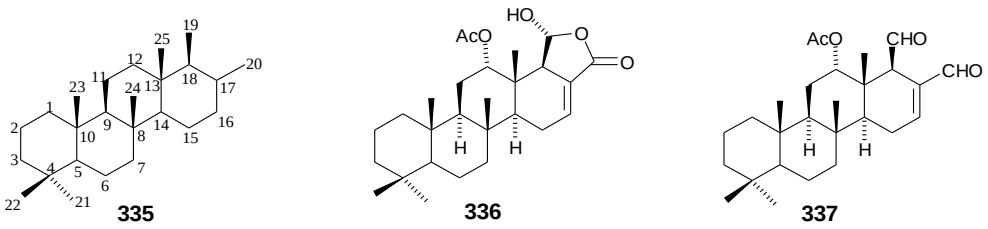


Figure 1.48. Representatives of scalarane sesterterpenoids.

Several scalarins and homoscalarins (methylscalarins) isolated and identified during the last 30 years possess important biological and pharmacological activities [93],[94],[95]. Due to this promising spectrum of potential applications this family of sesterterpenes has received in the recent years much attention from the synthetic point of view. This can be an indication that the synthesis of highly functionalized scalaranes is still a challenge to organic chemists, since natural sources provide scalaranes only in minute amounts, while gram quantities are necessary both for different biological assays and for clinical trials.

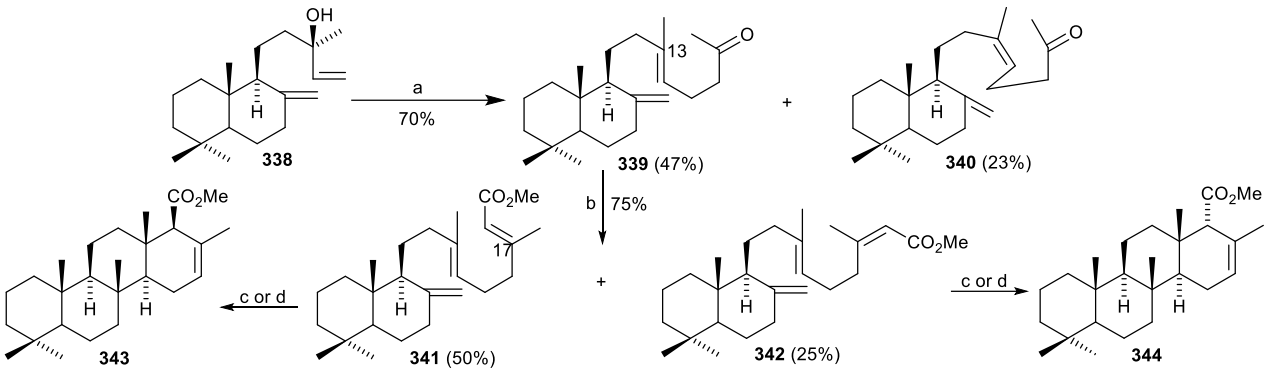
Different approaches have been used for the assembling of the scalaranic skeleton. All of the published synthesis of scalaranes can be grouped, basing on the synthetic path leading to tetracyclic frame. One can distinguish the following strategies:

- Synthesis of scalarane skeleton by electrophilic cyclization of bicyclic substrata. The sesterterpenic fragment is assembled by the elongation of the lateral chain of the labdanic diterpenoids and subsequent electrophilic cyclization of the obtained product provides the tetracyclic structure;
- Synthesis of scalaranic skeleton by electrophilic cyclization of aliphatic substrata. The C_{25} fragment is assembled from aliphatic precursors, being then subjected to a biomimetic – like electrophilic cyclization;
- Construction of the tetracyclic backbone using Diels-Alder addition;
- Other methods, based on sequential cyclization-elongation procedures.

All these approaches will be discussed below. Examples of application of these approaches to the synthesis of natural scalaranes has been included in the published review papers [101],[102].

Herz and Prasad [103] have synthesized the scalaranic esters **343** and **344** starting from manool **338** (Figure 1.49). The alcohol **338** has beeen subjected to the Carroll reaction with ethylacetoacetate to furnish the C-13 isomeric ketones **339** and **340**. The 13-*E*-ketone was futher olefinated with the Horner-Wadsworth phoshonate and the mixture of C17-isomeric esters **341** and **342** (~2:1) was

obtained. The cyclization of individual esters **341** and **342** with $SnCl_4$ (benzene, r.t., 1 h) led to scalaranic esters **343** and respectively **344** with moderate yields of 25% and 18% respectively.



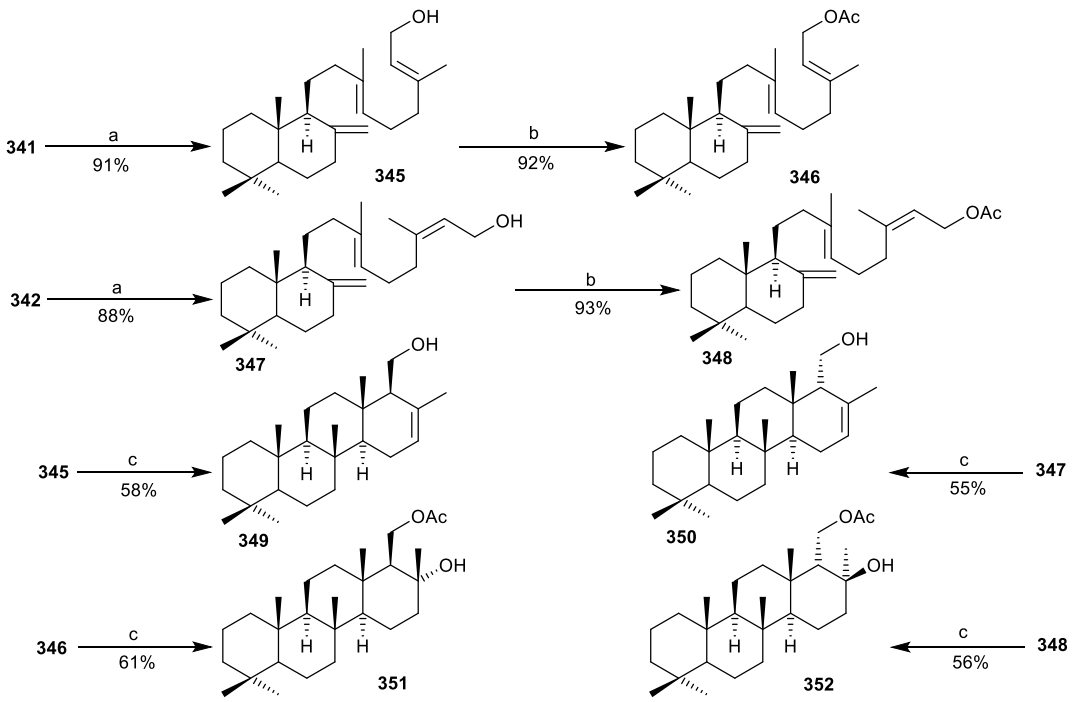
Reagents and conditions: (a) $CH_3COCH_2CO_2Et$, , (13E/13Z = 2:1); (b) $(MeO)_2P(O)CH_2CO_2Me$, NaH, DMSO, 75%, (17E/17Z = 2:1); (c) $SnCl_4$, r.t., 1h; (d) FSO_3H (20 equiv.), *i*-$PrNO_2$, -45 C, 30 min, then Et_3N.

Figure 1.49. Synthesis of scalaranic esters **343** and **344** [103].

Latter on, Vlad and collaborators [104],[105] have cyclized the same esters **341** and **342** to the scalaranes **343** and respectively **344** under the action of fluorosulfonic acid at low temperature. Fortunately, in this case the yields of the target scalaranes were higher (80% for **343** and 74% for **344**). The superacid FSO_3H proved to be a very effective cyclization agent for bicyclogeranylfarnesic esters, acting stereospecifically and with structural selectivity.

The first encouraging results on using the fluorosulfonic acid inspired Vlad and collaborators [106],[107] to investigate the behavior of bicyclic sesterterpenoids with other functional groups at α-terminus. So, the corresponding alcohols and acetates were subjected to superacidic induced cyclization. The above mentioned bicyclic esters **341** and **342** have been used as initial substrata (Figure 1.50). The alcohols **345** and **347** were obtained on the selective reduction of **341** and **342**, respectively. Acetylation of **345** and **347** provided acetates **346** and **348**.

The interaction of individual alcohols **345** and **347** with the superacid provided the scalaranic alcohols **349** and **350** with the yields of 58% and 55%. In the similar condition the acetates **346** and **348** are converted to the monoacetates **351** and **352**, derived from the corresponding scalaranic diols. The reaction is not only stereospecific, but structurally selective: except the target products **349**-**352** there was observed formation only of a small fraction of hydrocarbons (6-11%), along with some 20-30% of polymeric material.



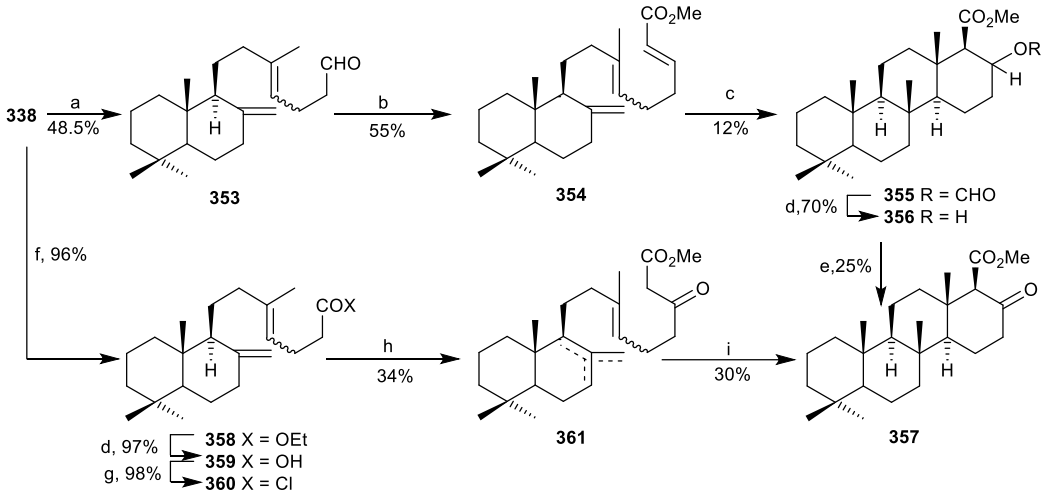
Reagents and conditions: (a) $LiAlH_3(OEt)$, Et_2O, r.t., 3h; (b) Ac_2O, Py, r.t., 5 h; (c) FSO_3H (25 equiv.), *i*-$PrNO_2$, -78 ^oC, 1 h, then Et_3N.

Figure 1.50. Synthesis of scalaranes by cyclization of alcohols and their acetates [106],[107].

These results, have obviously shown, that the superacidic cyclization of the bicyclic sesterterpenoids represent an effective method for assembling the scalaranic sesterterpenoids in the optically active form. The key cyclization reaction is stereospecific, structural and chemoselective. This method has proved to have also preparative value as it will be discussed below. The limitation of this approach is the rather laborious procedure for the separation of isomeric ketones **339** and **340**, as well as esters **341** and **342**, since columns with silver nitrate impregnated silica gel are employed, with benzene-ethylacetate mixtures as eluents. Nevertheless, the overall yield of scalaranes reaches the optimal values of 19 % [105] starting from readily available labdanes.

Another approach towards a nor-scalaranic compound **357** was described by Ragoussis and collaborators [108]. The synthetic path was developed from manool **338** by two different ways (Figure 1.51). First, manool **338** was converted to the mixture of stereoisomeric aldehydes **353** (C_{20} + C_2 elongation step), then to the trienic esters **354**. The cyclization of esters **354** with a mixture of sulfuric and formic acids leads to the formation of formates **355** with a poor yield (12 %). The latter on saponification and consequent oxidation provide the ketoester **357**. It is noteworthy to mention, that the overall yield (starting from manool **338**) is rather low and reaches the value of 0.6%. That is why the above mentioned authors designed the second approach, that consists of transformation the manool

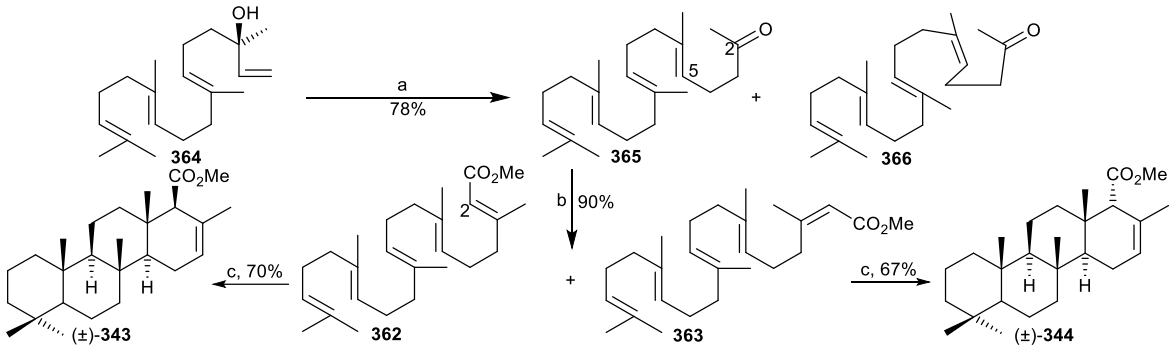
338 to the chloranhydride **360** in three steps and with a quite high overall yield. The latter was converted to the ketoester **361**, which on cyclization with $SnCl_4$ provided the ketoester **357**. In this case the overall yield of **357** starting from **338** is higher and constitutes 9.3%.



Reagents and conditions: (a) CH_2CHOEt, H_3PO_4, 120 °C, 24 h; (b) 1) $CH_2(CO_2H)_2$, Py, r.t. (0.5 h); 2) CH_2N_2, Et_2O; (c) H_2SO_4-HCO_2H, r.t., (3 h); (d) 10% NaOH/EtOH, r.t., 4 h; (e) PCC, CH_2Cl_2, NaOAc, r.t., 3 h; (f) $MeC(OEt)_3$, $EtCO_2H$, 120 °C, 48 h; (g) $(COCl)_2$, C_6H_6, 0 - 5 °C, (1 h), r.t., (2 h); (h) Meldrum acid, CH_2Cl_2, Py, 0 °C, (1 h), r.t., (overnight); (i) $SnCl_4$ (8.75 equiv.), CH_2Cl_2, -5 °C to 0 °C, (1 h), and r.t., (24 h).

Figure 1.51. A synthetic approach towards *nor*-scalaranes [108].

In the continuation of their research for exploiting superacids as cyclization agents, above mentioned authors [104],[105] investigated the biomimetic synthesis of the scalaranic esters directly from the open chain substrata **362** and **363** (Figure 1.52).



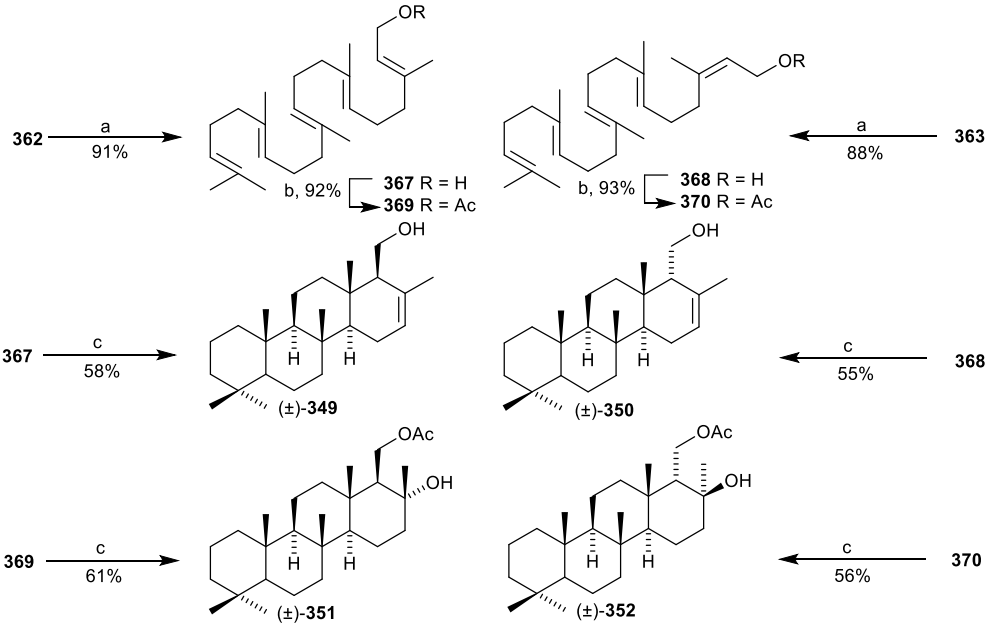
Reagents and conditions: (a) $CH_3COCH_2CO_2Et$, 220 °C, (13E/13Z = 2:1); (b) $(MeO)_2P(O)CH_2CO_2Me$, NaH, DMSO, 80 °C, (2E/2Z = 3:1); (c) FSO_3H (26 equiv.), *i*-$PrNO_2$, -40 °C, 1 h, then Et_3N.

Figure 1.52. A biomimetic synthesis scalaranes [104],[105].

The esters **362** and **363** have been obtained from geranyllynalool **364**. The superacidic low temperature cyclization of esters **362** and **363** led to the formation of the racemic esters **343** and **344**

with the yields of 70% and 67% respectively. It was for the first time when a biomimetic-like approach was employed for a one step conversion of an aliphatic pentaenic sesterterpenoid to tetracyclic scalaranes. The overall yield of scalaranes starting from diterpenic geranyllinalool constitutes cca. 27%.

The logic line of investigation the superacidic cyclization of esters, alcohols and acetates has been continued by Vlad et al. [107],[109] who have also investigated the superacidic cyclization of opened chain sesterterpenic alcohols and acetates. So, *E,E,E,E*- and *Z,E,E,E*-geranylfarnesols **367** and **368** along with the corresponding acetates have been synthesized from aliphatic esters **362** and **363** and subjected to the superacidic cyclization (Figure 1.53).



Reagents and conditions: (a) $LiAlH_3(OEt)$, Et_2O, r.t., 3 h; (b) Ac_2O, Py, r.t., 5 h; (c) FSO_3H (25 equiv.), *i*-$PrNO_2$, -80 ^oC, 1.5 h, then Et_3N.

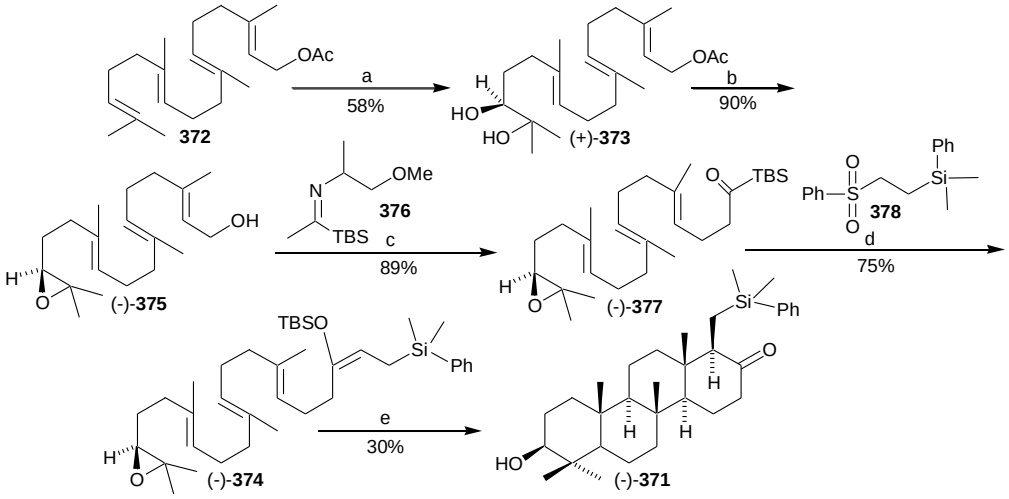
Figure 1.53. A biomimetic synthesis of scalaranes from alcohols and acetates [107],[109].

On cyclization of alcohols **367** and **368** with fluorosulfonic acid the corresponding racemic scalaranic alcohols **349** and **350** have been obtained with respective yields of 58% and 55%. On cyclization the acetates of *E,E,E,E*- and *Z,E,E,E*-geranylfarnesols **369** and **370** in the same superacidic conditions, the racemic hydroxyacetates **351** and **352** are obtained (yields of 58% and 54% respectively). It is noteworthy to mention, that the yields of the key cyclization reaction in the case of alcohols is a little diminished, in comparison with esters. This fact was explained that a competitive dehydration of alcoholic substrates takes place, that gives rise to small fraction of hydrocarbons. The

overall isolated yield of scalaranes in these cases is cca. 20% starting from commercially available geranyllinalool **364**.

Finally, the elaborated superacidic mediated procedures for the synthesis of scalaranes functionalized in the D-cycle has increased the accessibility of this compounds and opened new ways towards the synthesis of more complex scalaranes, including natural products with biological activity.

Later on, Corey and coll. [110] have enantioselectively synthesized the norscalaranic compound (-)-**371** in a biomimetic fashion, starting from geranylgeranylacetate **372** (Figure 1.54). The initial substratum was enantioselectively oxygenated at the terminal double bond to give the acetoxydiol **373**, which was converted to the norsesquiterpenic epoxyderivative **374** in six subsequent steps. The latter one was cyclized under the action of $MeAlCl_2$ into the tetracyclic compound **371**.

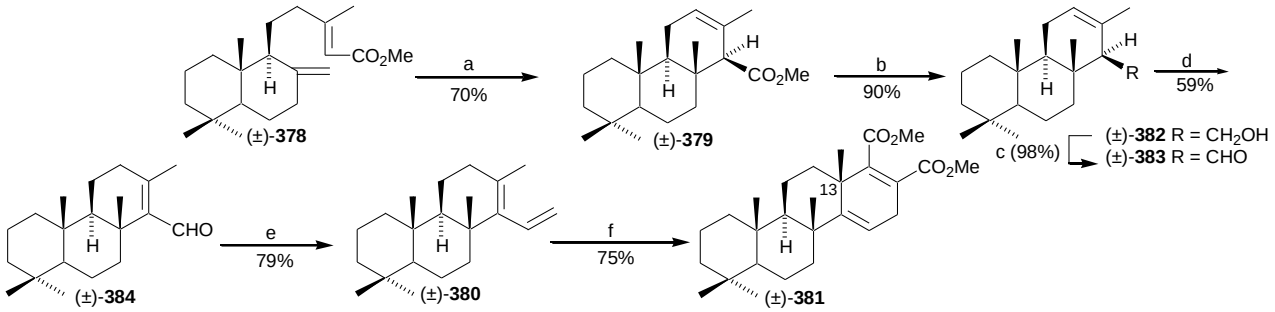


Reagents and conditions: (a) Corey-Noe-Lin- catalyst, $K_2OsO_4.H_2O$, $K_3[Fe(CN)]_6$, K_2CO_3, *t*-BuOH-H_2O (1:1), 0 ^oC, 6 h; (b) 1) MsCl, CH_2Cl_2, Py, 0 ^oC, 12 h; 2) K_2CO_3/MeOH, r.t., 5 h; (c) 1) MsCl, Et_3N, LiBr, THF, -40 ^oC to 0 ^oC, 1 h; 2) LDA, **376**, THF, -30 ^oC, 1 h; 3) Pentane-H_2O, AcONa/AcOH, 23 ^oC, 3 h; (d) *n*-BuLi, **378**, THF-Et_2O-HMPA (4.5:4.5:1), -78 ^oC, 20 min, 0 ^oC, 10 min, 75% at 80% conversion; (e) $MeAlCl_2$ (1.2 equiv), CH_2Cl_2, -94 ^oC, 30 min; CH_3CN, HF (aqueous); 10% KOH in MeOH, reflux, 3 h.

Figure 1.54. Enantioselective synthesis of the norscalaranic compound (-)-**371** [110].

It is noteworthy mentioning, that the overall yield of the optically active compound **371** reaches 10,5% after seven steps, starting from geranylgeranylacetate **372**. Compound **371** is a good scaffold for the synthesis of natural sesterterpenoids and their analogs.

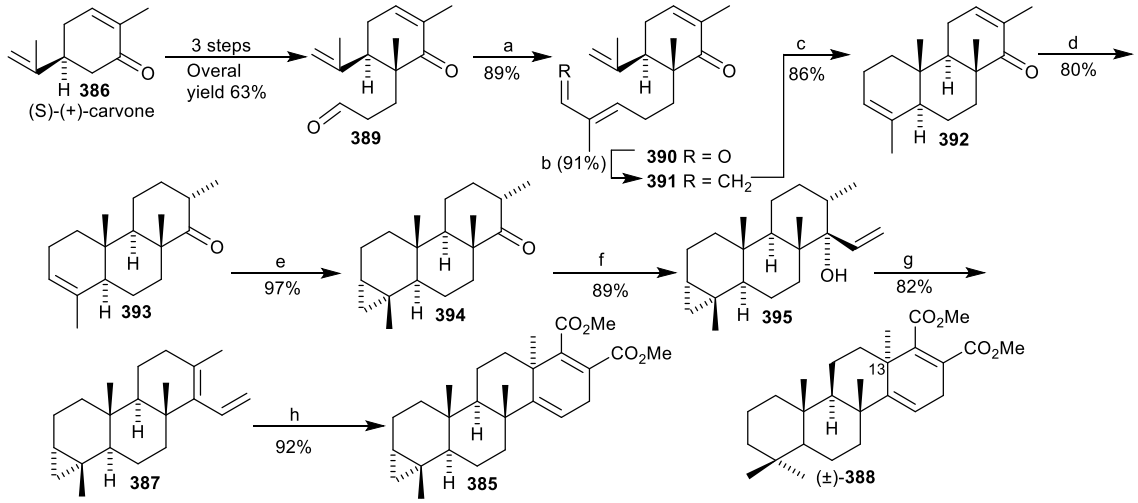
One of the first work on the synthesis of scalaranic skeleton based on Diels-Alder cycloaddition was described by Nakano and coll. [111]. The racemic methylcopalate **378** was converted into the isocopalic ester **379**, that after other four steps gave the diene **380** with an overall yield of 29% (Figure 1.55). Heating the diene **380** with dimethylacetilenedicarboxilate leads to the Diels – Alder abduct **381** in racemic form.



Reagents and conditions: (a) HCO_2H, reflux, 4 h; (b) $LiAlH_4$, Et_2O, reflux, 2 h; (c) $(COCl)_2$, DMSO, CH_2Cl_2, -60 ^oC, 20 min, then Et_3N; (d) *p*-TsOH, C_6H_6, 50 ^oC, 5 h; (e) $Ph_3P^+CH_3Br^-$, BuLi, THF, 1 h; (f) MeO_2CCCCO_2Me, 105 ^oC, 24 h.

Figure 1.55. Synthesis of scalaranic skeleton based on Diels-Alder cycloaddition [111].

More recently, Abad et al. [112] have obtained a similar diene **385** starting from (S)-(+)-carvone **386** (Figure 1.56). The synthetic path comprised 10 steps and provided the target diene in a 25% yield. Under the same conditions as described by Nacano et al. [111], the diene **387** was coupled with the dimethylacetilenedicarboxilate to the Diels – Alder adduct **385**. Its structure was determined carefully on the basis of the X-ray analysis. According to this investigations, the configuration of the methyl at C-13 is α. One can assume, that Nakano et al. [19] have obtained compound **388**, instead of its C-13 epimer **381**.

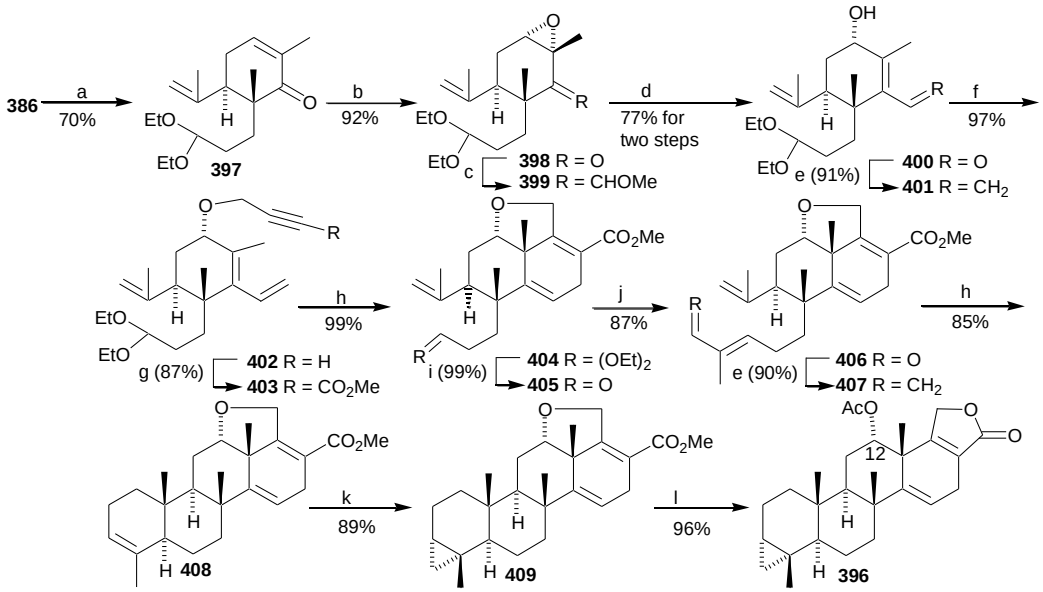


Reagents and conditions: (a) Ph_3P=CMeCHO; (b) Ph_3P=CH_2; (c) Δ, 190 ^oC; (d) 1) NaTeH; 2) NaOMe; (e) Et_2Zn-CH_2I_2; (f) CH_2=CHMgBr; (g) $SOCl_2$, Py; (h) MeO_2CCCCO_2Me, 120 ^oC.

Figure 1.56. Synthesis of diene **385** on the path to scalaranes starting from (S)-(+)-carvone [112].

Abad et al. [113] have also elaborated for the first time a synthetic scheme comprising 15 steps and leading to a C12 functionalized synthon **396**, starting from (S)-(+)-carvone **386** (Figure 1.57). Although the number of steps is elevated, the overall yield of compound **396** is relatively high (~20%,

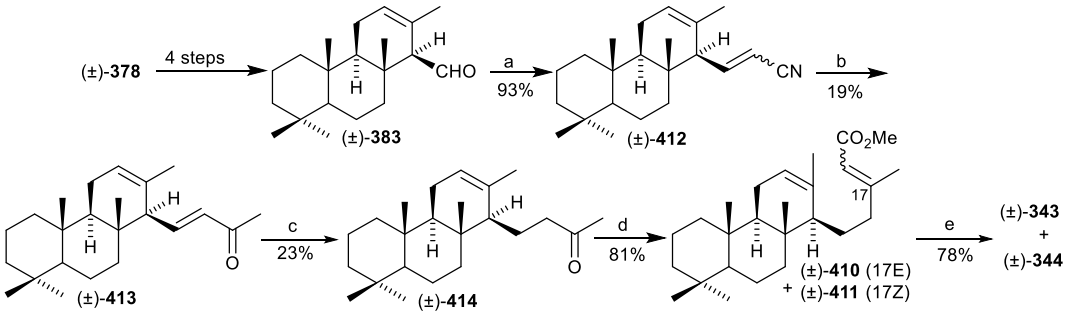
starting from carvone **386**). The utility of compound **396** for the synthesis of naturally occurring scalaranes is obvious.



Reagents and conditions: (a) 1) LDA, THF, -10 ^{o}C then CH_3I; 2) LDA, HMPA-THF, -78 ^{o}C then $(EtO)_2CHCH_2CH_2I$; (b) H_2O_2, NaOH, MeOH, r.t.; (c) $Ph_2P(O)CH(Li)OMe$, THF, 278 ^{o}C, then NaH, DMF, from 0 ^{o}C to r.t.; (d) chromatography on silica gel; (e) $Ph_3P{=}CH_2$, THF, 220 ^{o}C; (f) Bu_4NI, $BrCH_2CCH$, 60% NaOH, r.t.; (g) BuLi, THF, 278 ^{o}C then HMPA, $CNCO_2Me$; (h) toluene, 105 ^{o}C; (i) PPTS, acetone-H_2O, reflux; (j) $Ph_3P{=}CMeCHO$, C_6H_6, reflux; (k) Et_2Zn, CH_2I_2, toluene, r.t.; (l) ZnI_2, $(MeCO)_2O$, r.t.

Figure 1.57. Synthesis of a C12 functionalized scalarane precursor **396** [113].

One of the other methods of assembling the scalaranic backbone consists of the elongation of the lateral chain in isocopalic compounds with the following cyclization to scalaranes. The racemic methylcopalate **378** has served as initial substratum in the work of Ruveda et al. [114]. So, **378** was converted after four steps to the isocopalic aldehyde **383** (Figure 1.58).

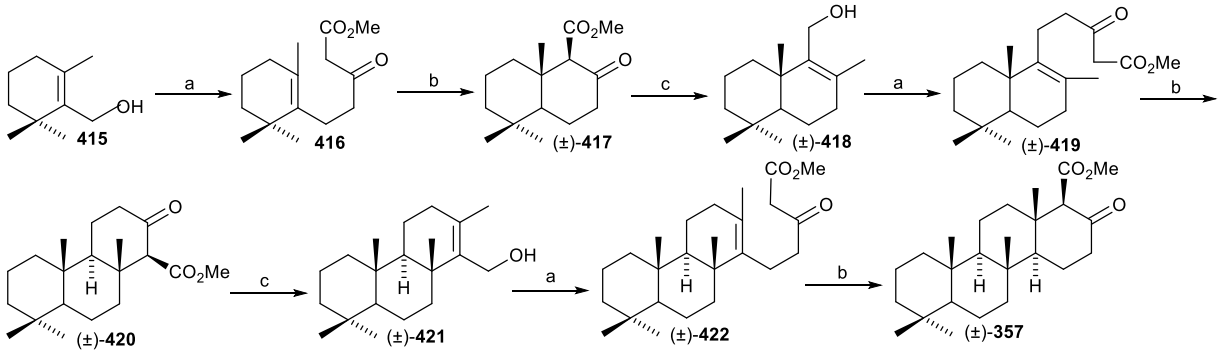


Reagents and conditions: (a) NaH, THF, $(MeO)_2P(O)CH_2CN$; (b) 1) MeLi, Et_2O, 0 C; 2) 1N H_2SO_4-Me_2CO (1:9), 1 h; (c) Na/NH_3 (liq.), 69 ^{o}C, 1h; (d) $(MeO)_2P(O)CH_2CO_2Me$; C_6H_6, NaOMe, 70 ^{o}C, 1h; (e) $SnCl_4$, C_6H_6, r.t., 4 h.

Figure 1.58. Synthesis of scalaranes from racemic methylcopalate **378** [114].

The latter one, after other four steps has been transformed into the cheilantanic esters **410** and **411**. Cyclization of these esters mixture with $SnCl_4$ gave a mixture of racemic scalaranic esters **343** and **344** with a yield of 78%. As the result, the overall yield of the scalaranic esters **343** and **344** after nine steps and starting from the labdane **378** is 0.9% and 0.5% respectively.

Recently, Katsumura et al. [115],[116] have elaborated a method of synthesis of a norscalaranic β-cetoester **357** by a cascade method, starting from a monoterpenic monocyclic substratum **415** (Figure 1.59). So, starting from β-ciclogeraniol **415** and employing 15 steps the racemic tetracyclic compound **357** was obtained in an overall yield of 15%. This original procedure is based on sequential homologations-cyclizations sequences. After these iterative manipulations the second cycle is built, then the third and finally the forth.



Reagents and conditions: (a) 1) PBr_3, Py, Et_2O; 2) NaH, THF, $CH_3C(O)CH_2CO_2Me$, 0 °C, nBuLi; (b) $SnCl_4$, CH_2Cl_2, -10 °C (0.5 h), r.t., (20 h); (c) 1) NaH, THF, 0 C, $ClP(O)(OEt)_2$, 0 °C to r.t. (10 min); 2) MeLi, CuI, Et_2O, -10 °C to 0 °C, 30 min; 3) $LiAlH_4$, Et_2O, r.t., overnight.

Figure 1.59. Synthesis of the norscalaranic β-ketoester **357** by an iterative homologation [115],[116].

1.4. Conclusions to chapter 1

To conclude, we can emphasize that all examples presenting the known works on the synthesis of totally cyclic or partially opened terpenoids are diffusely guided by different strategic principles: biomimetic applications represent singular events, heavily complemented by linear functional group oriented strategies and building block retrosynthetic approaches. Due to the fact, that the vast majority of terpenic compounds of practical value have complex carbon backbones and advanced functionalization with heteroatoms, such synthetic strategies represent complex schemes with multiple stage transformations. This is strongly discouraging potential applications of the obtained synthetic targets.

The main aim of the current work was to elaborate methods of synthesis for diverse classes of terpenoids by a flexible combination of biomimetic processes, including olygomerizations, cyclizations or other rearrangements and selective functionalizations. This random biomimetic approach represents the author's own contribution integrated in the current work.

The specific objectives which promote this concept in a concerted way are the following:

- Application of oligomerization strategies for the synthesis of linear α,ω-bifunctionalized terpenic compounds, having controlled configuration of the internal double bonds, as well as selective functionalization with heteroatoms in the chain.
- Application of selective functionalization strategies for the synthesis of α,ω-bifunctionalized terpenic compounds from the corresponding oligomers.
- Investigation of the biomimetic cyclization of α,ω-bifunctionalized terpenoids;
- Investigation of the biomimetic cyclization of terpenic compounds with specific functional groups intercalated inside the chain;
- Application of the degradation-rearrangement processes for the synthesis of some families of cyclic terpenoids;
- Application of spaceal radical processes for the post-cyclization functionalization of inactivated C-H bonds in sesterterpenoids of scalaranic structure;
- Application of non-conventional media, such as ionic liquids or aqueous solutions for biomimetic transformations;
- Synthesis of some natural terpenoids or their advanced precursors basing on elaborated biomimetic strategies.

METHODS FOR THE SYNTHESIS OF TERPENIC COMPOUNDS ACCORDING TO THE RANDOM BIOMIMETIC PRINCIPLE

Promotion of the random biomimetic principle concept presented in this work included an array of chemical transformations that mimic different terpene biosynthetic steps. The suggestion to combine these chemical manipulations in a random order has led to new reactivity that could have been explored for the synthesis of some families of terpenoids that otherwise require substantial effort. A detailed presentation of these achievements has been provided in the published review papers [1], [3]. An outline of the most representative synthetic works which refer to each relevant steps in terpene biosynthesis is given below. It is our strong belief, that following evolution of research in this direction will continuously deliver interesting and exciting examples of this strategy application.

2. SYNTHEIS OF TERPENIC COMPOUNDS WITH MULTIPLE FUNCTIONALIZATION VIA OLIGOMERIZATION OR DIRECT FUNCTIONALIZATION

The need to perform terpenes oligomerization *in vitro* is dictated by the fact that terpene raw materials are quite limited to lower representatives. Economically significant and renewable resources for terpene isolation are the wastes of wood processing industry first. The major part of these wastes is composed of monoterpenes. The use of other important higher natural terpenoids like sclareol or manool is also connected to the need of oligomerization, that's why elaboration of synthetic processes aimed to linkage of terpenic units has represented a priority of the research groups working in this field. The basic strategy relies on a biomimetic modular approach of connecting a α–functionalized building block to a α,ω-bifunctional fragment (Figure 2.1). Due to practical reasons, the α–functionalized fragment bears more complexity (cyclic structures, chirality, functional groups), and the α,ω-bifunctional fragment is a simple C_5 or C_{10} unit.

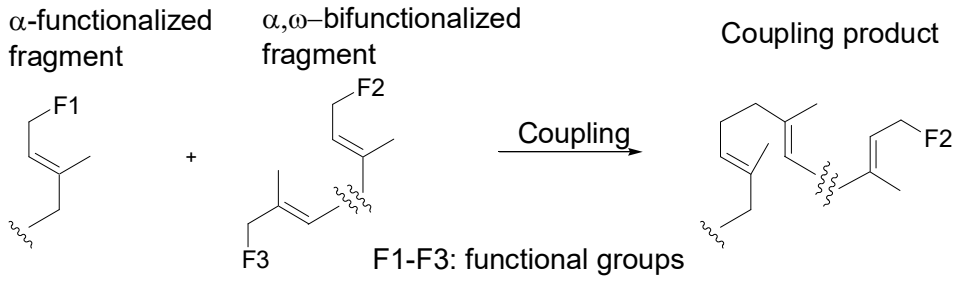


Figure 2.1. Strategy of terpene oligomerization by synthesis.

The activating functional groups F1 and F3 are selected in order to provide a pair of donor-acceptor synthons, which are able to efficiently combine and form the new C-C bond. Lithiated sulfones are often used as synthetic equivalents for donor synthons and halogenides or carbonyl compounds for acceptor ones.

This strategy was successfully reported by different research groups [117] due to its several advantages. First of all, the introduction of required sulfone and halogenide functional groups can be easily performed by routine techniques. The coupling yields vary from good to excellent and the

products incorporate the sulfone group which can be handled in a flexible manner: either substituted for a hydrogen atom or for other functional groups [118].

We have extensively used this strategy for the synthesis of polyfunctional higher terpenoids due to two basic reasons. First of all, by phenylsulfone coupling chemistry we achieve formation of new C-C bonds between more available lower building blocks into higher molecules.

Second, after the coupling reaction the resulting adduct of regular terpenic structure contains additional functional groups derived from both lower fragments. This is an opportunity to introduce functional groups in the isoprenic chain before other biomimetic transformations. The use of sulfone chemistry for the synthesis of such compounds is scarcely provided in the literature.

In order to implement this tandem coupling - functionalization strategy, we had to ensure reliable access to α,ω-bifunctionalized open chain terpenic fragments as building units for sulfone coupling strategy. Direct oxidation methods have been considered as an acceptable approach.

2.1 Direct functionalization of open chain terpenoids

There are several methods for the selective introduction of functional groups at the ω-terminus of the terpenic chain relating to direct functionalization by different oxidation reagents. Due to chemoselectivity issues, these methods can be successfully used for shorter homologues, and we applied selenium dioxide allylic oxidation to get α,ω-bifunctionalized derivatives from geraniol **423** [119],[120],[121],[122],[123] and farnesol **10** [124] (Figure 2.2).

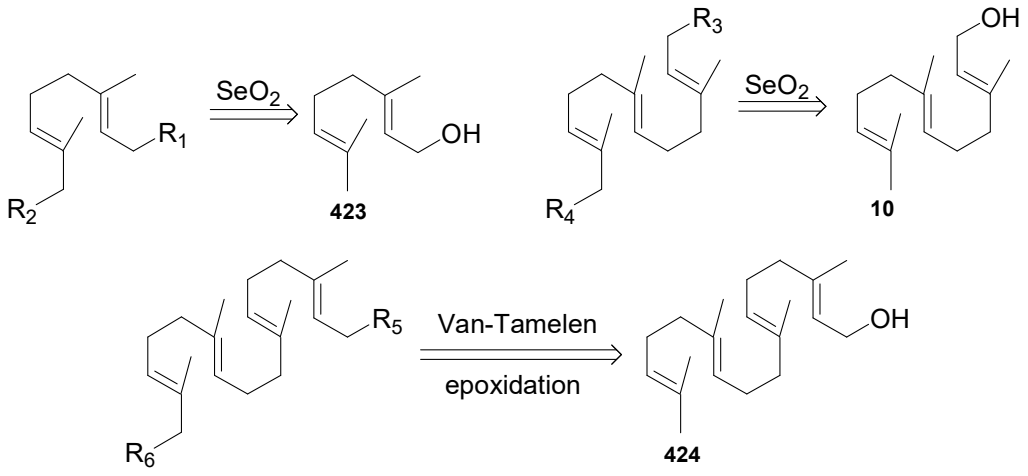
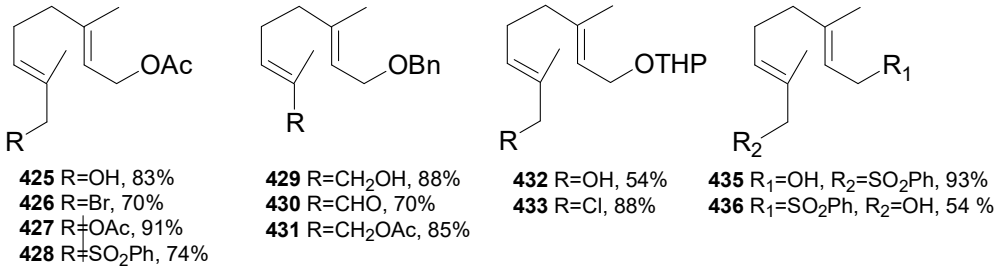


Figure 2.2. Synthetic strategies for direct functionalization of open chain terpenoids.

The similar transformation of the higher geranylgeraniol **424** was accomplished via a multistep procedure, involving Van Tamelen epoxidation followed by epoxide cleavage and Wittig olefination [125].

The best substrates for terminal functionalization by SeO_2 - mediated allylic oxidation are monoterpenic geraniol derivatives. The difference in the reactivity of C-H groups in allylic positions is more evident in this case, therefore the oxidation selectivity is higher.



425 R=OH, 83%
426 R=Br, 70%
427 R=OAc, 91%
428 R=SO_2Ph, 74%

429 R=CH_2OH, 88%
430 R=CHO, 70%
431 R=CH_2OAc, 85%

432 R=OH, 54%
433 R=Cl, 88%

435 R_1=OH, R_2=SO_2Ph, 93%
436 R_1=SO_2Ph, R_2=OH, 54 %

Figure 2.3. Monoterpenes obtained by direct oxidation of geraniol derivatives.

For a successful following use of the allylic oxidation products, protection of the free hydroxyl in **423** is required. Different protection groups have been used and their character influences the yield of the resulting terminal allylic alcohol. The benzylic protection was chosen in some cases in order to achieve a better stability under following acid-base catalyzed transformations. Acetates, phenylsulfones and even THP derivatives also represent suitable substrates and the corresponding allylic alcohols are also produced on SeO_2 treatment. For most substrates, a parallel overoxidation process has taken place and reaction products constituted mixtures of desired allylic alcohols and corresponding aldehydes. In this case a separate $NaBH_4$ reduction of the crude reaction mixture was necessary in order to convert the aldehyde to the desired allylic alcohols. The obtained α,ω-bifunctionalized geraniol derivatives are represented in figure 2.3. One of these compounds, namely the diacetate **427** represents a relevant practical utility, being a component of the pheromone of the Australasian predaceous bug *Oechalia schellenbergii* [126]. More detailed information on their preparation will be provided in the next section of this chapter.

The yield of allylic oxidation was acceptable in the case of monoterpenic substrates (> 54 %), but unfortunately dropped in the case of longer farnesol derivative [124], benzyl ether **437**, which was prepared according to a literature procedure and oxidized with SeO_2 (figure 2.4).

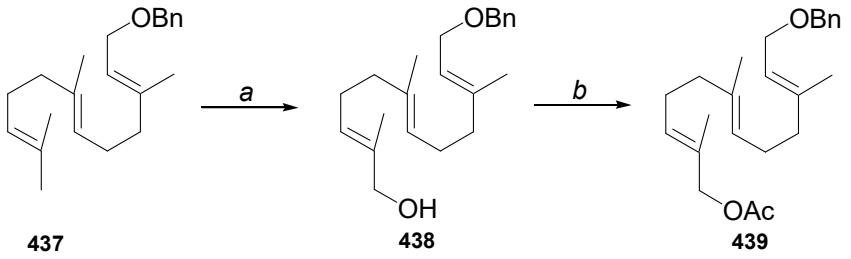


Figure 2.4. Reagents and conditions: (a) SeO_2, EtOH, reflux, 31%; (b) Ac_2O, Py, r.t., 92%.

The allylic alcohol **438** was isolated in a modest 31% yield. It was acetylated with acetic anhydride to deliver acetoxyether **439** (92%), which was used for cyclization experiments (see chapter 3 below).

The synthesis of the α,ω-bifunctionalized diterpenic derivative **440** was more challenging and direct allylic oxidation proved to be not effective. Therefore, a more complex transformation scheme was applied, involving a Van Tamelen epoxidation, followed by epoxide cleavage and Wittig olefination of the resulting aldehyde (Figure 2.5) [125]. The starting linear diterpenic substrate was geranyllinalool **441**, which was acetylated under standard conditions to geranyllinalylacetate **442**. It was further isomerized to the mixture (ca. 85 : 15) of (2*E*)- and (2*Z*)-geranylgeranyl acetates **443** under the action of $[PdCl_2(MeCN)_2]$ in refluxing THF [127].

This mixture was treated with N-bromosuccinimide (NBS) followed by K_2CO_3 according to the procedure of Van Tamelen and Curphey [128] to provide the mixture of compounds **444** and **445**. This mixture was separated by column chromatography on silica gel. The spectral data of racemic **444** were identical with those of known optically active product [129].

Periodate cleavage of the epoxy- compound **444** and protection of the free -OH group in **446** as the 3,4,5,6-tetrahydro-2H-pyranyloxy (-OTHP) group provided the substrate **447** for the Wittig olefination. This reaction proceeded in a good yield and selectivity: the (*E*)-isomer of the aldehyde **448** was isolated in 68% yield. Reduction of **448** with $NaBH_4$ to monoprotected diol **449** was followed by standard protecting group manipulations to afford the desired α,ω-bifunctionalized substrate **440**. The structure of **440** was confirmed by the spectral data.

The conversion of commercial geranyllinalool **440** to **444** and **445** included 4 steps and afforded the α,ω-bifunctionalized diterpenic epoxides with an acceptable 20% overall yield. Following manipulations to allylic alcohol **440** required some other 5 steps and the overall yield reached 1.6% (9 steps overall).

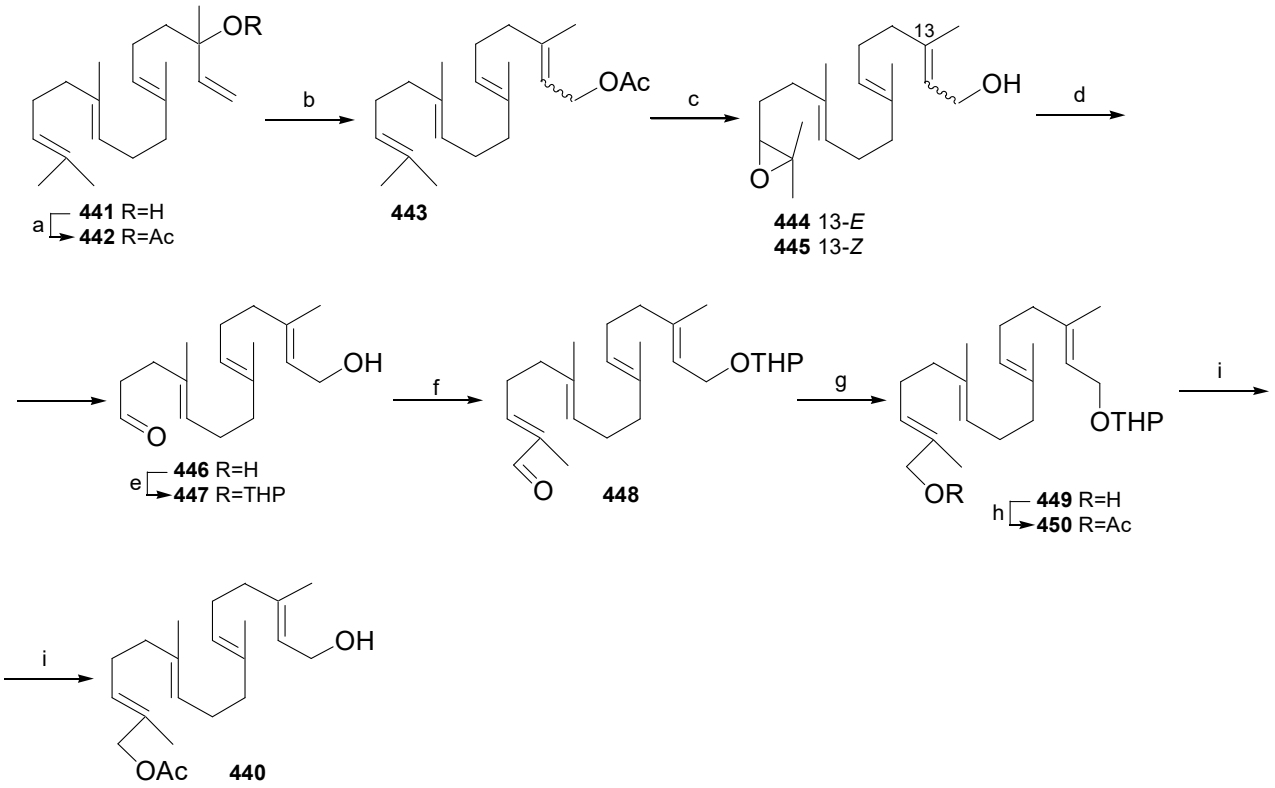


Figure 2.5. Synthesis of the α,ω-bifunctionalized diterpenic derivatives basing on the Van Tamelen epoxidation. Reagents and conditions: (a) Ac_2O, CH_2Cl_2, 4-(dimethylamino)pyridine (DMAP), 0 ºC, 1 h, r.t. 24 h; 63%. (b) [$PdCl_2(MeCN)_2$], THF, r.t, 18 h, 90%. (c) *1*) N-Bromosuccinimide (NBS), THF/H_2O, 0 ºC, 1.5 h, r.t. 2 h; *2*) K_2CO_3 , MeOH, r.t. 20 h; overall 34%. (d) **444,** $NaIO_4$, HIO_4, THF, r.t. 5 h; 35%. (e) 3,4-Dihydro-2H-pyran (DHP), CH_2Cl_2, pyridinium p-toluenesulfonate (PPTS), 12 h; 46%. (f) Ph_3P=C(Me)CHO, THF, reflux, 18 h; 79%. (g) $NaBH_4$, EtOH, 0 ºC, 1 h; 66%. (h) Ac_2O, Py, r.t., 1h; 96%. (i) TsOH, MeOH, r.t. 12 h; 53%.

It should be mentioned that our attempts to perform a direct allylic oxidation of the methyl group at C-15 of **443** with SeO_2 led to a complex mixture of products and the target allylic alcohol was not isolated. Therefore, the method based on the terminal epoxidation followed by epoxide cleavage and Wittig olefination represents a viable alternative procedure for selenium oxide mediated allylic oxidation of linear isoprenoids of regular structure. This method can be applied in a flexible manner for the introduction at the ω-terminus of the oligoprenyl chain of different functional groups, provided the versatility of Wittig olefination procedure.

Interpretation of the obtained results can be based on the known mechanism of selenium dioxide mediated allylic oxidations. It starts with the electrophilic attack of the positively polarized selenium atom on the π-electrons of the double bond (Figure 2.6).

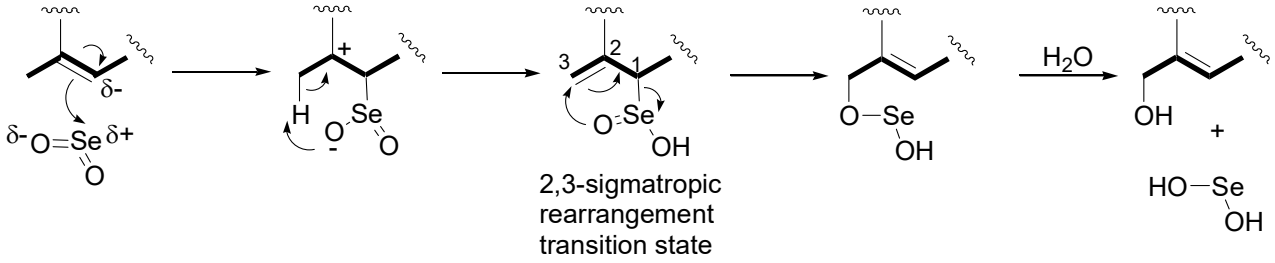


Figure 2.6. Mechanism of SeO_2-mediated allylic oxidation.

The intermediate selenium compound is stabilized by the elimination of a proton from the allylic position, leading to double bond migration. Here comes the main stereochemical constraint of this transformation, which is only possible when the allylic position has a *trans*-configuration in the initial olefin, that is aligned on the same side of the double bond with the Se-C bond formed after the first electrophilic attack of the oxidizing agent.

But this is not the only requirement for this reaction to be effective. The other very important pre-requisite of this transformation is connected to the electronic factors. Enriched π-systems, bearing electron donating alkyl substituents possess higher reactivity and direct electrophilic selenium attack selectively. This circumstance is of paramount importance in the case of polyenic systems, like linear terpenic oligomers, which include multiple allylic positions, all amendable to such transformations.

And finally, one of the factors that is often overlooked, connects to conformational behavior and mobility of the substrate. For substrates with rigid structures this is not a relevant issue, but for the long polyprenic chains present in terpenoids this is of paramount importance. Conformational aspect is directly connected to the stereochemical requirements for the critical step of the transformation, which include a 5-centered transitional state and oxygen transfer to the allylic position is achieved via a 2,3-sigmatropic rearrangement (Figure 2.6). An efficient sequence of both reaction steps (selenium attack and sigmatropic rearrangement) is strongly connected to the availability of stereochemical space, which directly depends on the molecule conformational mobility. In our opinion, for the process efficiency the concept of optimal conformational mobility should be addressed. It means that both lower and higher mobility are detrimental to the selective

transformations: at lower mobility the molecule is folded and physical access of the reagent is hindered, while at higher conformational mobility the flexible chain will impede the transitional state to be attained and transform into a concerted way to the rearranged oxygenated intermediate. Unfortunately, conformational mobility is affected by a series of factors which cannot be easily controlled. These are substrate-related factors (shorter chain vs. longer chain substrates), as well as temperature and solvent applied.

Now we can tentatively explain the difference in the reactivity of our substrates differing in the length of isoprenoidic chain. First of all, the monoterpenic substrate come into attention. It gave the highest yield of allylic alcohols for several reasons. Identification of these reasons is based on the factors influencing the reaction enumerated above. On examining the structure of geraniol derivatives interacted with selenium dioxide a series of conclusions can be made. First of all, these derivatives possess olefinic bonds with suitable allylic positions and some of them are in *trans*-configurations (Figure 2.7).

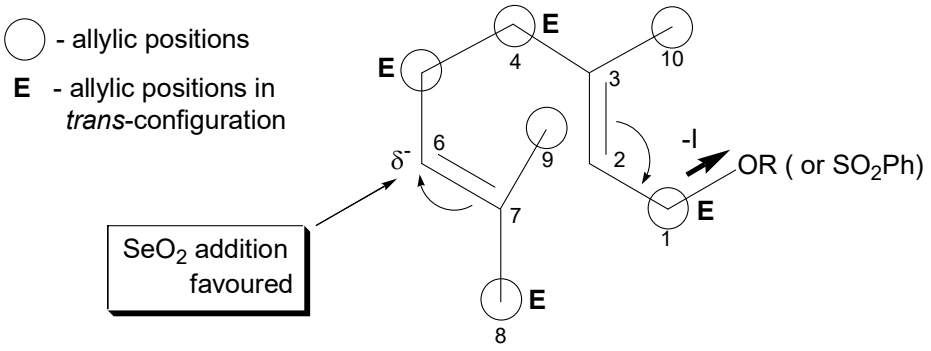


Figure 2.7. Reactivity centers for SeO_2-mediated allylic oxidation in geraniol derivatives.

These are positions at C(1), C(4), C(5) and C(8). But oxidations at C(1) and C(5) are disfavored, due to the fact that electrophilic attack of selenium dioxide at C(3) and C(7) are hindered by alkyl groups. Moreover, the polarization of terminal double bond is in opposite direction compared to what is required for addition of selenium at C(7). And finally, the π-electron density of the C(2) double bond is diminished by a negative inductive effect of oxygenated functional groups (-I) or phenylsulfonyl as in the case of phenylsulfone. This is the reason for lowered reactivity of the C(2) double bond in the direction of C(4) oxidation, which is also inhibited, inspite of the fact that addition of selenium at C(2) is not hindered by the corresponding vinylic proton.

Therefore, SeO_2 oxidation is only favored on electrophilic attack on the C(6) double bond, which has an enriched character due to the terminal methyls and is properly polarized for selenium addition at C(6).

On passing to the longer oligomer, farnesol benzyl ether **437**, the selectivity issue become more evident. An additional prenyl unit brings two extra allylic positions with *trans*- geometry which can compete with the terminal olefinic fragment in electrophilic interaction with selenium oxidant (Figure 2.8).

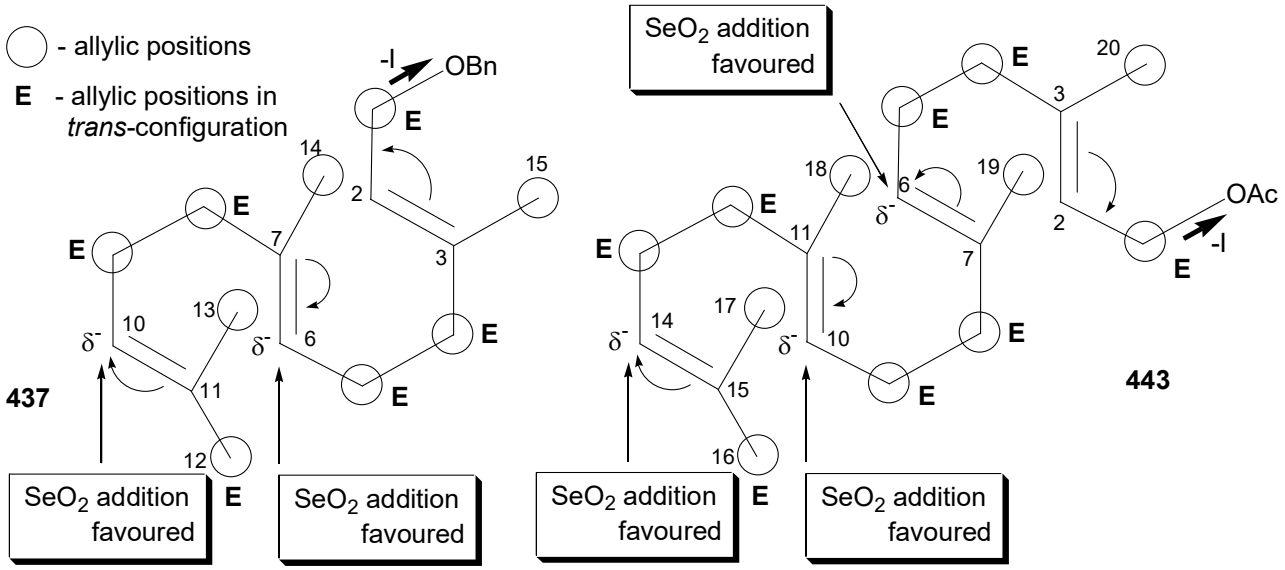


Figure 2.8. Reactivity centers for SeO_2-mediated allylic oxidation in farnesol and geranylgeraniol derivatives.

As the result, the molecule of **437** includes two centers with approximately the same reactivity towards oxidizing agent. In the diterpenic substrate **443**, the selectivity issue is worsened by other two extra prenyl units, bringing the number of potentional reactional centers to 3. Under these circumstances the yield of the terminal oxidation product decreases inevitably in the row mono-sesqui-diterpenic substrate.

This interpretation fits quite well with the experimental results, but there is still one aspect which should be clarified. It relates to the quite good performance of the Van Tamelen epoxidation of geranylgeraniol derivative **443**, that is in contrast with selenium dioxide mediated allylic oxidation of the same substrate. In order to bring light to this apparent discrepancy, we have carefully considered

the reaction conditions for both transformations. The mechanistic aspect in either cases should be similar, since Van Tamelen epoxidation involves in the first step an electrophilic attack of the bromonium ion derived from NBS. But there is still a difference between the two processes, namely due to the reaction media employed. In the case of selenium dioxide oxidation, the solvent is 96% aqueous ethanol, while the epoxidation procedure involves NBS treatment in a THF-water mixture. In our opinion, the difference in the solvent lipophilic-hydrophilic balance influences directly the conformational behavior of the substrates, bringing about improved selectivity in the case of epoxidation. This hypothesis still needs to be substantiated with additional experimental proofs.

2.2 Oligomerization approach in the synthesis of terpenes with multiple functionalization

An alternative approach which could be used for the synthesis of polyfunctionalized terpenoids relates to the oligomerization procedures. Given the high yield of allylic oxidation in the monoterpenic series of derivatives, these could be successfully applied in order to build higher derivatives, after a successive chain extension by C_5 or C_{10} units. We applied both variants of such oligomerizations and the results are provided below.

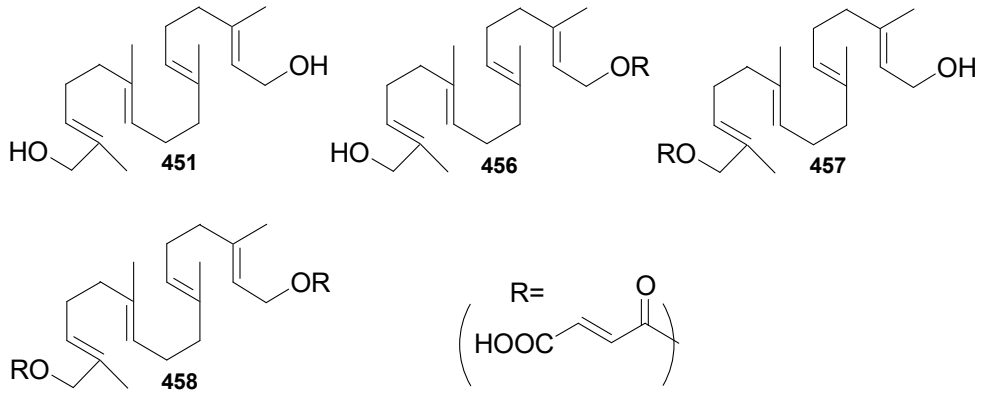


Figure 2.9. Representatives of natural diterpenic α,ω-bifunctional representatives.

The reported synthesis of natural product *trans*-16-hydroxygeranylgeraniol **451** and its derivatives **452**-**455** is the most relevant example in this context [122]. Natural aliphatic diterpenoids are usually monofunctional compounds, although certain α,ω-bifunctional representatives are also known. For example, the biologically active α,ω-bifunctional diterpenoids **451**, **456**-**458** depicted in

Figure 2.9 were isolated from the fungus *Boletinus cavipes* [130]. These compounds turned out to be inhibitors of peroxide formation in macrophagous cells and can be used to prevent health disorders caused by such compounds.

The synthesis of exclusively *trans*-16-hydroxygeranylgeraniol **451** and its α,ω-bifunctional analogs **452**-**455** (Figure 2.10) started from the commercially available monoterpenol geraniol **423**. The synthetic approach to the α,ω-bifunctional aliphatic diterpenoids **451**-**455** consisted of combination of separate fragments **433** and **435**, which were prepared from the single precursor **423**.

Compound **433** was synthesized in three steps. Protection of the alcoholic functional group in **423** with dihydropyran gave tetrahydropyranyl ether **459**. The terminal methyl was selectively oxidized by selenium dioxide to give hydroxyether **432**. Replacement of the hydroxyl for chlorine gave bifunctional derivative **433**.

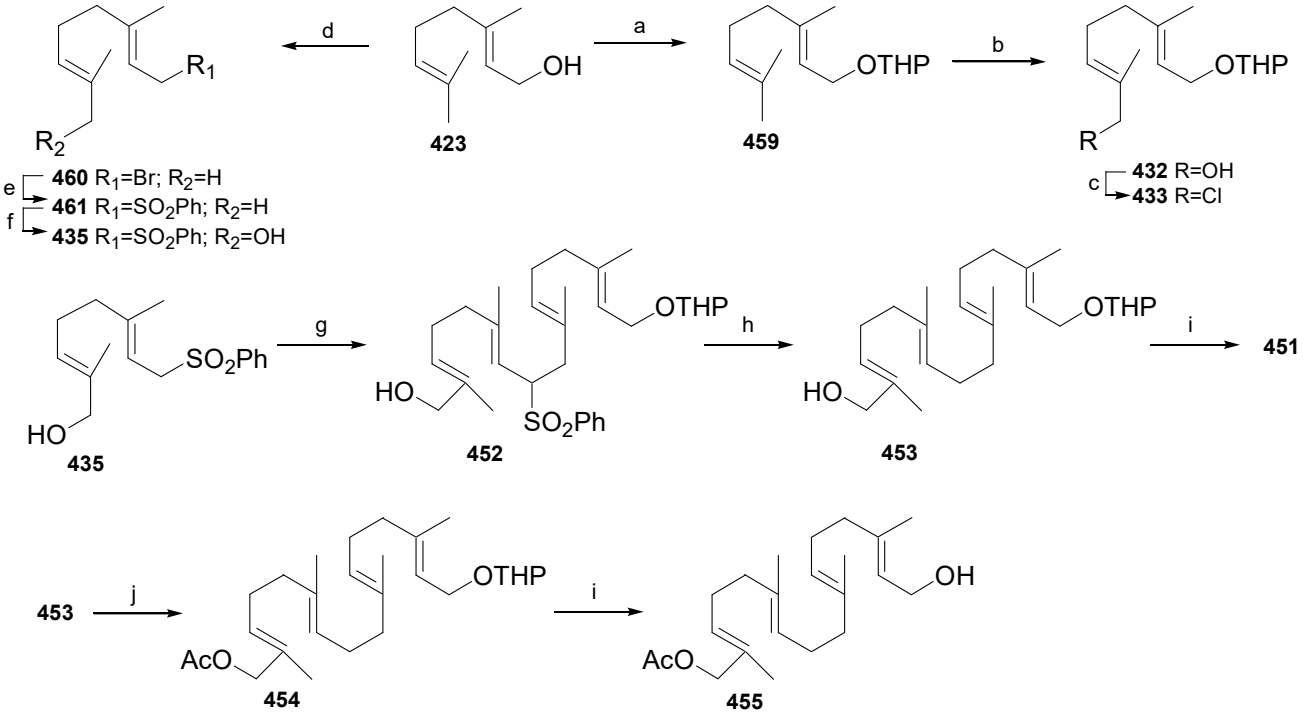


Figure 2.10. Synthesis of the α,ω-bifunctionalized diterpenic derivatives basing on the oligomerization strategy. Reagents and conditions: (a) DHP, DCM, PPTS, 94%; (b) SeO_2, EtOH/Py, 58%; (c) TsCl, DMAP, Et_3N, CH_2Cl_2, LiCl, 93%; (d) PBr_3, Et_2O, Py, 0 °C; (e) $NaSO_2Ph$, DMF, 84% after two steps; (f) SeO_2, EtOH, 54%; (g) BuLi, THF, -78 ºC, then **433**, 1.5 h to 0 °C, 91%; (h) Na/Hg (6%), Na_2HPO_4, MeOH, 73%; (i) *p*-TsOH, MeOH; (j) Ac_2O, Py, 99%.

The second synthon **435** was synthesized from **423** also in three steps. Geraniol **423** was brominated by phosphorus tribromide to **460**, which was used without further purification to give geranylphenylsulfone **461** in ~84% yield. The sulfone was selectively oxidized by selenium dioxide in 54% yield into hydroxysulfone **435**. The ^{1}H NMR spectrum of **435** contained signals for two methyls on double bonds, two vinyl protons, >C–CH_2O– and –CH_2– groups next to a –SO_2Ph group, a vinyl proton, and signals characteristic of five aromatic protons. These spectral data agreed with those published [131].

The connection of structural fragments **433** and **435** under mild conditions [132] formed racemic diterpene derivative **452** (91% overall yield). The ^{1}H NMR spectrum of the coupling product had signals for four methyls on double bonds, four vinyl and five aromatic protons, and two hydroxymethylene groups, one of which was isolated and the other, next to a vinyl proton. The spectral data confirmed the structure of **452**. Reduction of the phenylsulfone in **452** by sodium amalgam as reported [132] produced target α,ω-bifunctional diterpenoid **453** and a small (~10%) quantity of its isomer in which the double bond migrated from the C(10), C(11) position to the C(9), C(10) position. Compound **453** was purified by semi-preparative HPLC. The structure of reduction product **453** was established using spectral data. The ^{1}H NMR spectrum of this compound contained signals for four methyls on double bonds, four vinyl protons, two –CH_2O– groups and the THP protons. The spectral data and elemental analysis confirmed the structure of **453**. The THP group of **453** was removed by acid hydrolysis as reported [133] to produce 16-hydroxygeranylgeraniol **451**. Its spectral data (^{1}H and ^{13}C NMR) agreed with those published [134] and confirmed its structure.

Acetylation of **453** under standard conditions with acetic anhydride in pyridine gave in quantitative yield **454**, the structure of which was confirmed by spectral data and elemental analysis. The THP protection in **454** was removed as described [134] to give monoacetate **455** (59%) and a small (18%) amount of diol **451**.

This oligomerization strategy has been also applied in other our works connected to the synthesis of open chain or partially opened cyclic terpenes specifically "decorated" with functional groups. These include (2*E*,6*E*,10*E*,14*E*)-8-phenylsulfonylgeranylfarnesol **462** and (13*E*,17*E*)-12-phenylsulfonylbicyclogeranylfarnesol **463**, obtained on coupling 8-phenylsulfonylgeraniol **436** either to (2*E*,6*E*)-farnesylchloride **464** or *iso*-drimenylbromide **465** [120],[121]. The C_{10} building block was synthesized from the hydroxyacetate **425**. The coupling yield was good in the case of **464** and quite

modest when using the bromide **465** as coupling partner (Figure 2.11). This difference in reactivity was explained by steric hindrances caused by bicyclic system of **465**.

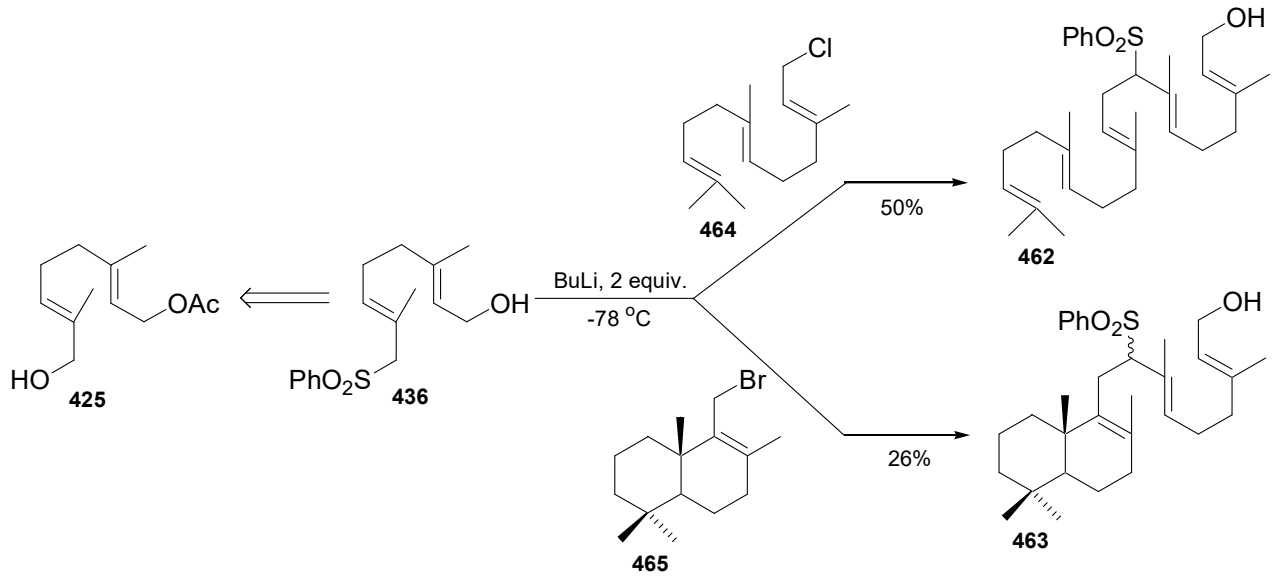


Figure 2.11. Synthesis of the bifunctionalized sesterterpenic derivatives basing on the oligomerization strategy.

A recent example relates to the synthesis of complex triterpenic bicyclic compounds **466** and **467** [123]. They derived from the oligomerization of the diterpenic bicyclic sulfone **468**, obtained from manool **220**. The coupling partner was the monoterpenic bifunctional aldehyde **430**, synthesized from geraniol **423**, via the benzyl ether **469** and alcohol **429**. The whole synthetic sequence leading to **466** and **467** is shown in Figure 2.12.

The yield of the key-coupling step was fairly good and the corresponding hydroxysulfone **466** was characterized as a mixture of diastereomers. Oxidation to the epimeric mixture of ketones **467** was best achieved on the use of Swern reagent. Chromium-based oxidants failed to provide reasonable oxidation yields.

A more specific example of oligomerization has been reported for the synthesis of the natural cheilanthane skeleton in optically active form [135].

Unlike all above mentioned examples, oligomerization in this case was not performed on using one or more isoprene units, but shorter C(3) and C(2) fragments, appended over a two-step sequence. Such a strategy was due to the broad availability [136] of the isoagath-12-en-15-ol **470**, representing

the tricyclic part of cheilanthanic skeleton and consequently requiring only attachment of a one C_5 unit in order to build the natural product framework. The severe steric hindrances inherent to the triciclic structure of **470** made us adopt a two-step $C_3 + C_2$ homologation strategy, which could be less sterically demanding than a direct C_5 coupling. Such a coupling strategy has been broadly reported for the synthesis of open chain isoprenoids basing on readily available allylic bromides or chlorides. In the case of alcohol **470**, converting to mesylate as a leaving group was the path of choice, due to the above mentioned stereochemical peculiarities (Figure 2.13).

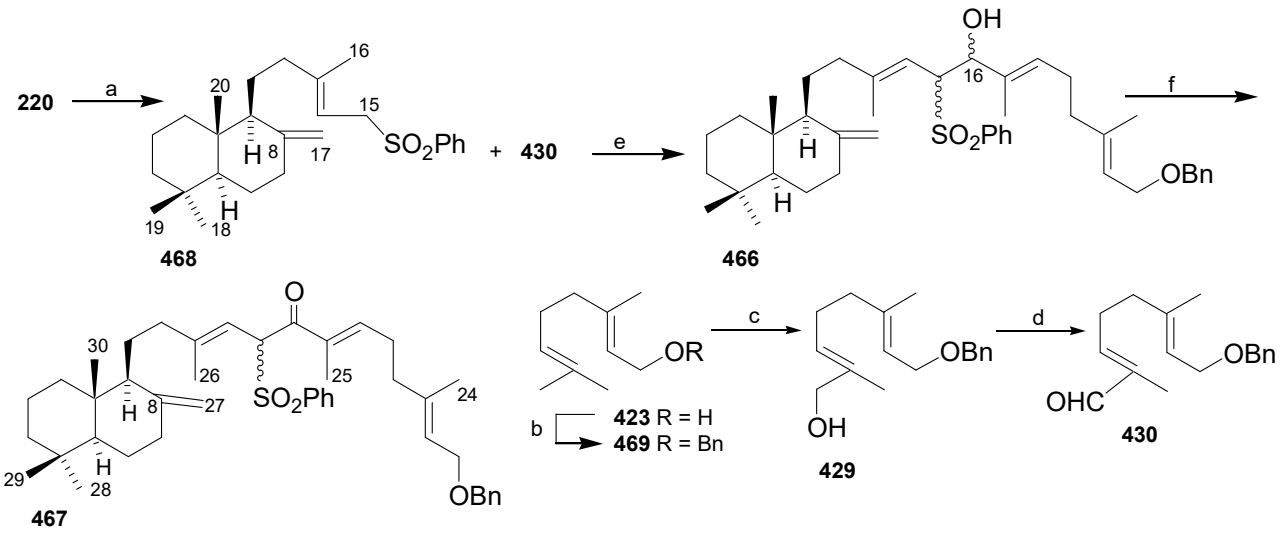


Figure 2.12. Synthesis of the bifunctionalized triterpenic derivatives basing on the oligomerization strategy. Reagents and conditions: (a) *1*. PBr_3/Et_2O; *2*. $NaSO_2Ph$/DMF, overall for two steps 74%; (b) NaH, BnCl, TBAI, CH_2Cl_2, r.t., 12 h, 92%; (c) SeO_2, EtOH, reflux, 3h, 45%; (d) PCC, CH_2Cl_2, r.t., 1.5h, 70%; (e) BuLi/THF, 66%; (f) Swern oxidation, 73%.

Preliminary attempts to use tosylate leaving group failed to provide a nucleophilic substitution reaction with the anion derived from ethylacetoacetate. The bulkier character of tosyl group impeded an efficient reaction and the main competing process was elimination to the corresponding conjugated diene.

The alcohol **470** was transformed into the corresponding mesylate **471**, that was coupled with sodium ethyl acetoacetate in toluene, to give ethylcarboxy-*ent*-isocopalylacetone **472**, along with *ent*-isocopala-12,14-diene **473** and starting compound *ent*-isocopalenol **470** (34%). Compound **472** was decarboxylated by NaOH/EtOH giving (-)-*ent*-isocopalylacetone **474**, thus providing a C_3 elongation.

This compound was submitted to a Wittig-Horner reaction with trimethylphosphonoacetate/MeONa in C_6H_6, to afford a mixture of 17*Z*- and 17*E*-cheilanthanic esters **410** and **411** in optically active form, separated by subsequent silica-gel and HPLC chromatography.

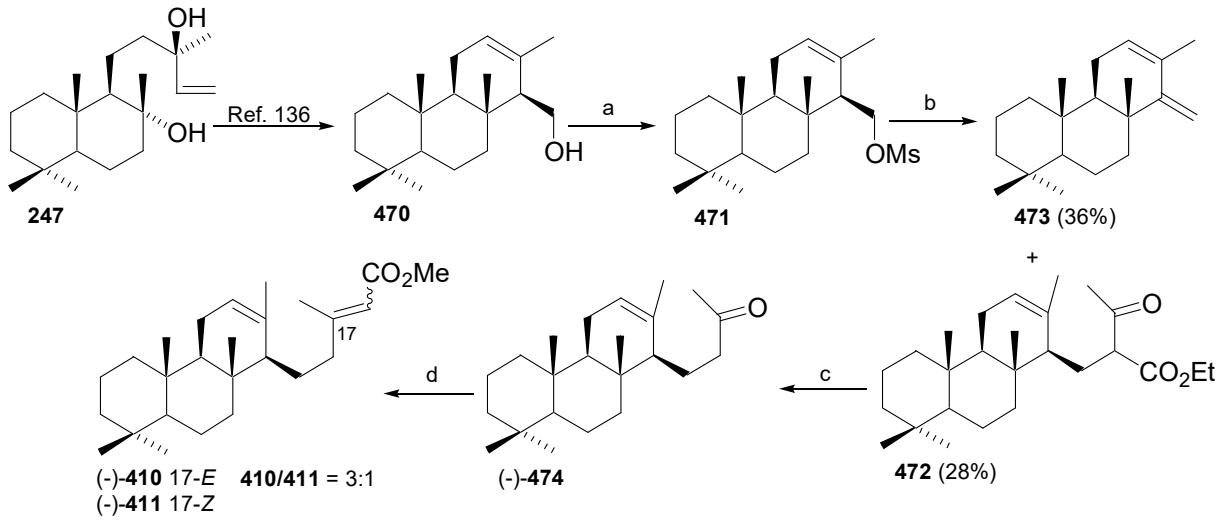


Figure 2.13. Synthesis of cheilanthanic sesterterpenes basing on the oligomerization strategy. Reagents and conditions: (a) MsCl, DMAP/Py, 0 °C, 93%; (b) $CH_3C(O)CHNaCO_2Et$, PhMe, reflux, 4 h; (c) NaOH/EtOH, reflux, 3 h, 85%; (d) $(MeO)_2PCH_2CO_2Me$, MeONa, Ph-H, 90%.

All proton and carbon NMR resonances of compounds **410** and **411** were assigned as reported in experimental part. The β-configuration of prenyl chain at C-14 was clearly indicated by their ^{13}C-NMR data. In fact, the carbon spectra of both **410** and **411** displayed up-field shifted values for C(23) (δ 14.3 in both **410** and **411**) and down-field shifted values for C(7) (δ 40.6 in **410**, 40.7 in **411**) and for C(9) (δ 55.0 in both **410** and **411**) compared with those of the corresponding 14α-isomers, according to literature data for natural 14β-cheilanthanes.

2.3 Synthesis of terpenic compounds with multiple functionalization via oligomerization or direct functionalization. Experimental methods and procedures

General methods

The general methods of organic synthesis have been applied in the current work. They include *in vitro* synthesis, followed by separation and identification of individual reaction products by modern techniques of analytical chemistry. Due to various nomenclature applied in the field of natural products, including terpenoids, the following guiding principles have been considered while naming compounds presented in the experimental part of the current work:

- Naming of the open chain compounds derives from the names of the corresponding mono-, sesqui-, di-, sester- and higher alcohols of regular terpenic structure.
- Naming of compounds containing cyclic fragments is based on the nomenclature recommended for specific terpenic skeleta (Dictionary of terpenoids, J. D. Connolly and R. A. Hill, Chapman & Hall, London, 1991). For newer compounds, names assigned in the original publications are used.

IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in chloroform-d ($CDCl_3$) on Bruker AM 400 and Bruker WM 300 spectrometers if otherwise not specified; chemical shifts are reported in ppm and are referred to chloroform ($CHCl_3$) as internal standard (δ 7.26 for proton and δ 77.0 for carbon). Optical rotations were measured in chloroform on a Jasco DIP 370 polarimeter, using a 10 cm cell. Low resolution EIMS were determined at 70 eV on a HP-GC 5890 series II mass spectrometer. High resolution ESIMS were performed on a Micromass Q-TOF MicroTM. All air and water sensitive reactions were performed in flasks flame dried and cooled under a positive flow of argon and conducted under an atmosphere of argon. The work-up of the reaction mixtures in organic solvents included exhaustive extraction with diethyl ether and washing with water up to neutral reaction, drying over anhydrous sodium sulfate, filtration and removal of the solvent in vacuum. Commercial Merck Si gel 60 (70-230 mesh ASTM) was used for flash chromatography, and Merck precoated Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% cerium (IV) sulfate in 2N sulfuric acid and heated at 80 °C for 5 min to detect the spots. Commercial reagents have been used as delivered by the supplier, if otherwise not specified. Organic solvents have been purified and dried according to standard procedures.

Specific reaction conditions and experimental details for the most relevant synthetic procedures are provided here and in the chapters below.

E,E-8-Hydroxygeranylacetate 425.

To the solution of geranylacetate (390 mg, 2 mmol) in 2 ml ethanol, freshly sublimated selenium dioxide (90 mg, 0.8 mmol) has been added in one portion and the resulting solution was refluxed for one hour. Dilution with water (5 ml) and extraction with ether (3 x 5 ml) was followed by successive washings with $(NH_4)_2S$ (5 ml, sat. sol.) and brine (5 ml). The ethereal extract was dried over anhydrous sodium sulfate and solvent was removed at reduced pressure. The crude residue (387 mg) was purified by chromatography on a column with 10 g Si-gel. Elution with a mixture of petroleum ether-EtOAc (19:1) provided 181 mg of recovered starting material. Elution with the same solvents mixture (4:1) resulted in isolation of 173 mg (0.82 mmol, 83%, basing on the recovered starting material) of acetoxyalcohol **425**. It was identified by chromatographic comparison with an authentic sample.

E,E-8-phenylsulfonylgeranylacetate 428.

A solution of phosphorus tribromide (9.12 g, 33.69 mmol) in dry ether (12 mL) was added dropwise to a stirred solution of 8-hydroxygeranylacetate **425** (5.20 g, 24.50 mmol) in dry ether (43 mL) with cooling on an ice bath. The mixture was stirred for 2 h at room temperature and treated with saturated $NaHCO_3$ solution. The ether layer was separated, washed with NaCl solution, dried, and concentrated in vacuum. The resulting bromide **426** (4.73 g, 70%) was added to a solution of the sodium salt of benzenesulfinic acid (3.40 g, 20.60 mmol) in dry DMF (24 mL). The mixture was stirred at room temperature under Ar in the dark for 3 h, treated with NaCl solution, and extracted with ether. The extract was worked up as usual to afford a liquid product that was chromatographed over a Si-gel (150 g) column with gradient elution by petroleum ether:AcOEt to elute *E,E*-8-phenylsulfonylgeranylacetate **428** (4.27 g, 74%) as a colorless oil, $C_{18}H_{24}SO_4$. IR spectrum (liquid film, ν, cm^{-1}): 1725, 1307, 1210, 1130. ^1H NMR spectrum (80 MHz, δH, ppm, J/Hz): 1.66 (6H, s, H_3-9 and H_3-10), 1.96 (3H, s, $OCOCH_3$), 3.63 (2H, s, H_2-8), 4.46 (2H, d, J = 7.0, H_2-1), 5.00-5.30 (2H, m, H-2 and H-6), 7.45-7.85 (5H, m, Ar–H).

***E,E*-8-Acetoxygeranylacetate 427.**

Acetic anhydride (5 ml) was added to a solution of 8-hydroxygeranylacetate **425** (2.5 g, 11.8 mmol) in 15 ml of dry pyridine and the mixture was kept for 6 h at r.t., followed by usual work-up. The crude product (2.8 g) was chromatographed on a column with 50 g Si-gel. Elution with a mixture of petroleum ether and EtOAc (93:7) gave 2.72 g (90.8 %) of diacetate **427** as a colorless viscous liquid. Found C, 66.03; H, 8.75. $C_{14}H_{22}O_4$. Calculated (%) C, 66.12; H, 8.72. IR spectrum (liquid film, ν, cm^{-1}): 1230, 1730. ^{1}H RMN (80 MHz, δ): 1.65 (s, 3H, CH_3-10), 1.70 (s, 3H, CH_3-9), 2.05 (s, 3H, OAc), 2.06 (s, 3H, OAc), 4.45 (broad s, 2H, CH_2-8), 4.59 (d, J=7.0 Hz, 2H, CH_2-1), 5.40 (m, 2H, H at C-2 and C-6).

Geranyl benzyl ether 469.

Geraniol **423** (12 g, 77.9 mmol) in 103 mL of dry THF was treated with 60% NaH (3.68 g), benzyl chloride (10.61 mL, 92.2 mmol) and tetrabutylammonium iodide (2.88 g, 7.79 mmol). The reaction mixture was left under stirring for 12 h at room temperature. Then, 10% aqueous solution of H_2SO_4 (20 mL) was added. Usual work up gave a crude reaction product (25 g), which was purified by flash chromatography using 1% ethyl acetate/light petroleum ether mixture to yield 17.52 g (92%) of geranylbenzyl ether **469** as a pale yellow oil. IR spectrum (liquid film, ν, cm^{-1}): 735, 1069, 1101, 1270, 1377, 1453, 1496, 1670, 1726, 2924, cm^{-1}. ^{1}H NMR (selected values): δ = 1.62 (*s*, 3H, C-9), 1.66 (*s*, 3H, C-10), 1.69 (*d*, *J* = 0.9 Hz, 3H, C-8), 2.06 (*m*, 2H, C-4), 2.12 (*m*, 2H, C-5), 4.04 (*dd*, *J* = 6.8, 0.3 Hz, 2H, C-1), 4.51 (*s*, 2H, C-1'), 5.12 (*m*, 1H, C-6), 5.42 (*m*, 1H, C-2), 7.34 (m, 5H, Ar-H) ppm. ^{13}C NMR: δ= 16.4 (*q*, C-10), 17.6 (*q*, C-9), 25.6 (*q*, C-8), 26.4 (*t*, C-5), 39.6 (*t*, C-4), 66.6 (*t*, C-1), 71.9 (*t*, C-1'), 138.6 (*d*, C-2), 124.0 (*d*, C-6), 127.5 (*d*, C-5'), 127.8 (*d*, C-3', 7'), 128.3 (*d*, C-4', 6'), 131.6 (*s*, C-7), 138.6 (*s*, C-2'), 140.3 (*s*, C-3) ppm. All physical properties and spectroscopic data were identical with those reported in literature [137].

***E,E*-8-Hydroxygeranyl benzyl ether 429.**

A suspension of selenium dioxide (1.45 g, 13.08 mmol) in ethanol (9 mL) was added to a solution of geranylbenzyl ether **469** (6.38 g, 26.15 mmol) in ethanol (89 mL). The mixture was refluxed for 3 h, cooled to 0 °C, treated with $NaBH_4$ (500 mg, 13.08 mmol) and stirred at the same temperature for 2 h. After, the reaction was quenched with a 10% soln. of H_2SO_4 (10 mL), and the

mixture was worked up as usual. The crude product (7.5 g) was submitted to flash chromatography (silica gel (200 g); increasing gradient of ethyl acetate in light petroleum ether) to give starting ether **469** (3.14 g, 12.9 mmol, 49%) and *E,E*-8-hydroxygeranylbenzyl ether **429** (3.05 g, 11.7 mmol, 88.3% BRSM). Colorless viscous oil. IR spectrum (liquid film, ν, cm^{-1}): 697, 736, 1067, 1453, 1639, 3429 cm^{-1}. ^{1}H NMR (selected values): δ = 1.65 (s, 3H, C-10), 1.66 (*s*, 3H, C-9), 2.08 (*t*, *J* = 7.3 Hz, 2H, C-4), 2.17 (*q*, *J* = 7.3 Hz, 2H, C-5), 3.97 (*s*, 2H, C-8), 4.02 (*d*, *J* = 6.8 Hz, 2H, C-1), 4.50 (*s*, 2H, C-1'), 5.39 (*m*, 2H, C-2 and C-6), 7.31 (*m*, 5H, Ar-H), ppm. ^{13}C NMR: δ = 13.6 (*q*, C-9), 16.4 (*q*, C-10), 25.8 (*t*, C-5), 39.1 (*t*, C-4), 66.5 (*t*, C-1), 68.9 (*t*, C-8), 72.1 (*t*, C-1'), 121.1 (*d*, C-2), 125.5 (*d*, C-6), 127.5 (*d*, C-5'), 127.8 (*d*, C-3', 7'), 128.3 (*d*, C-4', 6'), 135.1 (*s*, C-3), 139.9 (*s*, C-7) ppm. All physical properties and spectroscopic data were identical with those reported in literature [138].

***E,E*-8-Oxogeranyl benzyl ether 430**.

Hydroxyether **429** (1.41 g, 5.42 mmol) was dissolved in dry CH_2Cl_2 (83 mL) and PCC (1.75 g, 8.13 mmol) was added. After stirring the reaction mixture at room temperature for 1.5 h, it was diluted with diethyl ether (60 ml) and passed through a short silica gel pad. The crude product (1.9 g) was subjected to flash chromatography. Elution with 4% ethyl acetate/light petroleum ether mixture gave 980 mg (70%) of unsaturated aldehyde **430**. IR spectrum (liquid film, ν, cm^{-1}): 697, 736, 1069, 1116, 1381, 1453, 1686, 2857, 2975 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (*s*, 3H, C-10), 1.76 (*d*, *J* = 0.8 Hz, 3H, C-9), 2.23 (*t*, *J* = 7.6 Hz, 2H, C-4), 2.5 (*q*, *J* = 7.6 Hz, 2H, C-5), 4.06 (*d*, *J* = 6.7 Hz, 2H, C-1), 4.51 (*s*, 2H, C-1'), 5.46 (apparent *tq*, *J* = 6.7, 1.2 Hz, 1 H, C-2), 6.47 (*td*, *J* = 7.6, 1.3 Hz, 1 H, C-6), 7.31 (*m*, 5H, Ar-H), 9.39 (*s*, 1 H, C-8). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0 (*q*, C-9), 16.2 (*q*, C-10), 26.9 (*t*, C-5), 37.6 (*t*, C-4), 66.3 (*t*, C-1), 72.0 (*t*, C-1'), 121.9 (*d*, C-2), 127.4 (*d*, C-5'), 127.5 (*d*, C-3', 7'), 128.2 (*d*, C-4', 6'), 138.2 (*s*, C-2'), 138.3 (*s*, C-3), 139.3 (*s*, C-7), 153.5 (*d*, C-6), 194.8 (*d*, C-8). All physical properties and spectroscopic data were identical with those reported in literature [138].

***E,E*-8-Acetoxygeranyl benzyl ether 431.**

Acetic anhydride (1.8 ml) was added to a solution of *E,E*-8-hydroxygeranylbenzyl ether **429** (1.1 g, 4.23 mmol) in 5.5 ml of dry pyridine and the mixture was kept for 6 h at r.t., followed by usual work-up. The crude product (1.2 g) was chromatographed on a column with 50 g Si-gel. Elution with

a mixture of petroleum ether and EtOAc (97:3) gave 1.09 g (85 %) of acetate **431** as a colorless viscous liquid. Found (%): C, 75.31; H, 8.58. $C_{19}H_{26}O_3$. Calculated (%): C, 75.46; H, 8.67. IR spectrum (liquid film, ν, cm^{-1}): 1020, 1060, 1235, 1735. ^1H RMN (80 MHz, δ): 1.66 (s, 6H, CH_3-9 and CH_3-10), 2.06 (s, 3H, OAc), 4.03 (d, 2H, J=6 Hz, 2H, CH_2-1), 4.48 (d, J=4.6 Hz, 2H, CH_2-8), 5.40 (m, 2H, H la C-2 and C-6), 7.20-7.30 (m, 5H, Ar-H).

Geranyl tetrahydropyranyl ether 459.

A solution of geraniol **423** (4.393 g, 28.53 mmol) in CH_2Cl_2 (59 mL) was treated with dihydropyran (4.2 mL, 45.65 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.325 g, 1.29 mmol). The mixture was stirred for 12 h at room temperature. The usual work up gave crude product (6.431 g), which was chromatographed over a column of Al_2O_3 (40 g) with gradient elution by petroleum ether:AcOEt to afford **459** (6.395 g, 94%) as a colorless liquid. The spectral data (IR and ^1H NMR) were identical with those published.

***E,E*-8-Hydroxygeranyl tetrahydropyranyl ether 432.**

Selenium dioxide (415 mg, 3.74 mmol) was added to a solution of **459** (1.802 g, 8.04 mmol) in ethanol (15 mL) and pyridine (0.4 ml, 4.82 mmol). The mixture was stirred for 20 h at room temperature, diluted with water (100 mL), and extracted with AcOEt (3 × 50 mL). The extract was washed with NaCl solution (2 × 50 mL) and concentrated in vacuo to give a yellow oil (1.908 g). The product was chromatographed over a column of Al_2O_3 (54 g) with gradient elution by petroleum ether: AcOEt to afford starting **459** (502 mg, 2,11 mmol, 28%) and *E,E*-8-hydroxygeranyltetrahydropyranyl ether **432** (810 mg, 3.19 mmol, 54% on the basis of recovered **459**) as a colorless oil. Spectral data of **432** were identical with those published.

***E,E*-8-Chlorogeranyl tetrahydropyranyl ether 433.**

A solution of **432** (437 mg, 1.71 mmol) in dry CH_2Cl_2 (4.3 mL) was treated under Ar at ambient temperature with 4-dimethylaminopyridine (DMAP, 131 mg, 1.07 mmol), tosylchloride (408 mg, 2.14 mmol), and triethylamine (0.24 mL, 1.71 mmol). The mixture was stirred for 3 h at room temperature, treated with LiCl (145 mg, 3.40 mmol), and stirred for another 2 h at the same temperature. CH_2Cl_2 was removed in vacuo. The residue was treated with water (10 mL) and extracted with ether (3 × 5

mL). The combined ether extract was washed with NaCl solution (2 × 5 mL) and evaporated in vacuo to afford *E,E*-8-chlorogeranyltetrahydropyranyl ether **433** (411 mg, 1.51 mmol, 88%) as a yellow oil that was used without further purification. Spectral data of **433** were identical with those published.

Geranylphenylsulfone 461.

Phosphorus tribromide (4.3 mL, 12.255 g, 45.29 mmol) was dissolved in dry ether (16 mL) and added dropwise to a stirred solution of geraniol **423** (5.120 g, 33.25 mmol) in dry ether (47 mL) with cooling on an ice bath. The mixture was stirred for 12 h at room temperature and treated with saturated $NaHCO_3$ solution. The ether layer was separated, washed with NaCl solution, dried, and concentrated in vacuo. The resulting liquid product was added to a solution of sodium benzenesulfinate (6.55 g, 39.90 mmol) in dry DMF (46 mL). The mixture was stirred at room temperature under Ar in the dark for 3 h, treated with NaCl solution, and extracted with ether. The extract was worked up as usual to afford a liquid product that was chromatographed over a column of SiO_2 (260 g) with gradient elution by petroleum ether:AcOEt to afford **461** as a colorless oil (7.39 g, 84% yield in two steps). Spectral data of **461** were identical with those published.

***E,E*-8-Hydroxygeranylphenylsulfone 435.**

A suspension of selenium dioxide (1.84 g, 16.55 mmol) in ethanol (15 mL) was added to a solution of **461** (9.20 g, 33.09 mmol) in ethanol (25 mL). The mixture was stirred at 40 °C for 4 h, cooled to 0 °C, treated with $NaBH_4$ (670 mg, 16.50 mmol), stirred at the same temperature for 30 min, diluted with water (100 mL), and extracted with AcOEt (3 × 50 mL). The extract was washed with saturated NaCl solution (2 × 50 mL) and evaporated in vacuo. The resulting liquid product (9.5 g) was chromatographed over a column of SiO_2 (200 g) with gradient elution by petroleum ether:AcOEt to afford starting **461** (1.7 g, 6.12 mmol, 18%) and liquid *E,E*-8-hydroxygeranylphenylsulfone **435** (4.03 g, 13.71 mmol, 54% on the basis of recovered **461**). IR spectra and ^1H NMR spectra were identical with those published.

***E,E*-8-Phenylsulfonylgeraniol 436**.

A solution of acetoxysulfone **428** (4.77 g, 14.88 mmol) in EtOH (5.0 mL) was treated with KOH in alcohol (10%, 40 mL) and refluxed for 2 h. After the usual work up, the crude product (4.05 g) was

chromatographed over a Si-gel (120 g) column with elution by petroleum ether:AcOEt (9:1) to afford *E,E*-8-phenylsulfonylgeraniol **436** (3.90 g, 93%) as a colorless oil, $C_{16}H_{22}SO_3$. IR spectrum (liquid film, ν, cm^{-1}): 3640, 3550, 1300, 1135, 990. ^1H NMR spectrum (80 MHz, δH, ppm, J/Hz): 1.67 (6H, s, H_3-9 and H_3-10), 3.64 (2H, s, H_2-8), 4.05 (2H, d, J = 6.7, H_2-1), 5.05-5.35 (2H, m, H-2 and H-6), 7.50-7.75 (5H, m, Ar–H).

***E,E,E*-10-Hydroxyfarnesyl benzyl ether 438.**

To a solution of farnesol benzyl ether **437** (2.18 g, 6.99 mmol) in EtOH (4 mL) was added SeO_2 (410 mg, 3.68 mmol) and the solution was refluxed for 2 h. After removal of the precipitated Se, the solution was concentrated. Chromatography of the crude product (2.47 g) on silica gel afforded the starting ether **437** (645 mg, 30%) and *E,E,E*-10-hydroxyfarnesylbenzyl ether **438** (710 mg, 31%). IR spectrum (liquid film, ν, cm^{-1}): 3400, 2930, 1670, 1450, 1068, 770. ^1H NMR (300 MHz, $CDCl_3$, δ): 1.59 (s, 9 H, CH_3-13, CH_3-14 and CH_3-15), 3.83 (m, 2 H, H_2-12), 3.90 (d, 7 Hz, 2 H, H_2-1), 4.30 (s, 2 H, CH_2Ph), 5.10 (m, 2 H, H-2 and H-6), 5.35 (m, 1 H, H-10), 7.20-7.30 (m, 5 H, Ar-1H).

***E,E,E*-10-acetoxyfarnesyl benzyl ether 439.**

A solution of **438** (650 mg, 1.98 mmol) in anhydrous pyridine (5 mL) was treated with Ac_2O (1 mL) and the mixture was kept at r.t. for 2 h. H_2O (10 mL) was added carefully to the mixture and the product was extracted with Et_2O (3 × 10 mL). The extract was washed with 10% H_2SO_4 (2 × 5 mL), H_2O (2 × 10 mL), dried (Na_2SO_4) and concentrated. The crude reaction product (727 mg) was chromatographed on a silica gel column (petroleum ether/Et_2O, 97:3) to give 675 mg (92%) of **439**. IR spectrum ($CHCl_3$, ν, cm^{-1}): 1735, 1455, 1380, 1235, 1065, 1020. ^1H NMR (300 MHz, $CDCl_3$, δ): 1.56 (s, 3 H, CH_3-13), 1.60 (s, 3 H, CH_3-14), 1.65 (s, 3 H, CH_3-15), 2.07 (s, 3 H, $OCOCH_3$), 4.03 (m, 2 H, H_2-1), 4.44 (br s, 2 H, H_2-12), 4.50 (s, 2 H, CH_2Ph), 5.12 (m, 2 H, H-2 and H-6), 5.40 (m, 1 H, H-10), 7.20-7.35 (m, 5 H, Ar-H). Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.76; H, 9.22.

Geranyllinalylacetate 442.

Geranyllinalool **441** (138 mg, 0.476 mmol) and DMAP (116 mg, 0.952 mmol) were dissolved in dry CH_2Cl_2 (1 ml) under N_2. Acetic anhydride (0.09 ml, 0.952 mmol) was added and the reaction

mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (12 ml) and washed successively with sat. aq. $CuSO_4$ (4×5 ml), sat. aq. $NaHCO_3$ (2×5 ml) and brine (5 ml), dried and evaporated *in vacuo*. The residue was purified by flash chromatography on Si gel (3.3 g) using hexane : EtOAc (99:1) as eluent to yield **442** (100 mg, 63%) as a colorless oil. ^{1}H NMR (300 MHz): δ_H= 1.52 (*s*, 3H, CH_3), 1,57 (*s*, 9H, 3×CH_3), 1.65 (*s*, 3H, CH_3), 1.98 (*s*, 3H, CH_3CO), 1.9–2.2 (*m*, 12H, 6×CH_2), 5.04–5.07 (*m*, 5H, 5×CH), 5.95 (*dd*, *J* = 10.9 and 17.5 Hz, 1H, CH=C).

(2*Z*,6*E*,10*E*)- and **(2*E*,6*E*,10*E*)-Geranylgeranylacetates 443.**

Geranyllinalylacetate **442** (677 mg, 2.039 mmol) was dissolved in dry THF (23 ml), $PdCl_2(CH_3CN)_2$ (26 mg, 0.101 mmol) was added and the mixture was stirred under N_2 for 18 h. An additional portion of $PdCl_2(CH_3CN)_2$ (26 mg, 0.101 mmol) was added and stirring continued for another 12 h. The mixture was evaporated *in vacuo* and the residue was purified by flash chromatography on Si gel (4.5 g) using hexane: EtOAc (20:1) as eluent to yield the mixture of acetates **443** (609 mg, 90%) as a pale yellow oil. HPLC analysis showed an *E/Z* ratio of ~85:15. ^{1}H NMR (300 MHz): δ_H= 1.63 (*s*, 9H, 3×CH_3), 1.68 (*s*, 3H, CH_3), 1.73 (*s*, 3H, CH_3), 1.9–2.2 (*m*, 15H, 6×CH_2 and OAc), 4.56 (*d*, *J* = 7.1 Hz, 2H, CH_2), 5.10 (*m*, 3H, 3×CH), 5.32 (*t*, *J* = 7.1 Hz, 1H, CH).

Synthesis of 14,15-epoxy-*E,E,E*-geranylgeraniol 444.

To a solution of geranylgeranylacetates **443** (606 mg, 1.825 mmol) in THF (8.7 ml)-H_2O (2.9 ml) N-bromosuccinimide (357 mg, 1.825 mmol) was added at 0 °C on stirring. The reaction mixture was stirred for 1.5 h at 0 °C and 2 h at room temperature. Then it was diluted with water (20 ml) and worked-up as usual. The residue (846 mg) obtained after evaporation of the solvent was dissolved in methanol (11.5 ml) and treated with K_2CO_3 (756 mg, 5.48 mmol). The obtained suspension was stirred for 20 h at room temperature, filtered and the solvent evaporated *in vacuo*. The crude product (627 mg) was submitted to flash chromatography on Si gel (25 g). Elution with an increasing gradient of EtOAc in petr. ether gave racemic *trans*-epoxyalcohol **444** (192 mg, 34% after two steps). IR: ν_{max} (liquid film) 3413, 2923, 2854, 1667, 1448, 1379, 1249, 1120, 1010 cm^{-1}. ^{1}H NMR (300 MHz): δ_H= 1.25 (*s*, 3H), 1.29 (*s*, 3H), 1.59 (*s*, 3H), 1.61 (*s*, 3H), 1.67 (*d*, *J* = 1Hz, 3H), 1.94-2.23 (*m*, 11H), 2.70 (*t*, *J* = 6Hz, 1H), 4.14 (*d*, *J* = 7 Hz, 2H), 5.41 (*m*, 1H), 5.12 (*m*, 2H). ^{13}C NMR (75 MHz): δ_C = 16.4,

16.6, 19.1, 25.3, 26.7, 26.9, 27.8, 36.7, 39.9, 40.0, 58.5, 59.8, 64.6, 123.8, 124.3, 125.2, 134.4, 135.6, 140.0. ESIMS *m/z* (%) 307 (12) $[M+H]^+$, 289 (52), 271 (32), 259 (20), 221 (20), 203 (33), 191 (19), 161 (32), 153 (84), 135 (100), 121 (61), 109 (84). HREIMS *m/z* 306.2549 (calcd. for $C_{20}H_{34}O_2$ 306.2559).

Periodate cleavage of 14,15-epoxy-*E,E,E*-geranylgeraniol 444. *E,E*-12-(2-oxoethyl)-farnesol 446.

To a solution of epoxyalcohol **444** (182 mg, 0.597 mmol) in THF (4.5 ml) and H_2O (1 ml) were added successively $NaIO_4$ (75 mg, 0.35 mmol) and HIO_4 (149 mg, 0.66 mmol). After 4 h of stirring at room temperature another portion of $NaIO_4$ (75 mg, 0.33 mmol) was added and stirring continued for an additional 1 h. The reaction mixture was diluted with H_2O (10 ml) and extracted with $CHCl_3$ (3×20 ml). The combined organic phase was washed with brine to neutral and dried. After removal the solvent the crude residue (198 mg) was used in the next step without purification. An aliquot of the crude product was subjected to flash chromatography to provide a pure sample of aldoalcohol **446**. IR: ν_{max} (liquid film) 3406, 2925, 1723, 1668, 1446, 1382, 1108, 1016, 756 cm^{-1}. ^1H NMR (300 MHz): δ_H=1.59 (*s*, 3H), 1.60 (*s*, 3H), 1.67 (*s*, 3H), 1.70-1.74 (*m*, 8H), 2.24 (*t*, *J* = 7Hz, 1H), 2.40-2.48 (*m*, 1H), 4.15 (*d*, *J* = 7Hz, 2H), 5.06-5.15 (*m*, 2H), 5.37-5.44 (*m*, 1H), 9.74 (*t*, *J* = 2Hz, 1H). ^{13}C NMR (75 MHz)): δ_C= 16.3, 16.4, 16.6, 26.6, 26.8, 32.2, 38.9, 39.8, 42.4, 59.7, 123.7, 124.3, 125.7, 133.2, 135.4, 140.0, 203.2. ESIMS *m/z* (%) 265 (37) $[M+H]^+$, 247 (45), 229 (43), 217 (12), 203 (16), 189 (14), 177 (18), 161 (66), 149 (55), 135 (64), 121 (69), 111 (100). HREIMS *m/z* 264.2077 (calcd. for $C_{17}H_{28}O_2$ 264.2089).

THP-protection of aldoalcohol 446. *E,E*-12-(2-oxoethyl)-farnesyl tetrahydropyranyl ether 447.

To the solution of crude aldoalcohol **446** obtained in the previous step in CH_2Cl_2 (1.2 ml) were added successively pyridinium para-toluenesulfonate (PPTS) (68 mg, 0.271 mmol) and dihydropyrane (0.09 mL, 0.934 mmol). The reaction mixture was stirred overnight at room temperature and worked-up as usual. Removal of the solvent and flash chromatography on Si gel (6 g, elution with 4% EtOAc in petr. ether) gave 93 mg (46% after two steps) of THP-protected aldehyde **447**. IR: ν_{max} (liquid film) 3432, 2927, 2719, 1726, 1668, 1442, 1384, 1199, 1117, 1023, 905, 869, 814 cm^{-1}. ^1H NMR (300 MHz): δ_H= 1.58 (*s*, 3H), 1.60 (*s*, 3H), 1.67 (*s*, 3H), 1.94 - 2.14 (*m*, 8H), 2.3 (*t*, *J* = 7Hz, 1H), 2.53-2.47 (*m*, 1H), 3.47-3.54 (*m*, 1H), 3.85 - 3.92 (*m*, 1H), 3.99-4.05 (*m*, 1H), 4.20-4.26 (*m*, 1H), 4.61-4.63 (*m*,

1H), 5.07-5.15 (*m*, 2H), 5.33-5.37 (*m*, 1H), 9.74 (*t*, *J* = 2Hz, 1H). ^{13}C NMR (75 MHz): δ_C= 16.3, 16.4, 16.8, 20.0, 25.8, 26.6, 26.8, 31.0, 32.2, 39.8, 39.9, 42.5, 62.6, 64.0, 98.1, 120.9, 124.5, 125.7, 133.2, 135.3, 140.6, 203.1. ESIMS *m/z* (%) 349 (4) $[M+H]^+$, 331 (10), 307 (12), 289 (11), 263 (23), 247 (27), 229 (27), 219 (10), 201 (10), 177 (12), 161 (34), 154 (100), 136 (77), 121 24). HREIMS *m/z* 348.2603 (calcd. for $C_{22}H_{36}O_3$: 348.2664).

Olefination of aldehyde 447. *E,E,E*-16-oxogeranylgeranyl tetrahydropyranyl ether 448.

To the solution of aldehyde **447** (71 mg, 0.204 mmol) in dry THF (1.1 ml) the solution of $Ph_3P=C(CH_3)$-CHO (81 mg, 0.255 mmol) in a mixture C_6H_6-CH_2Cl_2 (1:1) (0.8 ml) was added. The rection mixture was refluxed for 18 h under Ar atmosphere. Dilution with water (5 ml) was followed by usual work-up to provide after the evaporation of the solvent the crude product (170 mg), which was submitted to flash chromatography on Si gel (15 g). Elution with 3% EtOAc in petroleum ether gave the THP-protected aldehyde **448** (54 mg, 79%), along with the unreacted aldehyde **447** (10 mg). The yield of compound **448** is presented basing on the recovered initial compound **447**.

E,E,E-16-oxogeranylgeranyl tetrahydropyranyl ether **448**: Colorless viscous oil. IR: ν_{max} (liquid film) 3430, 2925, 2710, 1726, 1689, 1442, 1383, 1260, 1199, 1117, 1023, 905, 814 cm^{-1}. ^{1}H NMR (300 MHz): δ_H= 1.53 (*s*, 3H), 1.56 (*s*, 3H), 1.61 (*s*, 3H), 1.68 (*d*, *J* = 1Hz, 3H), 1.88-2.12 (*m*, 8H), 2.34-2.44 (*m*, 2H), 3.40-3.48 (*m*, 1H), 3.79-3.85 (*m*, 1H), 3.92-3.99 (*m*, 1H), 4.14-4.20 (*m*, 1H), 4.54-4.57 (*m*, 1H), 5.02-5.10 (*m*, 2H), 5.32-5.27 (*m*, 1H), 6.38-6.43 (*m*, 1H), 9.31 (*s*, 1H). ^{13}C NMR (75 MHz): δ_C= 16.2, 16.3, 16.4, 16.8, 20.0, 25.8, 26.6, 26.9, 27.8, 32.2, 38.3, 39.9, 40.0, 62.6, 64.0, 99.2, 120.9, 124.4, 125.9, 133.7, 135.9, 140.5, 154.9, 195.7. ESIMS *m/z* (%) 389 (16) $[M+H]^+$, 305 (18), 303 (12), 287 (100), 263 (23), 247 (25), 229 (30), 203 (22), 177 (24), 161 (57), 149 (72), 135 (77). HREIMS *m/z* 388.2889 (calcd. for $C_{25}H_{40}O_3$ 388.2977).

Reduction of aldehyde 448. *E,E,E*-16-hydroxigeranylgeranyl tetrahydropyranyl ether 449.

The solution of aldehyde **448** (33 mg, 0.085 mmol) in ethanol (1 ml) was treated with $NaBH_4$ (6 mg, 0.145 mmol) at 0 °C on stirring. After 1 h at this temperature, the reaction mixture was quenched with a 10% solution of H_2SO_4 (1 ml) and worked-up as usual. The crude product was submitted to flash chromatography on Si gel (1.7 g). Elution with an increasing gradient of EtOAc in petr. ether gave alcohol **449** (22 mg, 66%) as a colorless viscous oil. IR: ν_{max} (liquid film) 3422, 2924,

2853, 1665, 1450, 1383, 1261, 1117, 1023 cm^{-1}. ^1H NMR (300 MHz): δ_H= 1.60 (*s*, 6H), 1.67 (*s*, 3H), 1.68 (*s*, 3H), 2.16-1.96 (*m*, 12H), 3.49-3.53 (*m*, 1H), 3.86-3.92 (*m*, 1H), 3.99 (*s*, 2H), 3.89-4.14 (*m*, 3H), 4.61-4.63 (*m*, 1H), 5.09-5.23 (*m*, 2H), 5.34-5.42 (*m*, 2H). ^{13}C NMR (75 MHz): δ_C= 14.1, 16.3, 16.8, 20.0, 25.9, 26.6, 26.7, 26.9, 26.9, 31.1, 39.7, 40.0, 62.6, 64.0, 69.4, 98.1, 120.9, 124.3, 124.8, 126.4, 126.5, 134.2, 135.5, 140.6. ESIMS *m/z* (%) 391 (1) $[M+H]^+$, 373 (7), 361 (11), 309 (8), 289 (15), 271 (52), 259 (19), 203 (20), 177 (11), 161 (24), 154 (100), 147 (35), 137 (94), 109 (64). HREIMS *m/z* 390.3099 (calcd. for $C_{25}H_{42}O_3$: 390.3134).

Acetylation of alcohol 449. *E,E,E*-16-Acetoxygeranylgeranyl tetrahydropyranyl ether 450.

The solution of alcohol **449** (10 mg, 0.026 mmol) in pyridine (0.05 ml) was treated with acetic anhydride (5 μl, 0.053 mmol). The reaction mixture was left overnight at room temperature and then worked-up as usual. The crude product (14 mg) was submitted to flash chromatography on Si gel (0.7 g). Elution with an increasing gradient of EtOAc in petr. ether gave the acetate **450** (12 mg, 96%) as a colorless viscous oil. IR: ν_{max} (liquid film) 3416, 2934, 1741, 1671, 1443, 1379, 1237, 1118, 1024, 906, 814 cm^{-1}. ^1H NMR (300 MHz): δ_H= 1.60 (*s*, 6H), 1.65 (*s*, 3H), 1.68 (*s*, 3H), 2.07 (*s*, 3H), 3.49-3.53 (*m*, 1H), 3.86-3.90 (*m*, 1H), 4.00-4.06 (*m*, 1H), 4.21-4.23(*m*, 1H), 4.45 (*s*, 2H), 4.62-4.64 (*m*, 1H), 5.11 (*td*, J_1 = 7Hz, J_2 = 1Hz, 2H), 5.45 (*m*, 1H), 5.36 (*m*, 1H). ^{13}C NMR (75 MHz): δ_C= 14.3, 16.4, 16.8, 20.0, 21.4, 25.8, 26.5, 26.7, 27.0, 31.0, 39.4, 40.0, 62.6, 64.0, 70.7, 98.1, 120.9, 124.3, 125.0, 130.0, 130.2, 134.7, 135.6, 140.6, 171.4. ESIMS *m/z* (%) 433 (16) $[M+H]^+$, 347 (12), 331 (37), 313 (9), 287 (23), 271 (100), 238 (9), 203 (50), 189 (22), 161 (33), 135 (97), 121 (33). HREIMS *m/z* 432.3179 (calcd. for $C_{27}H_{44}O_4$: 432.3240).

THP-deprotection of acetate 450. *E,E,E*-16-Acetoxygeranylgeraniol 440.

The solution of acetate **450** (509 mg, 1.18 mmol) in MeOH (10 ml) was treated with *p*-TSA (7 mg) and left at room temperature overnight. Then the reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 ml) and worked-up as usual. The crude product (440 mg) was submitted to flash chromatography on Si gel (15 g). Elution with an increasing gradient of EtOAc in petr. ether gave the acetoxyalcohol **440** (217 mg, 53%) as a colorless viscous oil. IR: ν_{max} (liquid film) 3423, 2925, 2855, 2361, 1740, 1668, 1447, 1379, 1235, 1023, 843 cm^{-1}. ^1H NMR (300 MHz): δ_H= 1.60 (*s*, 6H), 1.65 (*s*, 3H), 1.68 (*s*, 3H), 2.07 (*s*, 3H), 4.15 (*d*, *J* = 6.6 Hz, 2H), 4.44 (*s*, 2H), 5.11 (*m*, 1H), 5.42 (*m*, 2H). ^{13}C

NMR (75 MHz): δ_C= 14.4, 16.4, 16.7, 21.5, 26.7, 26.8, 27.0, 39.5, 40.1, 59.8, 62.4, 69.8, 70.8, 123.7, 124.2, 125.1, 128.0, 128.4, 134.8, 135.7, 140.2, 170.0. ESIMS *m/z* (%) 331 (5) [$(M+H)^+$-H_2O], 282 (12), 271 (34), 203 (11), 189 (10), 175 (11), 147 (55), 135 (100), 133 (54), 109 (74). HREIMS *m/z* 348.2652 (calcd. for $C_{22}H_{32}O_3$ 348.2664).

***E,E,E*-16-Hydroxy-9-phenylsulfonylgeranylgeranyl tetrahydropyranyl ether 452.**

A stirred solution of **435** (611 mg, 2.08 mmol) in dry THF (9 mL) and hexamethylphosphoramide (HMPA, 1 mL) was treated at -78°C under Ar with *n*-BuLi (4.16 mmol) in hexane. The temperature of the mixture was gradually increased to 0 °C over 1 h and then again reduced to -78 °C. The mixture was treated dropwise with **433** (471 mg, 1.73 mmol) in dry THF (8 mL) and HMPA (0.8 mL). The temperature was gradually increased to room temperature. The mixture was stirred at this temperature overnight and worked up as usual. The product was chromatographed over a column of SiO2 (46 g) with gradient elution by petroleum ether:AcOEt to afford *E,E,E*-16-hydroxy-9-phenylsulfonylgeranylgeranyl tetrahydropyranyl ether **452** (834 mg, 91%) as a colorless oil, $C_{31}H_{46}SO_5$. IR spectrum (liquid film, ν, cm^{-1}): 3450, 1665, 1582, 1310, 1140. ^{1}H NMR spectrum (80 MHz, δH, ppm): 1.50 (3H, s, H_3-19), 1.52 (3H, s, H_3-18), 1.64 (3H, s, H_3-17), 1.66 (3H, s, H_3-20), 3.58-3.75 (3H, m, H-9 and H_2-5′), 4.87 (1H, m, H-1′), 5.00 (2H, m, H-6 and H-10), 5.33 (2H, m, H-2 and H-14), 7.40-7.90 (5H, m, Ar–H).

***E,E,E*-16-Hydroxygeranylgeranyl tetrahydropyranyl ether 453.**

A mixture of **452** (530 mg, 1.0 mmol) and Na_2HPO_4 (568 mg, 4 mmol) in dry methanol (11 mL) was treated at 0 °C with an excess of freshly prepared sodium amalgam (4 g) and stirred at the same temperature overnight. The excess of the amalgam was decomposed with cold water. The mixture was extracted with ether. The extract was worked up as usual. The product (378 mg) was chromatographed over a column of SiO_2 (4 g) with gradient elution by petroleum ether:AcOEt to afford a product (357 mg) containing traces of other compounds. Then this product was purified by semi-preparative HPLC over a Nova-Pack C-18 column (MeOH:H2O, 95:5, elution flow rate 1.5 mL/min) to afford *E,E,E*-16-hydroxygeranylgeranyl tetrahydropyranyl ether **453** (284 mg, 73%) as a colorless oil, $C_{25}H_{42}O_3$. IR spectrum (liquid film, ν, cm^{-1}): 3423, 2920, 2850, 1450, 1370, 1210, 1020, 838. ^{1}H NMR spectrum (80 MHz, δH, ppm): 1.52 (6H, s, H_3-18 and H_3-19), 1.59 (6H, s, H_3-17 and H_3-20), 2.57 (1H, br.s,

OH), 3.49-3.82 (2H, m, H_2-5′), 3.90 (2H, br.s, H_2-16), 4.09 (2H, d, J = 7, H_2-2), 4.54 (1H, m, H-1′), 5.04 (2H, m, H-6 and H-10), 5.23 (2H, m, H-2 and H-14).

***E,E,E*-16-Hydroxygeranylgeraniol 451.**

A solution of **453** (105 mg, 0.269 mmol) in methanol (1.6 mL) was treated at room temperature under Ar with *p*-toluenesulfonic acid (1.5 mg, 0.0087 mmol). The mixture was stirred for 12 h and worked up as usual. The product (79 mg) was chromatographed over a column of SiO2 (3 g) with gradient elution by petroleum ether:AcOEt to afford **451** (68 mg, 83%) as a colorless oil. Spectra data (IR and ^{1}H NMR) were identical to those published for the natural product.

***E,E,E*-16-Acetoxygeranylgeranyl tetrahydropyranyl ether 454.**

A solution of **453** (480 mg, 1.23 mmol) in pyridine (2.5 mL) was treated at room temperature with acetic anhydride (0.24 mL, 2.55 mmol). The mixture was held overnight at the same temperature, poured onto ice, and extracted with ether. The extract was worked up as usual. The product (564 mg) was chromatographed over a column of SiO_2 (16 g) with gradient elution by petroleum ether:AcOEt to afford *E,E,E*-16-acetoxygeranylgeranyl tetrahydropyranyl ether **454** (530 mg, 99%) as a colorless oil, $C_{27}H_{44}O_4$. IR spectrum (liquid film, ν, cm^{-1}): 1725, 1660, 1440, 1360, 1230, 1020, 845. ^{1}H NMR spectrum (400 MHz, δH, ppm, J/Hz): 1.59 (6H, s, H_3-18 and H_3-19), 1.64 (3H, s, H_3-17), 1.67 (3H, s, H_3-20), 2.06 (3H, s, OAc), 2.62 (1H, br.s, OH), 3.50 (1H, m, HA-5′), 3.89 (1H, m, HB-5′), 4.02 (1H, dd, J_1 = 7.3, J_2 = 12.0, HA-2), 4.23 (1H, dd, J_1 = 6.4, J_2 = 12.0, HB-2), 4.44 (1H, s, H_2-16), 4.62 (1H, dd, J_1 = 3.1, J_2 = 3.9, H-1′), 5.11 (1H, m, H-6), 5.28 (1H, m, H-10), 5.35 (1H, t, J = 7, H-2), 5.44 (1H, t, J = 7, H-14).

***E,E,E*-16-Acetoxygeranylgeraniol 455.**

A solution of **454** (509 mg, 1.18 mmol) in methanol (7 mL) was treated at room temperature under Ar with *p*-toluenesulfonic acid (7 mg, 0.041 mmol), stirred for 12 h, and worked up as usual. The residue (440 mg) was chromatographed over a column of SiO_2 (15 g) with gradient elution by petroleum ether:AcOEt to afford *E,E,E*-16-acetoxygeranylgeraniol **455** (240.7 mg, 59%) and *E,E,E*-16-hydroxygeranylgeraniol **451** (64 mg, 18%).

***E,E,E*-16-acetoxygeranylgeraniol 455**: $C_{22}H_{26}O_3$, colorless oil. IR spectrum (liquid film, ν, cm^{-1}): 3423, 2920, 2850, 2360, 1730, 1670, 1445, 1380, 1235, 1023, 840. ^1H NMR spectrum (300 MHz, δH, ppm, J/Hz): 1.60 (6H, s), 1.65 (3H, s), 1.68 (3H, s), 2.07 (3H, s), 4.15 (2H, d, J = 6.6), 4.44 (2H, s), 5.11 (1H, m), 5.42 (2H, m). ^{13}C NMR spectrum (75.5 MHz, δC, ppm): 170.0 (s, $OCOCH_3$), 140.2 (s, C-3), 135.7 (s, C-15), 134.8 (s, C-11), 128.4 (s, C-7), 128.0 (d, C-14), 125.1 (d, C-2), 124.2 (d, C-10), 123.7 (d, C-6), 69.8 (t, C-16), 62.4 (t, C-1), 40.1 (t, C-4), 39.5 (t, C-8 and C-12), 27.0 (t, C-5), 26.8 (t, C-13), 26.7 (t, C-9), 21.5 (q, $OCOCH_3$), 16.7 (q, C-17), 16.4 (q, C-18 and C-20), 14.4 (q, C-19).

Synthesis of *E,E,E,E*-8-phenylsulfonylgeranylfarnesol 462.

A stirred solution of **436** (403 mg, 1.37 mmol) in dry THF (4 mL) and hexamethylphosphortriamide (HMPA, 0.4 mL) was treated at -78 °C under Ar with n-BuLi (2.74 mmol) in hexane. The temperature of the mixture was gradually increased to 0°C over 1 h and then again reduced to -78 °C. The mixture was treated dropwise with a solution of (*E,E*)-farnesyl chloride **464** (330 mg, 1.37 mmol) in dry THF (4 mL) and HMPA (0.4 mL). The temperature of the mixture was gradually increased to room temperature, at which it was stirred overnight and worked up as usual. The product (642 mg) was chromatographed over a SiO_2 (24 g) column with gradient elution by petroleum ether:AcOEt to afford *E,E,E,E*-8-phenylsulfonylgeranylfarnesol **462** (344 mg, 50%) as a colorless oil, $C_{31}H_{46}SO_3$. IR spectrum (liquid film, ν, cm^{-1}): 3458, 2922, 1446, 1304, 1145, 1084, 990. ^1H NMR spectrum (300 MHz, δH, ppm, J/Hz): 1.54 (3H, s, H_3-23), 1.55 (3H, s, H_3-22), 1.58 (3H, s, H_3-21), 1.61 (3H, s, H_3-20), 1.65 (3H, s, H_3-25), 1.68 (3H, s, H_3-24), 3.46 (1H, dd, J_1 = 4.0, J_2 = 11.7, H-8), 4.11 (2H, d, J = 6.7, H_2-1), 4.86 (1H, t, J = 6.5, H-18), 5.04 (1H, t, J = 6.7, H-14), 5.14 (1H, t, J = 6.9, H-10), 5.23 (1H, t, J = 6.7, H-2), 5.35 (1H, t, J = 7.5, H-6), 7.50-7.88 (5H, m, Ar–H). ^{13}C NMR spectrum (75.5 MHz, δC, ppm): 16.4 (q, C-24), 16.5 (q, C-25), 16.6 (q, C-23), 16.7 (q, C-22), 18.1 (q, C-21), 24.8 (q, C-20), 26.6 (t, C-5), 26.1 (t, C-9), 26.9 (t, C-17), 27.1 (t, C-13), 39.1 (t, C-16), 40.0 (t, C-12), 40.1 (t, C-4), 59.6 (t, C-1), 74.3 (t, C-8), 118.7 (d, C-10), 124.1 (d, C-14), 124.2 (d, C-2), 124.5 (d, C-18), 124.7 (d, C-6), 129.2 (d, C-3), 129.3 (d, C-2′), 131.7 (s, C-19), 133.9 (s, C-4′), 135.6 (s, C-15), 135.7 (s, C-11), 138.8 (s, C-3), 138.9 (s, C-7), 139.2 (s, C-1′). Mass spectrum (m/z, I, %): 499 (3) $[M + H]^+$, 480 (5), 408 (4), 367 (5), 355 (7), 339 (56), 310 (7), 271 (23), 189 (22), 135 (72), 109 (100).

Synthesis of 13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesol 463.

A solution of phosphorus tribromide (653 mg, 1.78 mmol) in dry ether (0.5 mL) was added dropwise to a stirred solution of *iso*-drimenol (395 mg, 1.78 mmol) in dry ether (3.1 mL) and pyridine (0.2 mL) with cooling on an ice bath and then stirred for 2 h at room temperature. The usual work up afforded crude bromide **465** (486.8 mg, 96%), which was used in the following step without further purification. A stirred solution of **436** (401 mg, 1.36 mmol) in dry THF (5.8 mL) and HMPA (0.65 mL) was treated at -78°C under Ar with n-BuLi in hexane (2.73 mmol). The temperature of the mixture was gradually increased to 0°C over 1 h. The mixture was cooled again to -78 °C and treated dropwise with crude **465** (389 mg, 1.36 mmol) in dry THF (5.8 mL) and HMPA (0.65 mL). The temperature of the mixture was gradually increased to room temperature, at which it was stirred overnight and worked up as usual. The product was chromatographed over a Si-gel (32 g) column with gradient elution by petroleum ether:AcOEt to afford **463** (180 mg, 26%) as a colorless oil. IR spectrum (liquid film, ν, cm^{-1}): 3452, 2930, 2860, 1445, 1380, 1307, 1140, 1085, 893. ^{1}H NMR spectrum (300 MHz, dH, ppm, J/Hz): 0.83 (3H, s), 0.89 (3H, s), 1.07 (3H, s), 1.52 (3H, s), 1.58 (3H, s), 1.65 (3H, s), 3.30-3.50 (2H, m), 3.98 (1H, d, J = 9.5), 5.20-5.25 (1H, m), 5.27-5.36 (1H, m), 7.52-7.90 (5H, m). ^{13}C NMR spectrum (75.5 MHz, dC, ppm): 14.7 (q, CH_3), 16.4 (t, CH_2), 18.5 (t, CH_2), 19.8 (q, CH_3), 20.1 (q, CH_3), 21.5 (q, CH_3), 24.8 (t, CH_2), 25.2 (q, CH_3), 27.5 (t, CH_2), 32.1 (q, CH_3), 32.4 (t, CH_2), 33.1 (s, C), 34.3 (t, CH_2), 38.6 (s, C), 44.2 (t, CH_2), 45.7 (t, CH_2), 51.4 (d, CH), 53.2 (d, CH), 60.1 (t, CH_2), 118.7 (d, CH), 122.4 (d, CH), 126.7 (s, C), 129.1 (d, 2CH), 129.3 (d, 2CH), 131.0 (s, C), 132.1 (s, C), 133.4 (s, C), 137.1 (d, CH), 139.8 (s, C).

Synthesis of (+)-13*E*-labda-8(17),13(14)-dienyl-15-phenylsulfone 468.

A solution of phosphorus tribromide (1.54 g, 5.69 mmol) in dry ether (5.0 mL) was added dropwise to a stirred solution of manool **220** (1.20 g, 4.14 mmol) in dry ether (10 mL) with cooling on an ice bath. The mixture was stirred for 2 h at room temperature and treated with saturated $NaHCO_3$ solution. The ether layer was separated, washed with brine, dried, and concentrated *in vacuo*. The resulting bromide (1.25 g, 86%) was added to a solution of the sodium salt of benzenesulfinic acid (0.90 g, 5.45 mmol) in dry DMF (10 mL). The mixture was stirred at room temperature under Ar in the dark for 3 h, treated with NaCl solution, and extracted with ether. The extract was worked up as usual to afford a liquid product that was chromatographed over a silica gel (42 g) column with gradient elution by petroleum ether:AcOEt to elute 13*E*-labda-8(17),13(14)-dienyl-15-phenylsulfone **468**

(1.09 g, overall for two steps ~74%) as colorless crystals, m.p. 87-88 °C (from hexane), $[\alpha]_D^{25}$ +32.2 (*c* 1.45, $CHCl_3$). IR (liquid film) ν_{max}: 730, 1149, 1306, 1447, 1587, 1642, 2927 cm^{-1}. ^1H NMR (selected values): δ = 0.65 (*s*, 3H, C(20)-H), 0.79 (*s*, 3H, C(19)-H), 0.86 (*s*, 3H, C(18)-H), 1.29 (*s*, 3H, C(16)-H), 3.80 (*d*, *J* = 8 Hz, 2H, C(15)-H), 4.42 (*d*, *J* = 1.2 Hz, 1H, C(17)-H_b), 4.80 (*d*, *J* = 1.4 Hz, 1H, C(17)-H_a), 5.14 (*td*, *J* = 8.0, 1.3 Hz, 1H, C(14)-H), 7.68 (*m*, 5H, Ph-H). ^{13}C NMR: δ = 14.5 (*q*, C-20), 16.2 (*q*, C-16), 19.4 (*t*, C-2), 21.7 (*q*, C-19), 21.8 (*t*, C-11), 24.4 (*t*, C-6), 33.6 (*s*, C-4), 33.6 (*q*, C-18), 38.3 (*t*, C-7), 38.6 (*t*, C-12), 39.1 (*t,* C-1), 39.7 (*s*, C-10), 42.1 (*t*, C-3), 55.5 (*d*, C-5), 56.1 (*t*, C-15), 56.3 (*d*, C-9), 106.2 (*t*, C-17), 110.0 (*d*, C-14), 128.6 (*d*, C-3", 5"), 128.9 (*d*, C-2", 6"), 133.4 (*d*, C-4"), 138.8 (*s*, C-1") 147.2 (*s*, C-13), 148.5 (*s*, C-8). Found (%): C, 75.42; H, 9.31. $C_{26}H_{38}SO_2$. Calculated (%): C, 75.31; H, 9.24.

Drim-8(27)-enyl-(13*E*,17*E*,21*E*-15-phenylsulfonyl-16-hydroxy)-farnesyl benzyl ether 466.

Compound **468** (529 mg, 1.28 mmol, 1.2 eq.) was dissolved in benzene then evaporated under reduced pressure, dried under high vacuum, dissolved in anhydrous THF (4.6 mL) and cooled to −78 °C. *n*-BuLi (1.7 M, 0.75 mL, 1.28 mmol, 1.2 equiv.) was added drop-wise to the **(+)**-13*E*-labda-8(17),13(14)-dienyl-15-phenylsulfone **468** solution over 2 min. under argon atmosphere. The resulting bright yellow solution was stirred at −78°C for 30 min. and gradually warmed to -40 °C over 1 h and then cooled to -78 °C. Aldehyde **430** (279 mg, 1.07 mmol, 1 equiv.) was dried under high vacuum, dissolved in THF (4.6 mL), cooled to −78 °C, and added drop-wise to the sulfone anion solution via syringe. After 30 min of stirring at −78 °C, the reaction mixture was gradually heated to -40 °C and sat. aq. NH_4Cl (4 mL) was added followed by usual workup. The residue (900 mg) was purified by silica gel flash column chromatography (10% ethyl acetate/light petroleum ether mixture) affording compound **466** (472 mg, 66%) as a clear yellow oil. IR (liquid film) ν_{max}: 730, 1144, 1230, 1446, 2191, 2290, 2947 cm^{-1}. ^1H NMR (selected values): δ = 0.64 (*s*, 3H, C-30), 0.79 (*s*, 3H, C-29), 0.86 (*s*, 3H, C-28), 1.11 (*s*, 3H, C-26), 1.49 (*s*, 3H, C-25), 1.61 (*s*, 3H, C-24), 3.95 (*m*, 1H, C-15), 4.00 (*d*, *J* = 6.7 Hz, 2H, C-23), 4.37 (*d*, *J* = 0.8 Hz, 1H, C-27, H_b), 4.49 (*s*, 2H, C-1'), 4.61 (*d*, *J* = 9.7 Hz, 1H, C-16), 4.67 (*m*, 1H, C-14), 4.80 (*d*, *J* = 0.9 Hz, 1H, C-27, H_a), 5.37 (*t*, *J* = 6.7 Hz, 1H, C-22), 5.42 (*t*, *J* = 6.8 Hz, 1H, C-18), 7.31 (*m*, 5H, Ar-H), 7.68 (*m*, 5H, Ph-H). ^{13}C NMR: δ = 10.6 (*q*, C-25), 14.5 (*q*, C-30), 16.1 (*q*, C-26), 16.5 (*q*, C-24), 19.4 (*t*, C-2), 21.7 (*q*, C-29), 24.4 (*t*, C-6), 26.0 (*t*, C-11), 29.7 (*t*, C-19), 33.3 (*s*, C-4), 33.6 (*q*, C-28), 38.3 (*t*, C-7), 38.8 (*t*, C-12), 38.9 (*t*, C-20), 39.2 (*t*, C-1),

39.8(*s*, C-10), 42.2 (*t*, C-3), 55.6 (*d*, C-5), 56.5 (*d*, C-9), 66.6 (*t*, C-23), 68.6 (*d*, C-15), 72.1 (*t*, C-1'), 76.5 (*d*, C-16), 106.2 (*t*, C-27), 114.0 (*d*, C-14), 121.3 (*d*, C-22), 127.5 (*d*, C-5'), 127. 8 (*d*, C-3', 7'), 128.3 (*d*, C-4', 6'), 128.8 (*d*, C-3", 5"), 129.4 (*d*, C-2", 6"), 130.2 (*d*, C-18), 133.4 (*s*, C-17), 133.8 (*d*, C- 4"), 137.7 (*s*, C-1"), 138.6 (*s*, C-2'), 139.6 (*s*, C-21), 145.3 (*d*, C-13), 148.5 (*s*, C-8). Found (%): C, 76.53; H, 8.89. $C_{43}H_{60}SO_4$. Calculated (%): C, 76.74; H, 8.99.

Drim-8(27)-enyl-(13*E*,17*E*,21*E*-15-phenylsulfonyl-16-oxo)-farnesyl benzyl ether 467.

A solution of DMSO (0.085 mL, 1.21 mmol) in CH_2Cl_2 (1.8 mL) was added dropwise to a stirred solution of oxalyl chloride (0.07 mL, 0.61 mmol) in CH_2Cl_2 (1.8 mL) cooled to –60 °C. After 5 min of stirring at this temperature, a solution of compound **466** (185 mg, 0.275 mmol) in CH_2Cl_2 (1.8 mL) was added dropwise. After 30 min of stirring (–60°C) triethylamine (0.5 mL, 3.03 mmol) was added to the reaction mixture, and after another 15 min the cooling bath was removed and water (3 mL) was added at room temperature. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phase was subsequently washed with a 20% H_2SO_4, a sat. $NaHCO_3$ solution, brine to neutral pH. Drying with Na_2SO_4 and subsequent evaporation of the solvent gave a crude reaction product, which was submitted to flash chromatography (8% ethyl acetate/light petroleum ether) to give polar ketone **467** (134 mg, 0.2 mmol, 73%). IR (liquid film) ν_{max}: 745, 1144, 1309, 1394, 1449, 1665, 1791, 2289, 2986, 3365 cm^{-1}. ^1H NMR (selected values): δ = 0.82 (*s*, 3H, C-29), 0.87 (*s*, 3H, C-28), 0.92 (*s*, 3H, C-30), 1.65 (*s*, 3H, C-26), 1.68 (*s*, 3H, C-24), 1.82 (s, 3H, C-25), 4.04 (*d, J* = 6.6 Hz, 2H, C-23), 4.42 (*d, J* = 0.9 Hz, 1H, C-27, H_b), 4.51 (s, 2H, C-1'), 4.82 (*d*, *J* = 1.0 Hz, 1H, C-27, H_a), 5.15 (*d*, *J* = 3.0 Hz, 1H, C-14), 5.46 (*t*, *J* = 6.6 Hz, 1H, C-22), 5.63 (*d*, *J* = 3.0 Hz, 1H, C-15), 6.69 (*m*, 1H, C-18), 7.31 (*m*, 5H, Ar-H), 7.65 (*m*, 5H, Ph-H). ^{13}C NMR: δ = 11.8 (*q*, C-25), 16.4 (*q*, C-24), 17.1 (*q*, C-26), 26.3 (*t*, C-11), 19.3 (*t*, C-2), 20.1 (*q*, C-30), 21.7 (*q*, C-29), 24.4 (*t*, C-6), 27.6 (*t*, C-19), 33.25 (*s*, C-4), 33.28 (*q*, C-28), 37.9 (*t*, C-20), 38.3 (*t*, C-7), 39.0 (*t*, C-1), 40.39 (*t*, C-12), 40.41 (*s*, C-10), 41.8 (*t*, C-3), 51.9 (*d*, C-5), 56.3 (*d*, C-9), 66.5 (*t*, C-23), 68.7 (*d*, C-15), 72.3 (*t*, C-1'), 106.2 (*t*, C-27), 113.5 (*d*, C-14), 122.2 (*d*, C-22), 127.5 (*d*, C-5'), 127.8 (*d*, C-3', 7'), 128.3 (*d*, C-4', 6'), 128.5 (*d*, C-3", 5"), 130.0 (*d*, C-2", 6"), 133.7 (*d*, C- 4"), 137.4 (*s*, C-1"), 137.8 (*s*, C-17), 138.4 (*s*, C-2'), 138.6 (*s*, C-21), 145.0 (*d*, C-18), 147.1 (*s*, C-13), 148.5 (*s*, C-8), 192.2 (*s*, C-16). Found (%): C, 76.83; H, 8.82. $C_{43}H_{58}SO_4$. Calculated (%): C, 76.97; H, 8.71.

***ent*-Isocopal-12-en-15-yl methanesulfonate 471.**

A solution of alcohol **470** (190.0 mg, 0.65 mmol) in dry pyridine (12.0 ml) was cooled at 0 °C and treated with mesyl chloride (0.6 ml) and 4-(dimethylamino)-pyridine (DMAP, 15.0 mg, 0.12 mmol). The reaction mixture was stirred at 0 °C for 6 h and at room temperature for 12 h. The usual work-up gave a crude product (239.0 mg) which was purified by silica-gel chromatography (7% ethyl ether/light petroleum ether) to give the pure *ent*-isocopal-12-en-15-yl methanesulfonate **471** (224.0 mg, 93%). Colorless viscous liquid, R_f = 0.44 (15% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –37.1 (c = 0.21, $CHCl_3$). IR (liquid film) ν_{max}: 2927, 2848, 1443, 1385, 1354, 1175, 974, 946, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.51 (1H, bs, H-12), 4.42 (1H, dd, J_{HH} = 3, 10 Hz, H-15a), 4.21 (1H, dd, J_{HH} = 6, 10 Hz, H-15b), 3.00 (3H, s, –OSO_2Me), 2.15 1H, bs, H-14), 2.06 (1H, m, H-7a), 1.92 (2H, m, H_2-11), 1.73 (3H, bs, H_3-16), 1.63 (1H, m, H-1a), 1.58 (2H, m, H-2b and H-6b), 1.39 (2H, m, H-2a and H-6a), 1.37 (1H, m, H-3b), 1.26 (1H, m, H-7b), 1.14 (1H, m, H-9), 1.13 (1H, m, H-3a), 0.89 (3H, s, H_3-17), 0.86 (3H, s, H_3-18), 0.82 (3H, s, H_3-20), 0.82 (1H, m, H-5), 0.81 (3H, s, H_3-19), 0.79 (1H, m, H-1b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.0 (s, C-13), 124.3 (d, C-12), 68.2 (t, C-15), 56.1 (d, C-5), 54.6 (d, C-9), 54.3 (d, C-14), 41.8 (t, C-3), 41.1 (t, C-7), 39.8 (t, C-1), 37.5 (q, –OSO_2Me), 37.3 (s, C-10 or C-8), 36.2 (s, C-8 or C-10), 33.4 (q, C-18), 33.1 (s, C-4), 22.5 (t, C-11), 21.6 (q, C-19 or C-16), 21.5 (q, C-16 or C-19), 21.5 (q, C-16 or C-19), 18.6 (t, C-6 or C-2), 18.4 (t, C-2 or C-6), 15.7 (q, C-20 or C-17), 15.5 (q, C-17 or C-20). EIMS: *m/z* (%) = 272 (20) [M+–$MeSO_2H$], 257 (31), 237 (7), 229 (8), 216 (7), 207 (13), 201 (11), 187 (16), 175 (16), 163 (21), 159 (20), 148 (51), 139 (80), 119 (100), 107 (47), 105 (67), 91 (66), 81 (41), 69 (44), 55 (44). HRMS (ESI): $(M+Na)^+$, found 391.2299. $(C_{21}H_{36}O_3S+Na)^+$ requires 391.2283.

Coupling reaction of *ent*-isocopal-12-en-15-yl methanesulfonate 471 with ethyl acetoacetate. Synthesis of epimeric 15-(1-ethylcarboxy)-acetonyl-*ent*-isocopal-12-enes 472.

Sodium metal (32.0 mg, 1.39 mmol) was added, under argon atmosphere, to a solution of ethyl acetoacetate (196.0 mg, 1.50 mmol) in toluene (1.5 mL) and the mixture was refluxed for 15 min. Then a solution of mesylate **471** (120.0 mg, 0.33mmol) in toluene (1.2 mL) was added. The reaction mixture was refluxed for 4 h. The usual work-up gave a crude product (125.0 mg) which was purified by silica-gel chromatography to give (100% light petroleum ether) hydrocarbon **473** [199] (31.9 mg, 36%), (1% diethyl ether/light petroleum ether) a mixture of epimeric 15-(1-ethylcarboxy)-acetonyl-

ent-isocopal-12-enes **472** (36.7 mg, 28%) and (5% diethyl ether/light petroleum ether) starting compound **471** (32.2 mg, 34%).

Mixture of epimeric 15-(1-ethylcarboxy)-acetonyl-*ent*-isocopal-12-enes 472: R_f = 0.52 (15% ethyl acetate/light petroleum ether). IR (liquid film) ν_{max}: 1725 (large) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.40 (1H, bs, H-12). 4.20 (2H, m, $–OCH_2CH_3$), 4.20 (2H, m, $–OCH_2CH_3$), 2.25 (s, H-18 epimer a), 2.22 (s, H-18 epimer b), 1.30 (3H, superimposed t, $–OCH_2CH_3$, epimer a), 1.27 (3H, superimposed t, $–OCH_2CH_3$, epimer b), 0.87 (3H, s, H_3-23), 0.85 (3H, s, H_3-22), 0.81 (3H, s, H_3-21), 0.75 (3H, s, H_3-24).

***ent*-isocopal-12,14-diene 473:** White crystals: m.p. 93-94 °C (CH_3CN). R_f = 0.86 (15% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +82.5 (c = 0.16, $CHCl_3$); $[\alpha]_D^{25}$ lit. [199] = +66.4. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.64 (1H, bs, H-12), 4.80 (1H, d, J_{H-H} = 15 Hz, H-15), 2.04 (2H, m, H_2-11), 1.97 (1H, m, H-7b), 1.79 (3H, d, J_{H-H} = 1.3 Hz, H_3-16), 1.62 (2H, m, H-1b and H-6b), 1.59 (1H, m, H-7a), 1.58 (1H, m, H-1b), 1.41 (2H, m, H-1a and H-6a), 1.37 (1H, m, H-3b), 1.24 (1H, dd, J_{H-H} = 6, 11 Hz, H-9), 1.12 (1H, ddd, J_{H-H} = 5, 13, 14 Hz, H-3a], 0.96 (3H, s, H_3-17), 0.93 (3H, s, H_3-20), 0.87 (3H, s, H_3-18), 0.84 (3H, s, H_3-19), 0.83 (1H, m, H-5), 0.80 (1H, m, H-1a). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6 (s, C-14), 131.0 (s, C-13), 126.6 (d, C-12), 103.8 (d, C-15), 56.2 (d, C-5), 53.5 (d, C-9), 41.9 (t, C-3), 40.0 (t, C-1), 39.4 (t, C-7), 38.0 (s, C-8 or C-10), 37.6 (s, C-10 or C-8), 33.4 (q, C-18), 33.2 (s, C-4), 23.1 (t, C-11), 22.4 (q, C-17), 21.7 (q, C-19), 20.5 (q, C-16), 18.6 (t, C-6 or C-2), 18.3 (t, C-2 or C-6), 16.0 (q, C-20). EIMS: *m/z* (%) = 272 (38) [M^+], 257 (72), 229 (20), 215 (10), 201 (16), 148 (87), 134 (100), 119 (70), 105 (65), 91 (85), 81 (60), 69 (65), 55 (70). HRMS (ESI): $(M+Na)^+$, found 353.2821. $(C_{23}H_{38}O+Na)^+$ requires 353.2820.

15-acetonyl-*ent*-isocopal-12-ene 474.

A 10% sodium hydroxide solution in ethyl alcohol (3.0 mL) was added to a solution of epimeric ketoesters mixture **472** (75.0 mg, 0.19 mmol) in ethyl alcohol (1.0 mL). The reaction mixture was refluxed for 3 h and then worked up as usual. The crude product obtained (61.5 mg) was purified by silica-gel chromatography (1% diethyl ether/light petroleum ether) to give 15-acetonyl-*ent*-isocopal-12-ene **474** (52.4 mg, 0.16 mmol, 85%). Colorless viscous liquid, R_f = 0.57 (15% ethyl acetate/light

petroleum ether). $[\alpha]_D^{25}$ = –21.7 (c = 0.91, $CHCl_3$). IR (liquid film) ν_{max}: 2931, 1718, 1461, 1362, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.38 (1H, bs, H-12), 2.63 (1H, m, H-16a), 2.44 (1H, m, H-16b), 2.13 (3H, s, H_3-18), 1.94 (1H, m, H-7b), 1.87 (2H, m, H_2-11), 1.72 (1H, m, H-15a), 1.65 (3H, bs, H_3-19), 1.62 (1H, m, H-14), 1.59 (2H, m, H-1a and H-15b), 1.56 (2H, m, H-2a and H-6a), 1.37 (1H, m, H-3a), 1.34 (2H, m, H-2b and H-6b), 1.15 (1H, m, H-3b), 1.10 (1H, m, H-9), 1.05 (1H, m, H-7a), 0.87 (3H, s, H_3-22), 0.85 (3H, s, H_3-21), 0.81 (3H, s, H_3-20), 0.80 (1H, m, H-5), 0.77 (1H, m, H-1b), 0.74 (3H, s, H_3-23). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.6 (s, C-17), 134.2 (s, C-13), 122.9 (d, C-12), 55.1 (d, C-9), 56.2 (d, C-5), 54.9 (d, C-14), 46.0 (t, C-16), 41.9 (t, C-3), 40.9 (t, C-7), 39.9 (t, C-1), 37.4 (s, C-10 or C-8), 37.2 (s, C-8 or C-10), 33.4 (q, C-21), 33.1 (s, C-4), 30.0 (q, C-18), 22.8 (t, C-11), 22.0 (q, C-20 or C-19), 21.7 (q, C-19 or, C-20), 20.8 (t, C-15), 18.8 (t, C-6 or C-2), 18.5 (t, C-2 or C-6), 15.5 (q, C-22), 14.4 (q, C-23). EIMS: *m/z* (%) = 330 (20) $[M^+]$, 312 (10), 297 (5), 272 (80), 257 (23), 229 (3), 215 (2), 207 (11), 190 (59), 159 (13), 149 (16), 135 (41), 119 (62), 95 (100), 81 (57), 55 (69).

Wittig-Horner reaction of ketone 474. 17*E*-Methylcheilantha-12,17-dienoate 410 and 17*Z*-methylcheilantha-12,17-dienoate 411.

Trimethylphosphonoacetate [$(CH_3O)_2P(O)CH_2CO_2CH_3$, 191.0 mg, 1.05 mmol] was added, under argon atmosphere, to a solution of ketone **474** (115.0 mg, 0.35 mmol) in anhydrous benzene (9.0 mL). Then sodium methoxide in methanol (24.0 mg of sodium metal in 0.7 mL of methanol) was slowly added to the solution under reflux. After refluxing for 2 h, the reaction mixture was worked-up as usual. The product recovered (134.0 mg) was purified by silica-gel flash chromatography (3% diethyl ether/light petroleum ether) to afford a mixture of *Z*- and *E*-esters (11/12, ~ 2:1) (45.5 mg) and a fraction containing pure 17*E*-methylcheilantha-12,17-dienoate **410** (75.8 mg, 0.20 mmol). The mixture was purified by preparative thin layer chromatography (10% ethyl acetate/light petroleum ether) to yield pure 17*Z*-methylcheilantha-12,17-dienoate **411** (11.7 mg, 0.03 mmol).

17*Z*-Methylcheilantha-12,17-dienoate 411: Colourless viscous liquid, R_f = 0.65 (15% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –17.9 (c = 1.17, $CHCl_3$). IR (liquid film) ν_{max}: 2931, 1724, 1442, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.64 (1H, bs, H-18), 5.37 (1H, bs, H-12), 3.68 (3H, s, –OMe), 2.72 (2H, m, H_2-16), 1.99 (1H, m, H-7b), 1.92 (2H, m, H_2-15), 1.91 (3H, s, H_3-25), 1.84 (2H, m, H_2-11), 1.77 (3H, bs, H_3-24), 1.69 (1H, m, H-14), 1.60 (1H, m, H-1b), 1.58 (2H, m, H-2b and H-6b), 1.38 (1H, m, H-3b), 1.37 (2H, m, H-2a and H-6a), 1.16 (1H, m, H-9), 1.15 (1H, m, H-3a), 1.13

(1H, m, H-7a), 0.87 (3H, s, H_3-21), 0.86 (3H, s, H_3-22), 0.83 (1H, m, H-5), 0.82 (3H, s, H_3-20), 0.79 (1H, m, H-1a), 0.72 (3H, s, H3-23). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (s, C-19), 160.6 (s, C-17), 135.0 (s, C-13), 122.2 (d, C-12), 115.6 (d, C-18), 56.2 (d, C-5), 55.6 (d, C-14), 55.0 (d, C-9), 50.8 (q, –OMe), 41.9 (t, C-3), 40.6 (t, C-7), 39.8 (t, C-1), 37.9 (s, C-10 or C-8), 37.3 (s, C-8 or C-10), 35.8 (t, C-16), 33.5 (q, C-21), 33.3 (s, C-4), 25.6 (t, C-15), 25.3 (q, C-25), 22.8 (t, C-11), 22.0 (q, C-24 or C-20), 21.7 (q, C-20 or C-24), 18.8 (t, C-6 or C-2), 18.6 (t, C-2 or C-6), 15.5 (q, C-22), 14.3 (q, C-23). EIMS: *m/z* (%) = 386 (23) [M^+], 371 (38), 355 (5), 339 (3), 312 (10), 273 (100), 245 (7), 231 (8), 217 (11), 191 (31), 177 (70), 149 (41), 135 (69), 114 (82), 95 (41), 81 (49), 69 (29). HRMS (ESI): $(M+Na)^+$, found 409.3068. $(C_{26}H_{42}O_2+Na)^+$ requires 409.3083.

17*E*-Methylcheilantha-12,17-dienoate 410: Colorless viscous liquid, R_f = 0.61 (15% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –26.4 (c = 0.95, $CHCl_3$). IR (liquid film) ν_{max}: 2927, 1725, 1647, 1437, 1224, 1148, 862 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (1H, bs, H-18), 5.38 (1H, bs, H-12), 3.69 (3H, s, –OMe), 2.36 (1H, m, H-16a), 2.17 (3H, s, H_3-25), 2.08 (1H, m, H-16b), 1.94 (1H, m, H-7a), 1.88 (2H, m, H_2-11), 1.65 (1H, m, H-14), 1.62 (1H, m, H-1a), 1.58 (1H, m, H-6a), 1.67 (3H, s, H_3-24), 1.37 (3H, m, H-2a, H-3b and H-6b), 1.35 (1H, m, H-15a), 1.15 (1H, m, H-9), 1.14 (1H, m, H-3a), 1.06 (1H, m, H-7b), 0.87 (3H, s, H_3-22), 0.86 (3H, s, H_3-21), 0.82 (3H, s, H_3-20), 0.79 (1H, m, H-1b), 0.73 (3H, s, H_3-23). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (s, C-19), 160.8 (s, C-17), 134.4 (s, C-13), 122.6 (d, C-12), 115.1 (d, C-18), 56.2 (d, C-5), 55.0 (d, C-9 and C-14), 50.8 (q, –OMe), 43.5 (t, C-16), 41.9 (t, C-3), 40.7 (t, C-7), 39.9 (t, C-1), 37.2 (s, C-10 or C-8), 36.9 (s, C-8 or C-10), 33.4 (q, C-21), 33.3(s, C-4), 22.8 (t, C-11), 22.0 (q, C-24 or C-20), 21.7 (q, C-20 or C24), 19.0 (t, C-25 or C-15), 18.8 (q, C-15 or C-25), 18.8 (t, C-6 or C-2), 18.6 (t, C-2 or C-6), 15.5 (q, C-22), 14.3 (q, C-23). EIMS: *m/z* (%) = 386 (8) [M^+], 356 (5), 346 (5), 273 (100), 269 (5), 255 (5), 221 (10), 205 (16), 189 (18), 163 (26), 143 (28), 137 (51), 123 (51), 109 (44), 95 (33), 81 (15), 69 (18). HRMS (ESI): $(M+Na)^+$, found 409.3071. $(C_{26}H_{42}O_2+Na)^+$ requires 409.3083.

2.4 Conclusions to chapter 2

The synthesis of α,ω-bifunctional linear terpenoids has been successfully performed by diverse strategies. For monoterpenes direct allylic oxidation proved to be satisfactory [119],[120],[121],[122],[123].

Sesquiterpenic derivatives showed a lower selectivity in selenium dioxid mediated allylic oxidations, but still acceptable to allow preparative applications [124].

Direct oxidation of diterpenes was demonstrated basing on the Van Tamelen epoxidation procedure. Following periodate cleavage of the epoxidic ring and Wittig olefination allowed for the synthesis of diverse α,ω-bifunctional diterpene synthesis [125].

Introduction of terminal and internal functionalization in diterpenes have been performed preferable by a oligomerization approach, making use of monoterpenic phenylsulfones as suitable donor synthons. An original method for synthesizing the natural product exclusively *trans*-16-hydroxygeranylgeraniol **451** was developed for the first time a basing on a convergent strategy. This α,ω-bifunctionalized diterpenoid was prepared from commercially available geraniol **423** in 12% overall yield. The synthetic scheme included 4 steps in its longest sequence. α,ω-Bifunctionalized derivatives **452**-**455** were synthesized under standard conditions. They represent suitable building blocks for preparing hardly accessible biologically active natural aliphatic diterpenoids [122].

The synthesis of sesterterpenic compounds of cheilanthane family in optically active form has been performed basing on a $C_{20}+C_3+C_2$ strategy, and a readily available isoagath-12-en-15-ol **470** as starting material. Stereochemical issues connected to hindrance of the tricyclic skeleton of **470** have been overcome by the use of a less bulky mesyl leaving group [135].

Higher terpenoids of triterpene series, containing bicyclic fragments and lateral chains, with intercalated heteroatomic functional groups have been prepared basing on the sulfone coupling chemistry [123].

3. SYNTHESIS OF CYCLIC TERPENIC COMPOUNDS BY SELECTIVE CYCLIZATION SEQUENCES

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

Terpenoid cyclizations represent the classical example of biomimetic approach in the synthesis. The major part of the elaborated reactions is based on the mechanism including carbonium ion generation via selective protonation (Figure 4, Introduction). Different cyclisation agents have been reported, most of them possess strong acidic properties. The major challenges connected to this strategy relates to the need of controlling reaction selectivity, since the number of reaction pathways, and the range of possible products increases dramatically along with the number of isoprene units of the molecule. Therefore, cyclisation methods evolved to the use of lower reaction temperatures and stronger acid initiators. It is understandable that lower temperature influences the conformational flexibility of the molecule, in an attempt to mimic the action of the enzyme, which practically locks the substrate in one single conformation, making the cyclisation process totally specific. Solid acids like zeolites and acidic resins have been also reported to contribute to this problem solution. Their advantage consists in reaction conditions close to ambiental but unfortunately their selection is mostly empirical, they are very substrate-specific, thus limiting the process versatility. More practical from this point of view turned out to be superacids [1], which can initiate cyclisation sequences at temperatures as low as -78 ºC or even lower. Consequently, the process selectivity is beneficially influenced. A significant advancement in this field represents our finding that additional functional groups placed at certain positions of aliphatic terpenic chain, can influence the reaction course, allowing either selective initiation or termination of the cascade.

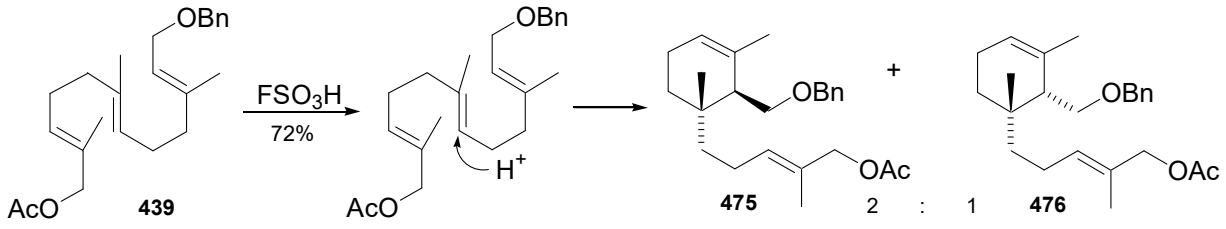


Figure 3.1. Cyclisation of α,ω-bifunctionalized sesquiterpenic substrate **439**.

The pioneering work relating in this directions deals with the superacidic cyclisation of α,ω-bifunctionalized sesquiterpenic substrates [124]. The presence in the substrate **439** of the acetoxy-group at the ω-terminus hindered the initiation of the cyclisation sequence from the extreme isoprene unit and allowed a selective protonation of the middle double bond, leaving in the resulted products **475** and **476** a pendant prenyl group attached to the monocyclic backbone (*seco*-eudesmanic structure, Figure 3.1).

Table 3.1. ^{1}H and ^{13}C NMR spectral data ($CDCl_3$) of compounds **475** and **476.**[a]

Assignments[b]	Compound **475**				Compound **476**			
	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]
1	5.42	m	122.4	d	5.40	m	122.1	d
2	1.94	m	22.7	t	1.97	m	22.8	t
3	1.52	dt (13, 8)	29.9	t	1.23	m	30.1	t
	1.30	m	---		1.49	dt (13, 8)	---	---
4	---		34.4	s	---		34.5	s
5	1.86	m	48.4	d	1.84	m	49.1	d
6	---		133.6	s	---		133.6	s
7	1.72	d (1.5)	23.2	q	1.74	bs	23.4	q
8	0.96	s	23.9	q	0.89	s	23.0	q
9	1.32	m	38.2	t	1.39	ddd (13, 11, 5)	39.1	t
	1.27	m	---		1.26	m	---	---
10	3.52	dd (10, 6)	70.6	t	3.51	dd (10, 5)	70.7	t
	3.43	dd (10, 3)	---		3.38	dd (10, 3)	---	---
11	1.98	m	22.2	t	2.05	m	22.0	t
12	5.43	m	130.6	d	5.40	m	131.0	d
13	---		129.3	s	---		129.3	s
14	4.44	bs	70.3	t	4.43	bs	70.5	t
15	1.64	s	13.8	q	1.63	bs	13.7	q
1'	4.48	s	73.0	t	4.46	s	73.1	t
2'	---		138.6	s	---		138.6	s
3',7'	7.33	m	127.6	d	7.32	m	127.7	d
4',6'	7.33	m	128.2	d	7.32	m	128.4	d
5'	7.27	m	127.4	d	7.27	m	127.4	d
$COCH_3$	2.07	s	21.0	q	2.07	s	21.0	q
$COCH_3$	---		171.0	s	---		171.1	s

[a] Assignments made by 2D NMR experiments [^{1}H-^{1}H COSY, HETCOR, HMBC (J=10 and 6 Hz)].

[b] Assignments refer to the numbering of the carbon atoms of the molecule.

[c] Denotes the multiplicity of the peak.

Superacidic cyclization of **439** was carried out by treatment with 5 equivalents of fluorosulfonic acid (-78 °C, 15 min) affording a 2:1 mixture of compounds **475** and **476** (72%). The reaction mixture was purified by reverse-phase HPLC giving individual **475** and **476**.

^{1}H and ^{13}C NMR data (Table 3.1) of **475** and **476** were very similar, indicating that the two reaction products displayed the same carbon skeleton. In particular, both ^{1}H NMR spectra showed signals attributable to two methyl groups at carbon atoms carrying a double bond and two olefinic protons, suggesting that the molecules retained two of the three trisubstituted double bonds of the starting compound **439** and, consequently, should be monocyclic.

Indeed, the presence of a singlet methyl signal (H_3-8), and of an ABX system, assignable to the methylene group (H_2-10) linked to the benzyloxy- moiety, further coupled with an angular methine (H-5), strongly supported a monocyclic structure for both compounds, bearing a homoacetoxyprenyl chain and a methyl at C-4. Being epimers, the two molecules differed only in the stereochemistry at the chiral center C-4. In order to establish the relative configuration for each compound, both a series of NOE difference experiments and conformational analysis were performed. First of all, an energy minimization calculation on the two possible stereoisomers using a DMM software, revealed that for each molecule the energetically more favored conformation exhibited the chain at C-5 in pseudoequatorial orientation. Therefore, based on this fixed chiral center, the *trans*-isomer should display an equatorial homoprenyl chain at C-4, whereas in the cis-isomer the same homoprenyl moiety should be axially oriented. The irradiation of the proton H-5 resulted in a diagnostic enhancement of the methyl signal at C-4 in the isomer 6, while a NOE interaction was observed between H-5 and H2-9 in the isomer **475**. These results strongly supported a *trans*- relative stereochemistry at C-4 and C-5 for compound **475**, whereas **476** was suggested to be the corresponding *cis*-isomer. According to this assignment, a 2:1 ratio of **475**/**476** was obtained with predomination of thermodynamically more favored *trans*- isomer. All the proton and carbon resonances of **475** and **476** were easily assigned by 2D NMR experiments (^{1}H-^{1}H COSY, HETCOR and HMBC) and are reported in the Table. The formation of compounds **475** and **476** implies that the cyclization process occurred by protonation of the internal $\Delta^{6,7}$- double bond in the starting compound **439**. To the best of our knowledge, only two reports [13],[14] describing such kind of cyclization have appeared in the literature.

This unusual cyclization could be explained as follows. On treatment with superacid, the ω-acetoxy- group of **439** is protonated to give a carboxonium-ion, which does not allow the protonation of the terminal double bond because this would bring about the formation of an energetically

unfavorable 1,3-dicationic system, whereas the protonation of $\Delta^{6,7}$- double bond occurs with the formation of a monocyclic dication, transformed into both reaction products on deprotonation. The dication with two equatorial chains is more stable and consequently compound **475** predominates over its diastereomer **476**. In summary, the ω-allylic acetoxy- group in the farnesol skeleton deactivates the terminal double bond. The cyclization process, starting from the internal double bond, gives rise to monocyclic terpenoids with terminal pendant prenylation.

This reaction mechanism was further exploited for the biomimetic synthesis of sacculatane-like diterpenoids [125]. On these bases, it was logical to assume that a hypothetic α,ω-bifunctionalized diterpenic substrate **477**, under the action of the superacid would also lead to the protonation of the internal double bonds giving either the monocyclic diterpenic compounds with carbon skeleton **478** or/and bicyclic compounds with the sacculatane skeleton **479** (Figure 3.2).

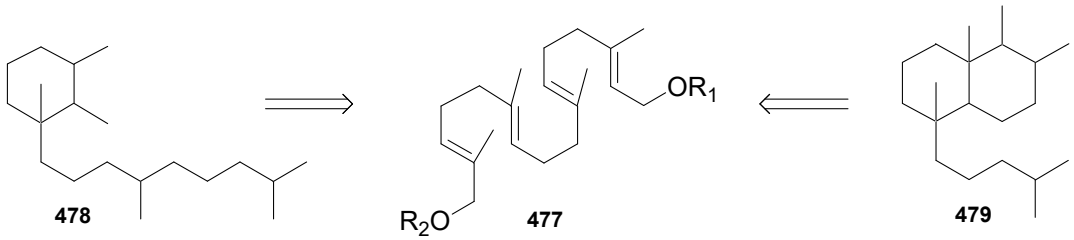


Figure 3.2. Possible retrosynthetic paths based on the cyclisation of a hypothetical α,ω-bifunctionalized diquiterpenic substrate **477**.

The possibility of obtaining structures similar to **479** in such a straightforward and biomimetic fashion was appealing, so we undertook an investigation of the superacidic cyclization of aliphatic α,ω-bifunctionalized diterpenoid substrate **440** obtained from commercially available geranyllinalool **441** (Figure 3.3) [125].

Superacidic cyclization of **440** was carried out by treatment with 5 equivalents of fluorosulfonic acid (-78 °C, 15 min) affording a mixture (~3:1) of racemic compounds **480** and **481** (total yield 25%). The reaction mixture was purified by reverse-phase HPLC to give individual pure compounds **480** and **481**. Analysis of the spectral data of the both reaction products suggested a close structural similarity between them, indicating the presence of the same carbon skeleton. Compounds **480** and **481** are isomers with the molecular formula $C_{22}H_{36}O_3$ as follows from HRMS containing the molecular peak at *m/z* 348, that implied five unsaturation degrees. The ^{1}H NMR spectra of both

molecules contained signals belonging to two vinyl methyls (H_3-12 and H_3-20) and two olefinic protons (H-7 and H-17) indicating the presence of two trisubstituted double bonds.

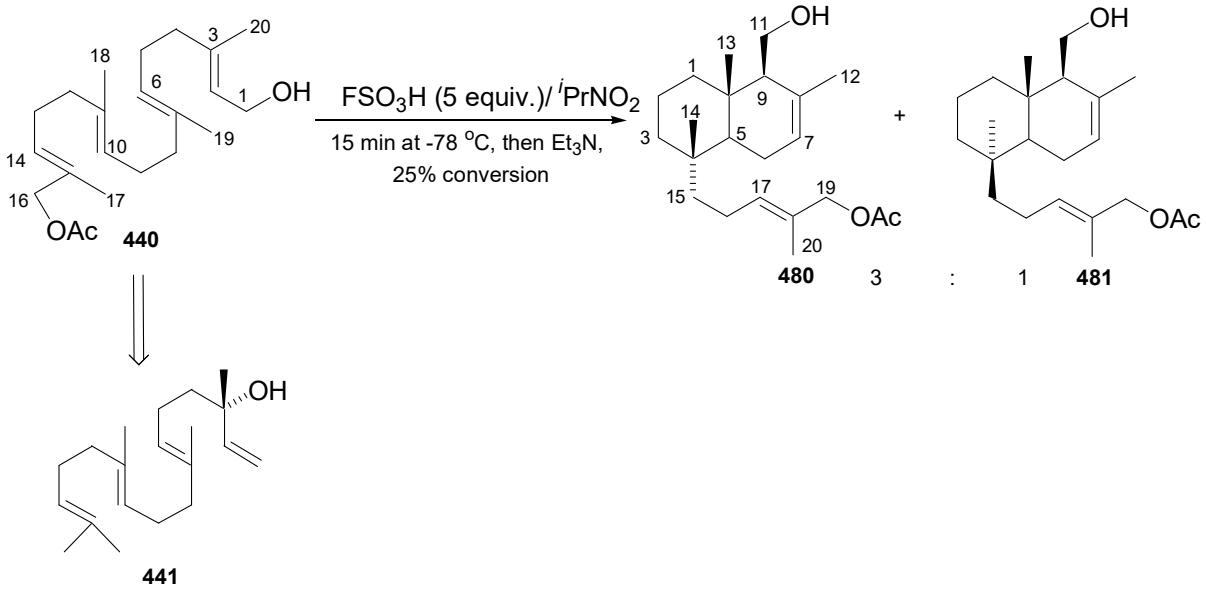


Figure 3.3. Superacidic cyclization of α,ω-bifunctionalized diterpenic substrate **440.**

In addition to the signal attributed to the terminal acetoxy-methylene H_2-19, two 3H singlets due to the methyls H_3-13 and H_3-14, linked to quaternary sp^3 carbons, were also observed in both ^{1}H NMR spectra that were completed by the presence of an ABX system attributed to a methylene bearing hydroxyl group (H_2-11) and further connected with an allylic methine (H-9). These data indicated that both the cyclization products retained two of the four double bonds of the starting compound **440** and that the two remaining unsaturation degrees required by the molecular formula were due to two rings. A detailed analysis of NMR experiments led us to assign to both compounds **480** and **481** a bicyclic structure bearing an angular methyl (H_3-13) at C-10, and acetoxy- homoprenyl chain and a geminal methyl at C-4. These data are consistent with the presence in compounds **480** and **481** of the sacculatane skeleton. In particular, comparison of the NMR values of the major reaction product **480** with those reported in the literature for model sacculatane diterpenes [139] showed a good agreement of the δ_C values of carbon atoms of the bicyclic core of the molecules implying the same relative stereochemistry.

NMR values of isomer **481** (see experimental part) were substantially similar with those of **480**, the main differences being in the ^{13}C NMR resonances of C-5 (δ 47.6 in **480**, δ 52.1 in **481**), C-14 (δ

20.8 in **480**, δ 29.0 in **481**), and C-15 (δ 43.6 in **480**, δ 32.2 in **481**). These data indicated that compound **481** had a different relative stereochemistry at C-4, with the methyl H_3-14 equatorial and consequently the homoprenyl chain axially oriented. So, compound **481** was the C4-epimer of **480**.

It is interesting to note that the natural sacculatanes so far reported have the same stereochemistry as the epimer **480**, which is formed in major amount by the cyclization reaction. The proposed reaction mechanism for cyclization of monoester **440** is shown in Figure 3.4.

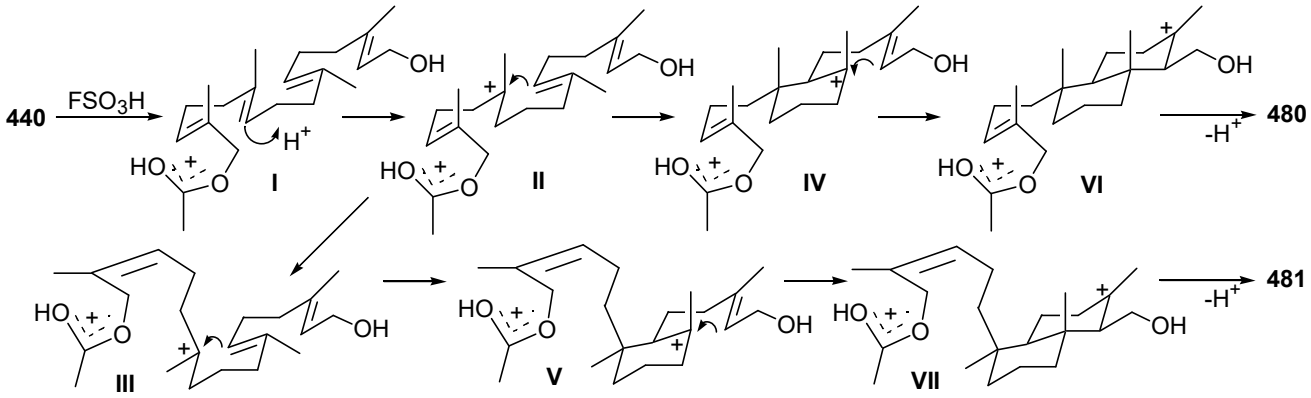


Figure 3.4. Suggested reaction course for cyclization of **440**.

On treatment with superacid, the ω-acetoxy group of **440** is protonated to give the carboxonium-ion **I**, which does not allow the protonation of the terminal double bond, as it was mentioned above, whereas the protonation of $\Delta^{10,11}$-double bond occurs with the formation of the dications **II** or **III**, transformed respectively into dications **IV** and **V**. Their further cyclization and deprotonation led to the final compounds **480** and **481**, respectively. The prevalence of isomer **480** in the reaction products explained by the fact that the pre-reactive conformation **II** with the bulky group in quasi-equatorial position is energetically more favorable then the conformation **III** which leads to compound **481** having the bulky group in axial configuration. The proposed reaction mechanism mimics the biosynthetic pathway that leads to sacculatane skeleton [140]. Basing on biogenetical reasons, formation of the prenylated bicyclic core of sacculatanes can only take place by a selective cyclization process of the open chain diterpenic precursor, as shown in the hypothetical scheme (Figure 3.5). The direct biosynthetic attachment of the C-5 unit to the bicyclic core is unlikely to occur.

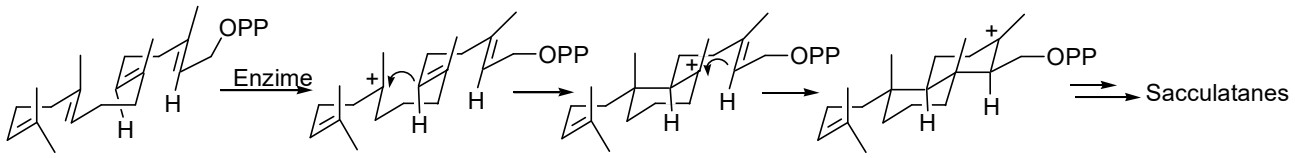


Figure 3.5. The hypothetical mechanism of sacculatane biosynthesis.

It is noteworthy mentioning that a substrate analogue to **440**, but without a functional group at ω-end, provides under similar conditions a totally cyclized tricyclic compound [141].

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

Having achieved a controlled cyclization of α,ω-bifunctionalized open chain sesqui- and diterpenic compounds we turned our attention to substrates containing double bond with alternating configuration (*trans*- vs. *cis*-). The impetus for these investigations was provided by a remarkable class of natural isoprenoids – polyprenols. These compounds are higher oligomers, containing from 5 to 11 or even more isoprene units. They are usually found in plants [142] and are potentially regarded as precursors of condensed polycyclic substances found in fossil sediments. Biomimetic-like cyclization of long-chain polyprenols have also been investigated and successful attempts of both enzymatic [143] and superacidic [144] cyclization have been reported. But only prenols with all-*trans*-configuration have been used as substrates. Available data concerning the cyclisation reaction of substrates with internal *cis*-double bonds are relatively scarce and relate only to sesquiterpenes [145]. On the other hand, it is known that most of the natural long chain polyprenols possess the di- or three-*trans*-poly-*cis*-configuration. To the best of our knowledge none of these compounds have been used as substrates for biomimetic cyclizations.

In order to check the feasibility of this idea, we have initiated a program on superacidic isomerization of selected polyprenols. The most representative di-*trans*-poly-*cys*- substrates have been chosen. As it was expected, all the substrates, independently on the chain length have shown reactivity on superacidic treatment. But the conclusions on the reaction mechanism could have been drawn only for lowest C-25 representatives, esters **482** and **483** [146],[147].

Synthesis of sesterterpenic esters **482** and **483** was based on a sequential homologation methodology [107], quite similar to that for the synthesis of cheilantanes **410** and **411**. The starting material in this case was not a bicyclic alcohol, but the open chain 2*Z*-geranylgeraniol **484** [148]. Its bromination with phosphorus tribromide provided the known bromide **485** [149], which was submitted to alkylation with sodium ethylacetoacetate (Figure 3.6).

The obtained ketoester **486** was decarboxylated on refluxing with an ethanolic solution of potassium hydroxide. The resulting ketone **487** was olefinated with trimethylphosphonoacetate to provide the mixture of esters **482** and **483**. This mixture was separated on a semipreparative normal phase HPLC column to provide pure esters **482** and **483**.

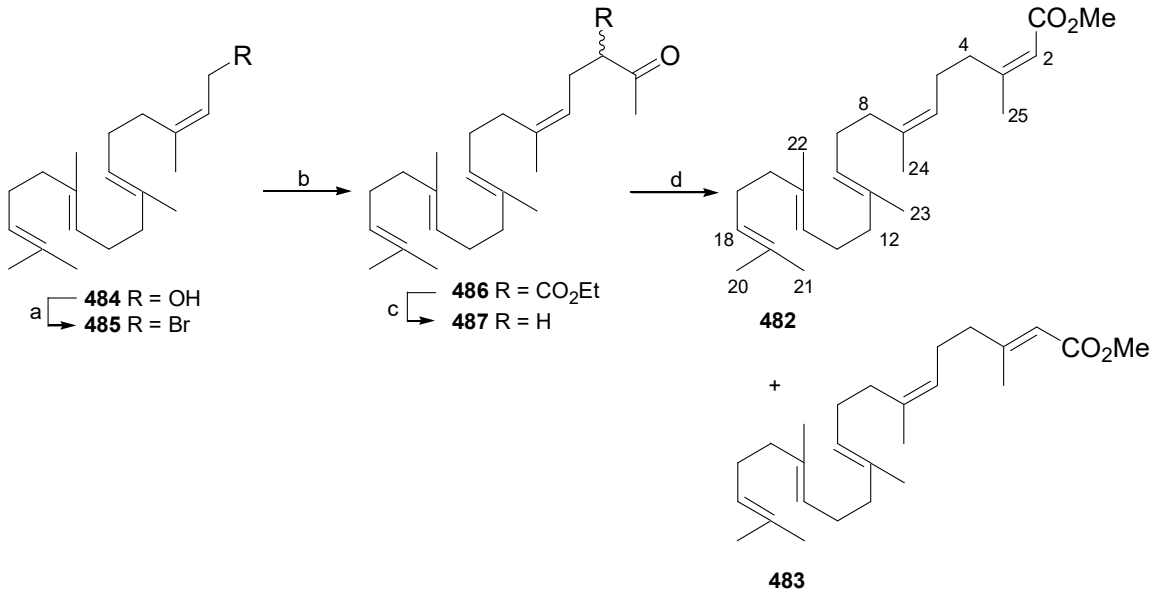


Figure 3.6. Synthesis of sesterterpenic polyprenol-like esters. Reagents and conditions: (a) PBr_3, Py, Et_2O, 0 °C, 2 h and 12 h, r.t., 97%; (b) $MeC(O)CH_2CO_2Et$, Na, PhMe, reflux, 2 h, 87%; (c) 10% KOH in EtOH, reflux, 2 h, 64%; (d) $(MeO)_2P(O)CH_2CO_2Me$, MeONa, C_6H_6, reflux 3 h, 82% (**482**/**483** = 1:3).

We decided to investigate the superacidic cyclization of esters **482** and **483**, instead of their corresponding alcohols (Figure 3.7). The reason for this selection was based on our earlier observations that long-chain terpenic alcohols tend to sediment at low temperatures, under standard conditions of superacidic cyclizations. Evolving of the biphasic system favors local temperature jumps, so that elimination reaction prevails. Both the products yield and the selectivity of the

cyclization process were affected. The tentative to modify the cyclization procedure changing the order of reagents addition (substrate to the solution of superacid) have not improved the overall reaction performance.

As it was expected, the solubility of the esters **482** and **483** at low temperature was satisfactory. Most likely that hydrogen bonding in free prenols, together with the hydrophobic chain, cause precipitation of substrates at low temperatures. In the case of the esters, the factor of hydrogen bonding was eliminated and in spite of their long chain, esters do not sediment even at temperatures as low as -78 °C. Although it is known that esters can tolerate superacidic media even at the temperatures of -40 °C [105], one can expect lowering the reaction selectivity at more elevated reaction temperatures. Based on these reasons, we performed cyclization of **482** and **483** at -78 °C.

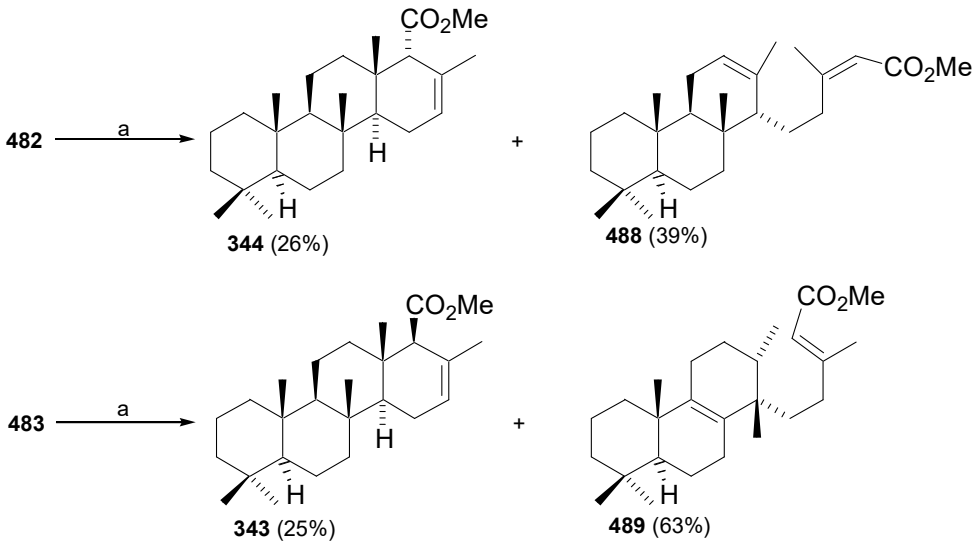


Figure 3.7. Superacidic cyclization of polyprenol-like esters.Reagents and conditions: (a) FSO_3H (5 equiv.), *i*-$PrNO_2$, -78°C, 15 min, then Et_3N.

Treatment of the 2-nitropropane solution of **482** with a solution of fluorosulfonic acid in the same solvent provided a product that was homogeneous on normal phase TLC. However, the NMR spectrum of this crude product was rather complex, showing that a mixture of compounds was obtained. At this point we decided to make use of a simple procedure for the separation of the reaction products. It consisted in the saponification of the crude reaction product on refluxing with an ethanolic potassium hydroxide solution. Application of this procedure to the mixture of the ester **482** cyclization

products proved to be successful: after 2 h of reflux, TLC showed a mixture of compounds, consisting of an unpolar spot at the level of the crude cyclization product (unsaponifiable ester) and a polar compound having a characteristic carboxylic acids tailing on TLC. This hydrolysis mixture was submitted to flash chromatography on silica gel and the unpolar and polar compounds were isolated. According to the NMR spectrum, the unpolar product was the known scalarane **344** [103]. The polar compound was methylated with an ethereal solution of diazomethane and the obtained methyl ester was identified on the basis of NMR data as the cheilanthane **488** [114]. The molecular formula $C_{26}H_{42}O_2$ of **488**, deduced from HREIMS on the molecular ion at m/z 386, indicated six degrees of unsaturation. ^{1}H NMR spectrum showed singlets at δ 0.84, 0.88, 0.887 and 0.893 attributable to four tertiary methyls, a singlet at δ 3.67 due to $–CO_2Me$ group and two broad singlets at δ 1.71 and 1.91 attributable to two vinyl methyls (Table 3.1). The presence of two trisubstituted double bonds, one of which conjugated to the ester carboxyl group, was indicated by both ^{1}H NMR spectrum (two olefinic broad singlets at δ 5.23 and 5.63 coupled with methyls at δ 1.71 and 1.91, respectively) and ^{13}C NMR spectrum [signals at δ 119.6 (d), 136.5 (s), 115.6 (d) and 160.5 (s)]. All ^{1}H and ^{13}C NMR resonances (Table 3.1), assigned by analysis of 2D NMR spectra (^{1}H–^{1}H COSY, HMQC and HMBC experiments), were consistent with the proposed tricyclic structure **488**, exhibiting a 14-*epi* cheilanthane skeleton. According to the trans-antiparallel addition principle, the prenyl chain at C(14) was axially oriented. This configuration was further supported by ^{13}C NMR data. In fact, the carbon spectrum of **488** showed down field shifted values for C(23) (δ 23.3) and C(9) (δ 47.2) and an up field shifted value for C(7) (δ 37.1), according to literature data for 8,14-*syn* isomer [150].

The overall yield of the esters **344** and **488** was ~65%. The cheilanthanic ester **488** predominates and this is an indication that the 6*Z*-double bond in the initial substrate **482** plays an essential role in this selectivity.

Superacidic cyclization of the 2*E*,6*Z*-ester **483** under the same reaction conditions, led to a products mixture that was submitted to hydrolysis with an ethanolic solution of potassium hydroxide. After a short-time reflux and work-up, the crude reaction product was separated by flash chromatography. Separation provided the scalaranic ester **343** (25%) which was identified by comparison of its spectral data (^{1}H, ^{13}C NMR, IR) with those of an authentic sample.

The second polar compound was methylated with an ethereal solution of diazomethane and re-purified on a short Si-gel column. The rearranged cheilanthanic ester **489** was isolated (63%) and its

spectral data (^{1}H, ^{13}C NMR, IR) match the suggested structure. The molecular formula of **489**, $C_{26}H_{42}O_2$, the same as **488**, was derived from both EIMS and elemental analysis.

Table 3.2. NMR data[a,b] for compounds **488** and **489**.

	Compound **488**					Compound **489**				
Position	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]	Long range connectivities[d]	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]	Long range connectivities[d]
1	0.85	m	40.1	t	H-2a, H-9, H_3-22	1.01	ddd,13,12,4	37.0	t	H_3-22
	1.61	m				1.75	m			
2	1.38	m	18.7	d	H-1a, H_2-3	1.45	m	19.2	t	H-3a
	1.60	m				1.55	m			
3	1.14	ddd,14,13,4	42.0	t	H-2a, H_3-20, H_3-21	1.13	ddd,13,13,4	41.6	t	H-1a, H_3-20, H_3-21
	1.38	m				1.38	m			
4	---		33.2	s	H_2-3, H-5, H_3-20, H_3-21	--		33.2	s	H-3a, H-5, H-6a, H_3-20, H_3-21
5	0.84	m	56.8	d	H-3a, H_2-6, H_3-20, H_3-21	1.06	dd,13,4	51.5	d	H-1a, H_2-6, H_2-7, H_3-20, H_3-21, H_3-22
6	1.38	m	18.6	t	H-5, H_2-7	1.35	m	19.4	t	H-5, H_2-7
	1.60	m				1.65	m			
7	1.37	m	37.1	t	H-5, H-9, H-14, H_3-23	2.02	m	27.2	t	H-5, H_2-6
	1.68	m								
8	--		37.2	s	H_2-6, H_2-15, H_3-23	---		130.8	s	H_2-7, H-11a, H-13, H_2-15, H_3-23
9	1.22	m	47.2	d	H_3-22, H_3-23	---		137.3	s	H_2-7, H_2-11, H_3-22
10	---		37.2	s	H-5, H_3-22	---		38.3	s	H_2-6, H_3-22
11	1.90	m	23.1	t	H_2-7, H-9	1.85	m	20.0	t	H_2-12
	1.80	m				1.95	m			
12	5.23	bs	119.6	d	H-11a, H_3-24	1.40	m	26.1	t	H_2-11, H_3-24
						1.72	m			
13	---		136.5	s	H_3-24	1.60	m	34.7	d	H_3-23, H_3-24
14	1.21	m	54.7	d	H-7a, H-9, H-12, H_2-16, H_3-23	---		39.0	s	H-12a, H_2-15, H_3-23, H_3-24
15	1.30	m	30.4	t	H-14, H_2-16	1.40	m	34.1	t	H-13, H_2-16, H_3-23
	1.65	m				1.55	m			
16	2.53	ddd,12,12,4	35.5	t	H-14, H-15a, H-18, H_3-25	2.08	m	35.5	t	H_2-15, H-18, H_3-25
	2.75	ddd,12,12,6								
17	---		160.5	s	H-18, H_2-16, H_3-25	---		162.0	s	H_2-15, H_2-16, H-18, H_3-25
18	5.63	bs	115.6	d	H_2-16, H_3-25	5.68	d,1	114.6	d	H_2-16, H_3-25
19	---		166.4	s	H-18, OMe	---		167.3	s	H-18, H_3-25, OMe
20	0.84	s	21.9	q	H-3a, H_3-21	0.83	s	21.8	q	H-3a, H-5, H_3-21
21	0.887	s	33.5	q	H_2-3, H_3-20	0.87	s	33.2	q	H-3a, H-5, H_3-20
22	0.893	s	15.6	q	H-1a, H-5, H-9	0.96	s	19.8	q	H-1a, H-5, H-11a
23	0.88	s	23.3	q	H-9, H-14, H-7a	1.04	s	26.6	q	H-13, H_2-15
24	1.71	d,l	23.5	q	H-12, H-14	0.85	d,7	14.7	q	H-12a, H-13
25	1.91	d,l	25.3	q	H_2-16, H-18	2.17	d,1	19.2	q	H_2-16
OMe	3.67	s	50.8	q	H-18	3.67	s	50.7	q	--

[a] Bruker AM 500 MHz and WM 400 MHz spectrometers, $CDCl_3$, chemical shifts (ppm) referred to $CHCl_3$ (δ 7.26) and to $CDCl_3$ (δ 77.0).
[b] Assignments made by ^{1}H-^{1}H COSY and HMQC experiments.
[c] By DEPT sequence.
[d] HMBC experiments (J = 10 Hz).

Comparison of both ^{1}H and ^{13}C NMR spectra with those of **488** (Table 3.2) indicated the presence of a different carbon skeleton, exhibiting one secondary and four tertiary methyls, along with a vinyl methyl. In fact, ^{1}H NMR spectrum of **489** displayed 3H singlets at δ 0.83, 0.87, 0.96 and 1.04,

a 3H doublet at δ 0.85 and a broad 3H singlet at δ 2.17, together with the singlet at δ 3.67 attributable to $–CO_2Me$ group. The presence of a tetrasubstituted double bond was indicated by two quaternary sp^2 carbons at δ 137.3 and 130.8 in the ^{13}C NMR spectrum, which also displayed signals due to the E-trisubstituted double bond conjugated with the ester carboxyl group [δ 162.0 (s), 114.6 (d), 167.3 (s)].

These data suggested a tricyclic rearranged structure related to **489** [22(8->14)-*abeo*-cheilanthane skeleton], in which a double bond is located in the rings B and C junction position and consequently the angular methyl at C(8) is shifted to C(14), retaining the β- orientation.

The relative trans-orientation of the two vicinal methyls at C(13) and C(14) was suggested by ^{13}C NMR values of C(24) (δ 14.7) and C(23) (δ 26.6), which were in accordance with literature data for natural bioactive terpenoids exhibiting the same partial structure [151]. The relative stereochemistry at chiral centers of ring C was further supported by diagnostic NOE effects between H_3-24 (δ 0.85) and H-11a (δ 1.95) and between H_3-22 (δ 0.96) and H-11b (δ 1.85). All ^1H and ^{13}C NMR resonances of **489** (Table 3.2) were assigned by analysis of 2D NMR spectra (^1H–^1H COSY, NOESY, HMQC and HMBC).

These results on the cyclisation of both substrates **482** and **483** showed clearly that predominant reaction products in both cases are tricyclic compounds **488** and **489**, having the α-prenyl unit pendant. These compounds belong to the cheilanthane family and their biomimetic synthesis turned out to be a very efficient preparative tool. In fact, in the case of polyprenol-like substrates cyclisation is suspended to a tricyclic compound, due to the presence of an internal *cis*-double bond. This functionality plays a crucial role in the conformational behavior of the substrate, by interrupting the cyclisation cascade via a complex conformational-steric effect.

This finding and our work connected to the synthesis of bioactive sesterterpenoids with cheilanthane skeleton, led to the necessity of deeper investigating the superacidic cyclisation involving substrates with *cis*-internal double bonds. Due to practical reasons, using bicyclic starting materials in optically active form is more convenient. First of all, investigation of such substrates will prove if the regularities previously observed for cyclisation of open chain esters **482** and **483** are valid also for partially cyclic substrates.

Next, using these optically active substrates with a fixed stereochemistry of A and B rings would bring more light upon the mechanism and regularities of electrophilic cyclisation in general and of the superacid induced process in particular.

And finally, bicyclic sesterterpenoids are easily available from diverse labdanes after a C_5 homologation sequence. We have chosen the well-known manool **220** as the starting material for the synthesis of isomeric 13Z-bicyclogeranylfarnesoic acid methyl esters **490** and **491** as substrates for the synthesis of cheilanthanes by a selective suspended cyclization [152].

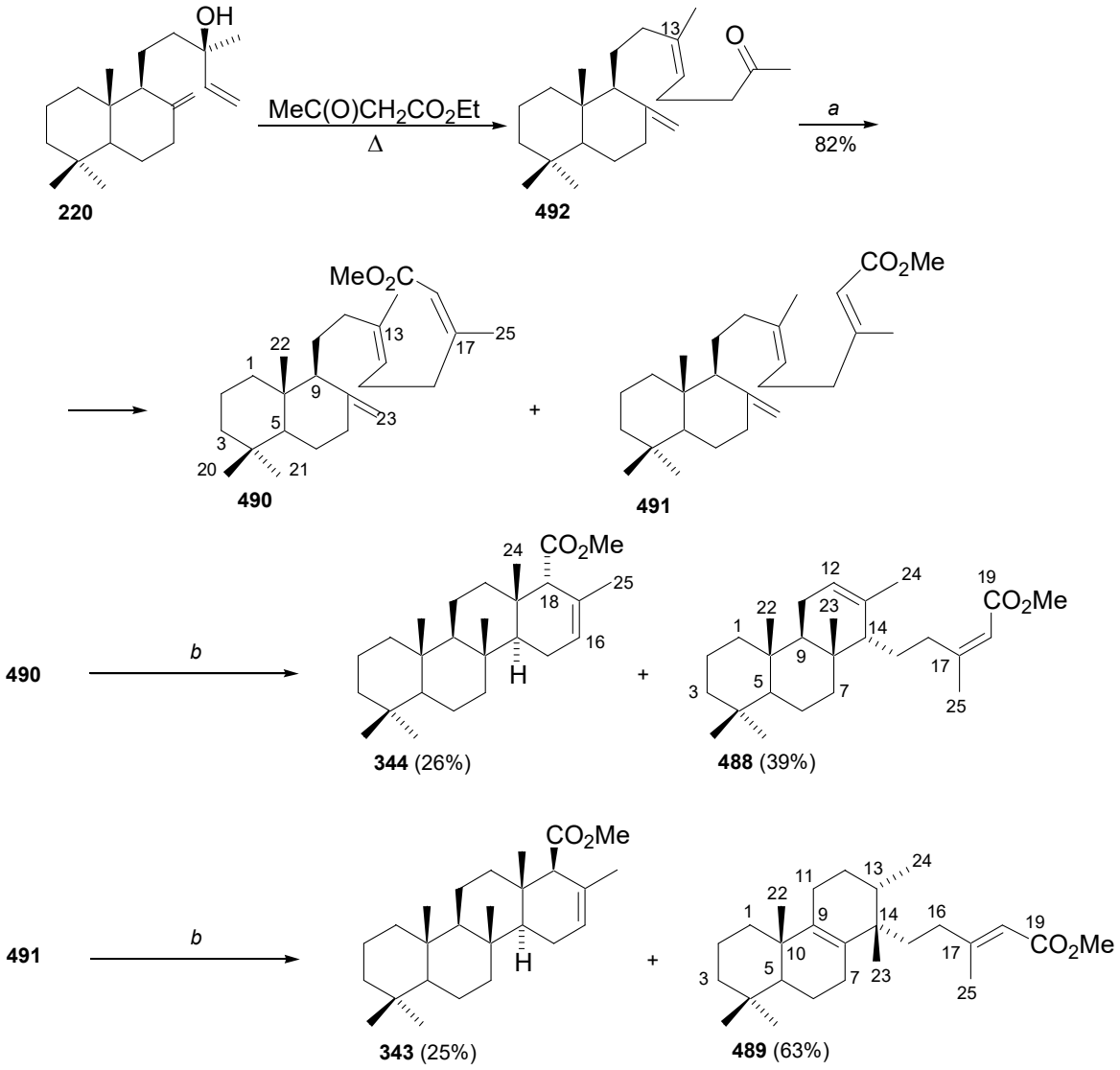


Figure 3.8. Synthesis and cyclization of 13Z- bicyclic sesterterpenic esters. Reagents and conditions: (a) FSO_3H (5 equiv.), *i*-$PrNO_2$, -78°C, 15 min, then Et_3N.

The 13Z-bicyclogeranylgeranylacetone **492** was prepared from **220** by a known method [153] (Figure 3.8). The Wittig type reaction of ketone **492** with the trimethylphosphonoacetate leads to a

mixture of 17Z- and 17E-isomeric esters **490** and **491** (82%, ratio 1:3), which were separated by flash chromatography on a silica gel column impregnated with silver nitrate.

The cyclisation reaction of 13Z,17Z-ester **490** was conducted with 5 mol equiv. of FSO_3H at -78 °C over a period of 15 min, quenching the reaction mixture with a solution of Et_3N in hexane (1:1). The crude reaction product, obtained after usual work-up, was analyzed by ^1H NMR, revealing that two cyclisation products, esters **344** and **488**, were formed.

In order to separate the two components, that exhibited similar chromatographic behavior, the mixture was subjected to hydrolysis with a 10% ethanolic solution of KOH at reflux (2 h). Under these conditions, only the ester **488** was hydrolyzed, leaving **344** intact. After usual work-up, the reaction mixture was chromatographed on a silica-gel column to give, in order of increasing polarity, the known 18-*epi*-scalaranic ester **344** (26% isolated yield), identified by comparison of spectral data with those of an authentic sample, and a fraction containing the acid corresponding to ester **488**. This fraction was treated with diazomethane to obtain **488**, which was finally purified by reversed phase HPLC (39% isolated yield). All its spectral data were consistent with the proposed tricyclic structure **488**, exhibiting a 14-*epi* cheilanthane skeleton.

The superacidic cyclisation of 13*Z*,17*E*-ester **491** with FSO_3H was conducted in similar conditions as above described for compound **490** (5 mol equiv. of FSO_3H, -78 °C, 30 min, Figure 3.8). The reaction mixture was quenched with a solution of Et_3N in hexane (1:1), then the usual work-up afforded a crude reaction product, which was analyzed by ^1H NMR, showing that also in this case two cyclisation products, esters **343** and **489**, were formed. The two reaction products were separated using the same procedure described above for esters **344** and **488**. The mixture was subjected to hydrolysis with a 10% ethanolic solution of KOH at reflux (2 h). Under these conditions, only ester **489** was hydrolyzed, whereas **343** did not react. After usual work-up, the reaction mixture was chromatographed on a silica-gel column to give, in order of increasing polarity, the known scalaranic ester **343** (25% isolated yield), identified by comparison of spectral data with those of an authentic sample, and a fraction containing the acid corresponding to ester **489**, which was methylated with diazomethane to give pure **489**. All its spectral data were consistent with the proposed tricyclic structure **489**, exhibiting a rearranged cheilanthane skeleton.

A tentative explanation of the cyclisation reaction course for both open chain and bicyclic substrates is given in Figure 3.9.

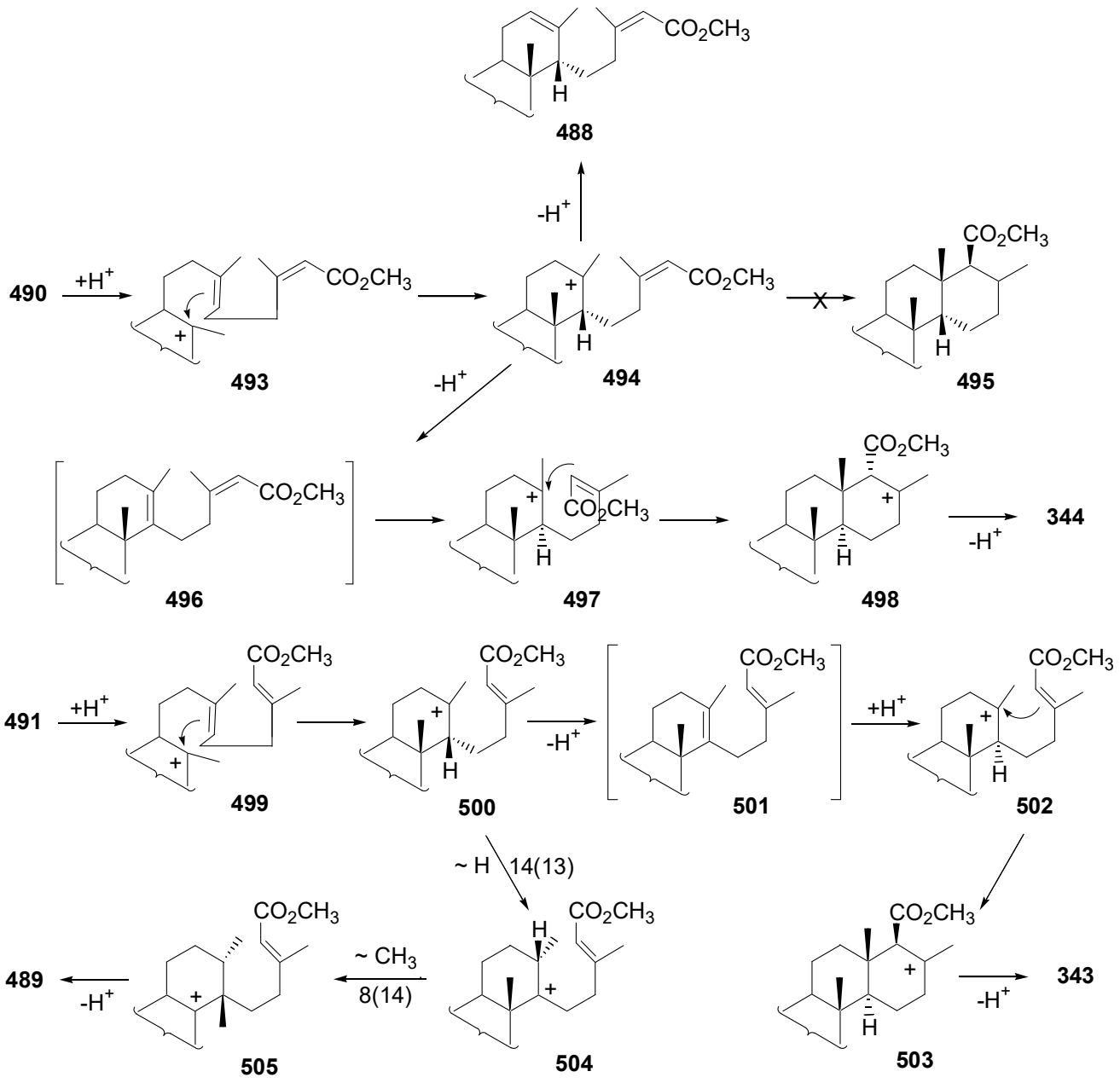
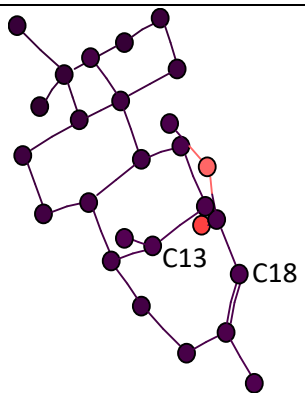
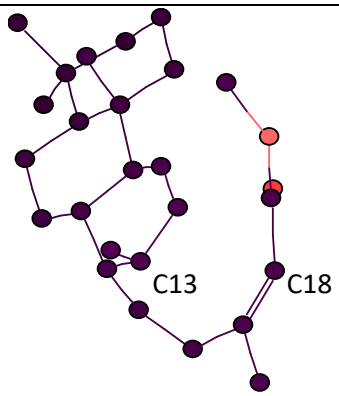
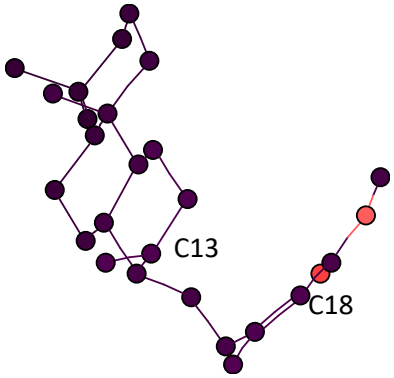


Figure 3.9. Proposed mechanisms for cyclisation reaction of esters **490** and **491**.

Protonation of the ester **490** generates the carbocation **493**, which is then attacked by the $\Delta^{13(14)}$ - double bond from the α-side of the molecule (less sterically hindered), forming the tricyclic intermediate carbocation **494**. The hydrogen at C-14 has the β-orientation, due to the *cis*-configuration of the internal double bond in **490**. Although one can assume that carbocation **494** is stable at low temperatures in the superacidic media, nevertheless the closing of the D ring to give the C/D-cis fused scalarane **495** does not take place. Most likely, this is due to the steric hindrance created by the cyclic

backbone to the lateral chain. This has been revealed on simulation molecular models using a MM2 method [154].

Table 3.3. MM2 simulations of the steric energy for the intermediate **494** conformers.

Iteration 0	Iteration 19	Iteration 417 (optimal)
		
Steric Energy *5354 kcal/mol* Distance C_{13}-C_{18} *2.005 Å*	Steric Energy *378 kcal/mol* Distance C_{13}-C_{18} *2.795 Å*	Steric Energy *52 kcal/mol* Distance C_{13}-C_{18} *3.555 Å*

Minimization of the steric energy for the carbocation **619** shows that the spatial arrangement of the lateral chain in **494**, so that the distance between C(13) and C(18) is lower than 3 Å, is accompanied by a high steric repulsion energy (Table 3.3). The carbocation **494** leads by deprotonation to the cheilanthane trisubstituted isomer **488** and, most likely, also to the tetrasubstituted isomer **496**, which however was not detected.

The subsequent protonation of **496** from the α-side gives rise to carbocation **497**, which due to the *cis*-configuration of the Δ^{17}-double bond, undergoes cyclisation from the α-side generating the carbocation **498**. Deprotonation of **498** leads to the ester **344**, having the α-oriented $-CO_2Me$ group.

Protonation of the ester **491** generates the carbocation **499**, which cyclizes from the α-side of the molecule (sterically less hindered) to form the intermediate carbocation **500**, where, analogously with carbocation **494**, the hydrogen at C(14) has the β-orientation. As in the case of transformation sequence of ester **490**, carbocation **500** undergoes deprotonation giving the cheilanthanic ester **501**, which can be further re-protonated. Protonation at C(14) from the α-side leads to carbocation **502**, which cyclizes into the carbocation **503**. The orientation of the $-CO_2Me$ group in **503** should be β-, due to the trans-configuration of the Δ^{17}-double bond. Accordingly, the scalaranic ester **343** [103] is

formed by deprotonation of **503**. At the same time, carbocation **500** by hydride shift leads to **504**, which can give the rearranged carbocation **505** by migration of the methyl group from the C(8) to C(14). The subsequent deprotonation of **505** leads to 22(8->14)-*abeo*-cheilanthane compound **489** (Figure 3.9).

The same synthetic scheme starting from manool **220** has been iterated with the labdanic diterpenoid sclareol **247**, which represents a relatively cheap compound, produced commercially as a by-product of *Salvia sclarea* essential oil processing. It interacts with ethylacetoacetate in the same way as manool **220** does, to give a mixture of isomeric ketones **506** (Figure 3.10). Our finding, that formation of scalaranes is not influenced by the *E-Z* configuration of the internal double bond has allowed elaboration of an efficient method for the synthesis of scalaranes and cheilanthanes in an integrated process [155]. Its value is given by the possibility of separation the scalaranic compounds from cheilanthanic without chromatography. Following this idea, the mixture of esters **507** and **508** obtained after Horner olefination of **506** was submitted to superacidic cyclization.

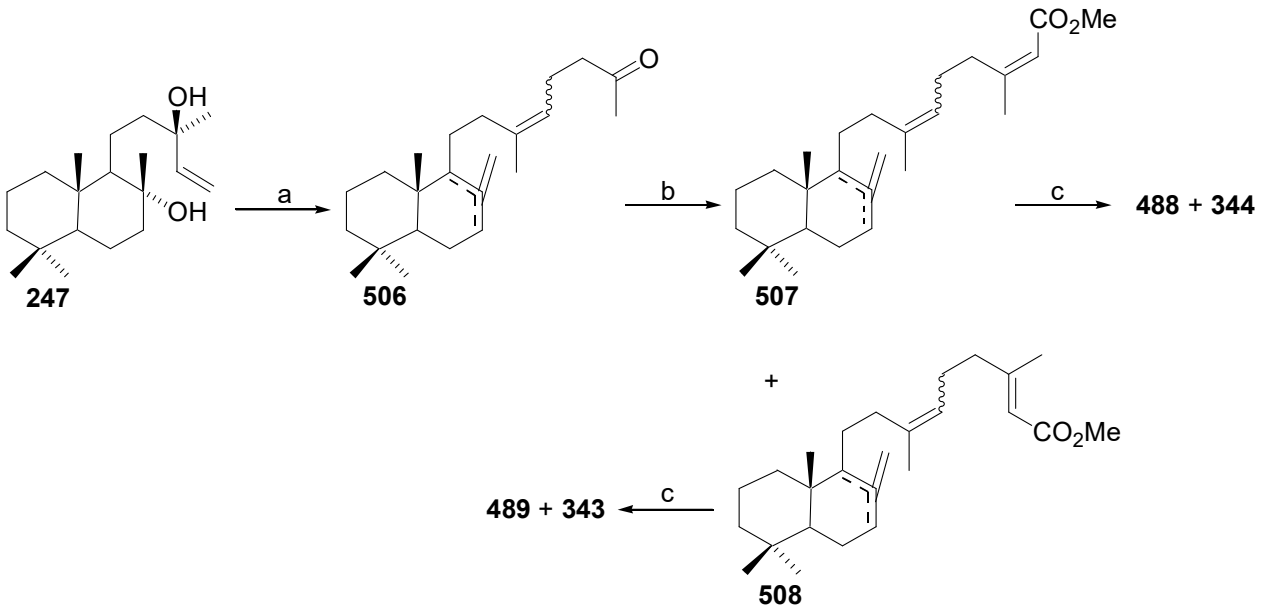


Figure 3.10. Synthesis of 13Z- bicyclic sesterterpenic esters from sclareol and their superacidic cyclization. Reagents and conditions: (a) $CH_3C(O)CH_2CO_2Et$, Δ; (b) $(MeO)_2PCH_2CO_2Me$; (c) FSO_3H, -78 °C.

After batch cyclisation of **506** and **507**, hydrolysis of the reaction products led to the scalaranic esters which does not hydrolyze under the reaction conditions, and cheilanthanic acids.

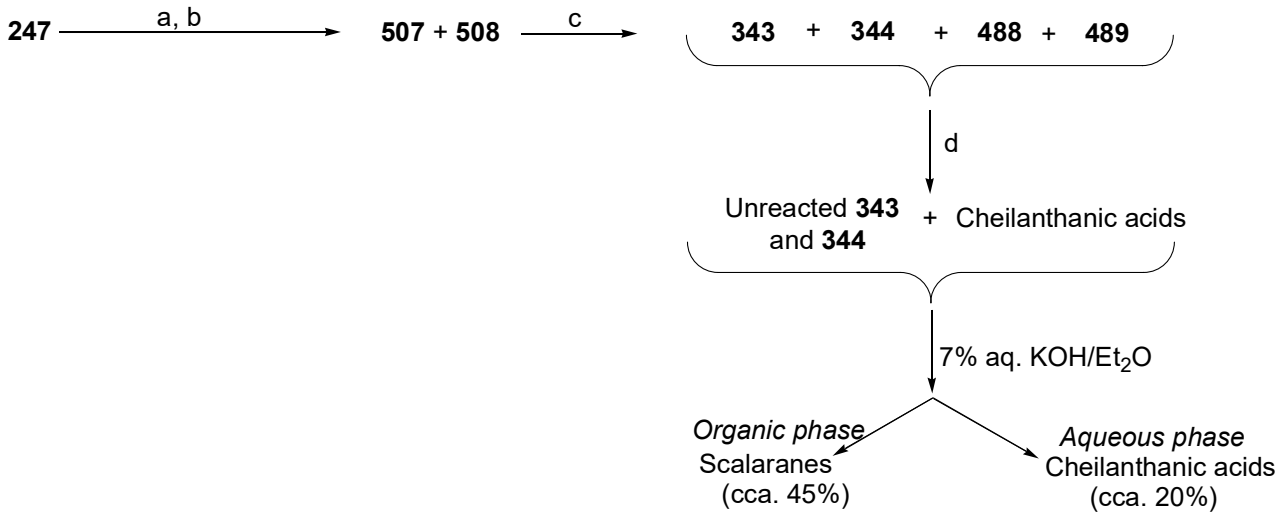


Figure 3.11. The flowchart of the integrated process for scalaranes and chilanthanes synthesis. Reagents and conditions: (a) Carrol rearrangement; (b) $(MeO)_2PCH_2CO_2Me$; (c) FSO_3H, -78 ºC; (d) KOH/EtOH, reflux.

Separation of the acidic and neutral part gives the intact scalaranic esters **343** and **344** in neutral fraction, while cheilanthanic acids can be recovered from the acidic fraction. The flowchart of this procedure is represented in Figure 3.11. The only disadvantage of this preparative scheme relates to the difficulties of controlling the E-/Z-configuration of the internal double bond, which directly influences the yields of scalaranes versus cheilanthanes. The Carrol rearrangement that allows to install the internal double bond occurs with a selectivity towards the E- isomer, disfavoring the final yield of cheilanthanes **488** and **489**.

In order to circumvent this problem, we considered other heteroatomic functional groups intercalated in the linear chain of the terpenic substrates, as tools to control the cyclization cascade. The most convenient solution represented the corresponding phenylsulfones, which have already been shown above as intermediates in the synthesis of diverse terpenic oligomers.

Normally, after coupling a lithiated sulfone with a suitable electrophile, the sulfone group is reductively removed. We considered that such electron-withdrawing functionalities can have a significant impact on the electrophilic cyclization cascade, once they are intercalated into the linear terpenic chain. Generally, it is quite difficult to foresee the behavior of such structural fragments in the superacid-induced cyclization reactions. Previous studies [1], have shown that phenylsulfones can tolerate well the superacidic media and once attached to the head terminus of the polyprenylic chain

undergo complete cyclization under the action of fluorosulfonic acid (Figure 3.12, substrate **A**, R=H_2).

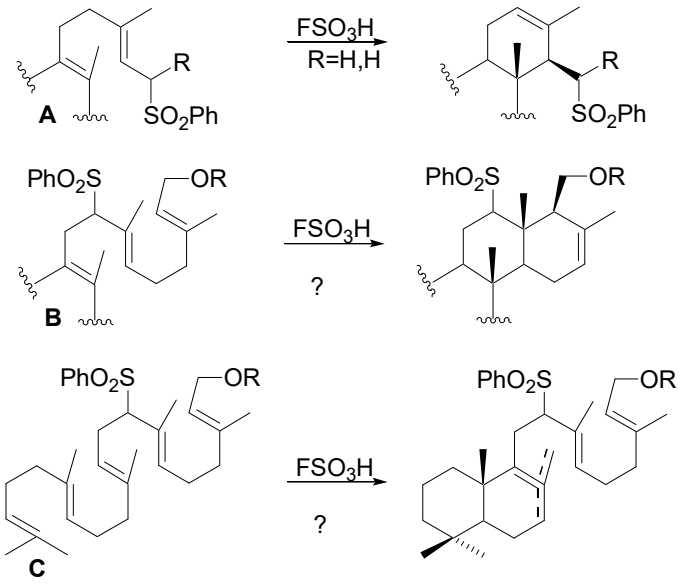


Figure 3.12. Alternative superacidic isomerization pathways of terpenic phenylsulfones.

But in the case of integration of the phenylsylfonyl moiety within the chain, the superacidic treatment can follow more complicated pathways. Basically, two scenarios are possible. The less probable one assumes no interfering of the phenylsulfonyl functional group with the cyclization cascade. A substrate of general formula **B** would have also led to totally cyclized compounds. The synthetic value of such a transformation would be given by the integration of an additional functional group in the cyclic framework, with its following transformation opportunities (reductive elimination, sulfinic acid elimination, oxidative conversion, lithiation and following alkylations).

One could hardly believe though, that such an electron-demanding functional group will not influence the nearby double bonds, diminishing their nucleophilicity and contributing to the inhibition of the cyclization cascade. As a result, we could have expected a substrate of general formula **C** to undergo a partial cyclization with the suspension of the reaction sequence to a cyclic compound with the pendant head prenyl residue. This pathway is also interesting, since the phenylsulfonyl functional group intercalated in the middle of the terpenic chain represents a convenient tool to control the cyclization cascade of the substrate by its selective suspension. In order to reveal these subtle features of the reactivity under electrophilic cyclization of such substrates, the phenylsulfone **509** (type C,

R=THP, Figure 3.12) has been synthesized and submitted to superacidic treatment [120][121]. The results were not exactly in line with our initial expectations.

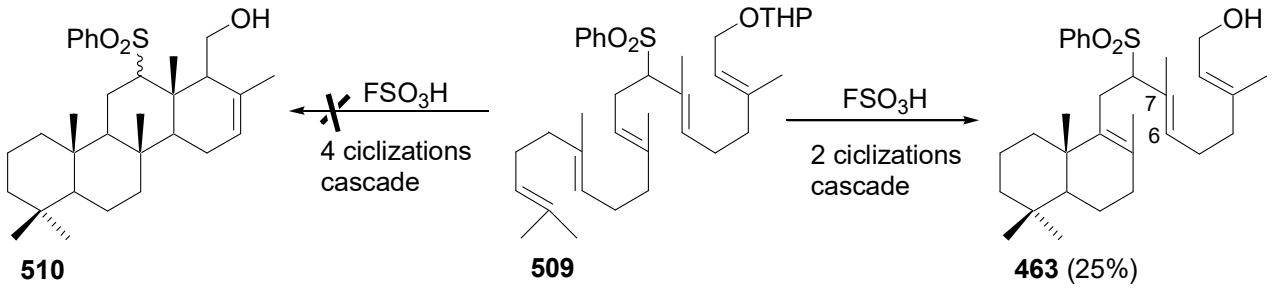


Figure 3.13. Selective bicyclization directed by a phenylsulfonyl group.

Intercalation of the phenylsulfonyl functional group in the middle of the polyenic chain has been envisioned as a way to include the extra-functional group in the structure of the eventual scalaranic product **510**, derived from a hypothetical cascade of four cyclizations (Figure 3.13).

But this hypothesis was not confirmed experimentally. Treatment of polyene **509** with an excess of fluorosulfonic acid at -78 °C provided as a major reaction product the bicyclic compound **463**, which forms on the selective suspension of the cyclization cascade, directed by the phenylsulfonyl group from within the chain.

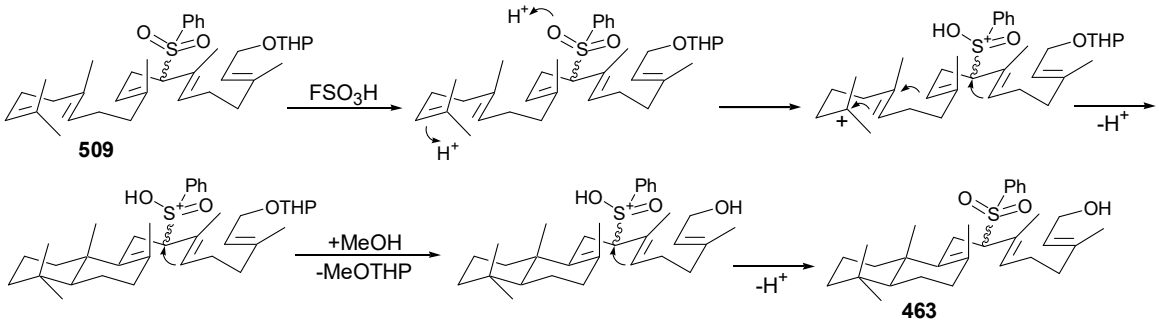


Figure 3.14. The mechanism of cyclization cascade suspension by a phenylsulfonyl group.

This result was explained by a simultaneous protonation of three centers in the substrate **509**: the terminal double bond, phenylsulfonyl group and tetrahydropyranyl protection group at the head extremity of the chain (Figure 3.14). As a result, a cascade of two cyclization is initiated at the terminal end of the chain, which cannot advance to a tri- or tetracyclization, due to the sulfone protonation and diminishing the nucleophilicity of the $\Delta^{6,7}$ double bond by a pronounced allylic effect.

The resulting bicyclic compound **463** is a product of a suspended cyclization and THP protection group removal. A minor (8%) amount of THP-protected derivative of alcohol **463** has also been isolated from the crude reaction product, making the total yield of the partial cyclization over the 30%.

The structure of the formed partially cyclized compound has been unambiguously demonstrated by a concurrent synthesis from two building blocks: the bicyclic sesquiterpenic fragment in optically active form, derived from iso-drimenol and the open chain fragment including a α,ω-bifunctionalized monoterpenic substrate. This piece of work has been shown in detail in the chapter 2 above.

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

Ionic liquids have recently found a broad use in organic synthesis thanks to several of their important properties such as a sufficient temperature range at which reactions can be carried out, the simplicity of working up reaction mixtures, nonvolatility, the ability to be re-cycled after the reaction procedures, etc. [156],[157],[158]. We investigated the reactions of several aliphatic sesquiterpene derivatives with fluorosulfonic acid in ionic liquids [159],[160].

Despite the use of the liquids as reaction media in many organic reactions, their application for carrying out electrophilic cyclization of terpenoids has not been reported. It is well known that this reaction plays an important role in the development of biomimetic synthetic methods for many cyclic terpenoids, among which are practically important compounds.

Existing information on biomimetic cyclization of regularly constructed terpenoids demonstrated convincingly that the preferred reagents for it are superacids at low temperatures. The reaction is chemically and structurally selective and stereospecific [141]. It seemed interesting to determine if superacid cyclization could be carried out in suitable ionic liquids and its efficiency.

The substrates were *E,E*-farnesol **10**, its acetate **511**, *E,E*-farnesylphenylsulfone **512**, and the methyl ester of *E,E*-farnesoic acid **2**. The ionic liquids were (1-butyl-3-methylimidazolium) tetrafluoroborate [bmim]BF_4 **513** and (1-butyl-3-methylimidazolium) hexafluorophosphate [bmim]PF_6 **514**.

Ionic liquid **513** was preferred because reactions in it could have been carried out at temperatures around -45 to -50 °C. As mentioned above, superacid cyclization in ordinary solvents is carried out at temperatures as low as -70 to -80 °C. Ionic liquid **514** solidifies at 0 °C. This would have a substantial

effect on the product yields. Table 3.3 lists the results and reactions conditions. CH_2Cl_2 was used as a co-solvent because of the high viscosity of the ionic liquids. The best results for reactions carried out in **513** were obtained for cyclization of **2** and **512**. The yields of bicyclic products **517** [161] and **518** [162] were 89 and 86%, respectively.

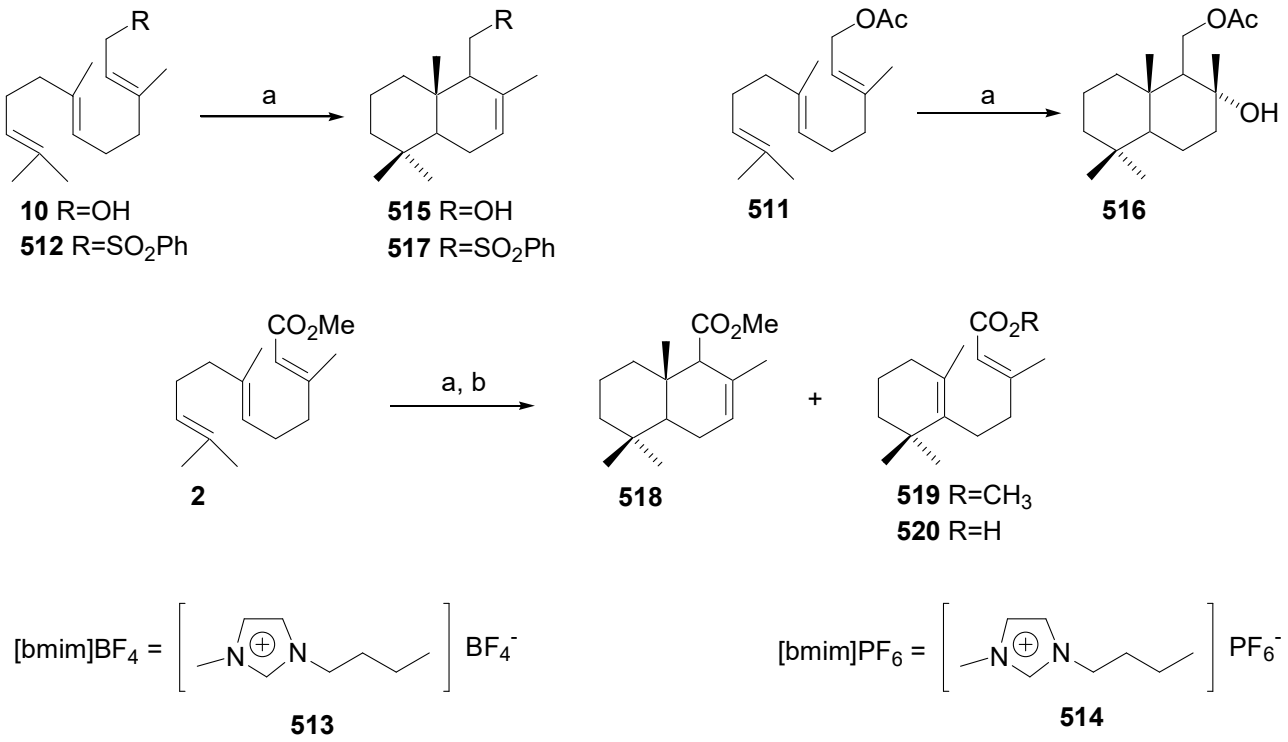


Figure 3.15. Superacidic cyclizations in ionic liquids. Reagents and conditions: (a) FSO_3H (5 equiv.), [bmim]BF_4 **513**, CH_2Cl_2, -45°C, 15 min; (b) 10% KOH, EtOH, reflux for 2 h.

For farnesol **10** and its acetate **511**, which contain functional groups that are sensitive to the acids, the yields of bicyclic products **515** and **516** [153] were relatively low (36 and 32%, respectively) because rather large quantities of hydrocarbons were formed. Apparently the functional groups of both starting **10** and **511** and cyclization products **515** and **516** were solvolyzed. On cyclization of **2**, a small quantity (5%) of the ester of β-monocyclofarnesyl acid **519** and the product of full cyclization **518** were formed. Esters **518** and **519** were separated by selective saponification of monocyclic ester **519** on refluxing the products in alcoholic KOH for 2 h. Acid **520** was separated by methylation with diazomethane. Ester **519** was identified by comparison with an authentic sample prepared by the previously reported method [145].

Table 3.4. Cyclization of aliphatic sesquiterpenoids **2**, **10**, **511** and **512** by fluorosulfonic acid in ionic liquids **513** and **514**.

Substrate	Substrate, mg (mmol)	CH_2Cl_2 volume, mL	Ionic liquid 513 or 514, mL	t, °C	Reaction time, min	Product composition, %		
						Cyclic product	Hydrocarbon fraction	Polymer fraction
10	70 (0.315)	1.4	0.70 (**513**)	-45	15	36 (**515**)	19	45
10	72 (0.324)	1.5	0.72 (**513**)	-45	5	33 (**515**)	15	52
10	65 (0.293)	1.3	0.65 (**514**)	0	5	0 (**515**)	69	31
511	88 (0.333)	1.8	0.88 (**513**)	-45	15	32 (**516**)	29	39
512	64 (0.185)	1.3	0.64 (**513**)	-45	30	89 (**517**)	0	11
512	22 (0.064)	0.4	0.20 (**514**)	0	5	73 (**517**)	0	27
2	44 (0.169)	0.9	0.44 (**513**)	-45	30	86 (**518**) and 5 (**519**)	0	9
2	46 (0.169)	0.9	0.46 (**514**)	0	15	41 (**518**) and 7 (**519**)	0	51

If the cyclization was carried out in **514**, the yield was high (89%) only for cyclization of **512**. Cyclization of **2** formed a mixture of **518** and **519** in yields of 41 and 7%, respectively. Compounds **10** and **511** reacted with fluorosulfonic acid in [bmim]PF_6 to give only hydrocarbons and polymeric products. In all instances products were isolated in pure state by column chromatography over silica gel and were identified spectrally and chromatographically by comparison with authentic samples.

3.4 Synthesis of cyclic terpenic compounds by selective cyclization sequences. Experimental methods and procedures

Superacidic cyclization of *E,E,E*-10-acetoxyfarnesyl benzyl ether 439. 10-Benzyloxy-14-acetoxy-10,12-secoeudesma-1(6),12E-dienes 475 and 476.

To a solution of **439** (70 mg, 0.19 mmol) in 2-nitropropane (1.5 mL) cooled to -78 °C, was added a solution of FSO_3H (95 mg, 0.95 mmol) in the same solvent (1 mL) with vigorous stirring. After 15 min of stirring at the same temperature, the mixture was quenched by adding a 50% excess of Et_3N in hexane (1:1, 0.35 mL). H_2O (5 mL) was added carefully to the mixture and the product was

extracted with Et_2O (3 × 5 mL). The extract was washed with 10% H_2SO_4 (2 × 5 mL), H_2O (2 × 10 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated in vacuum and the crude product (69 mg) was purified on a silica gel column (1.0 g) (petroleum ether/Et_2O, 97:3) to give 50.2 mg (72%) of a 2:1 mixture of **475** and **476**. The mixture of **475** and **476** was separated by HPLC [semipreparative Nova-Pack C-18 column, MeOH/H_2O (95:5), flow rate 1.5 mL/min], affording pure **475** (19.5 mg) and **476** (9.2 mg).

10-Benzyloxy-14-acetoxy-10β-10,12-secoeudesma-1(6),12E-diene 475: IR ($CHCl_3$; ν , cm^{-1}): 1741, 1453, 1378, 1232, 1101, 756. MS: m/z (%) = 370 (M+, 2), 310 (M+-AcOH, 9), 262 (4), 219 (42), 202 (100), 189 (98), 175 (28), 161 (79), 119 (97), 91(99). Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.77; H, 9.21. For NMR data – see table 3.1.

10-Benzyloxy-14-acetoxy-10α-10,12-secoeudesma-1(6),12E-diene 476: IR ($CHCl_3$; ν , cm^{-1}): 1741, 1452, 1375, 1233, 1096, 741. MS: m/z (%) = 370 (M+, 1), 310 (4), 262 (13), 219 (60), 202 (100), 189 (78), 175 (32), 161 (74), 119 (99), 91 (98). Anal. calc. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.83; H, 9.20. For NMR data – see table 3.1.

Superacidic cyclization of *E,E,E*-16-acetoxygeranylgeraniol 440.

The solution of compound **440** (137 mg, 0.39 mmol) in 2-nitropropane (1.8 ml) was chilled at -78 °C and treated with a solution of FSO_3H (117 mg, 1.17 mmol) in 2-nitropropane (0.4 ml), chilled at the same temperature. After 15 min of stirring at the same temperature the reaction mixture was quenched with a solution of NEt_3 in hexane (1:1) (1 ml). Dilution with H_2O (5 ml) and usual work-up gave a crude product (154 mg), submitted to flash chromatography on Si gel (4 g). Elution with an increasing gradient of EtOAc in petr. ether gave a mixture (3:1 according to ^1H NMR) of sacculatanic compounds **480** and **481** (34 mg, 25%). This mixture was separated by semipreparative HPLC on a normal phase Kromasil silica (25×0.9 cm) column. Elution was performed with 1% isopropanol in hexane.

11-Hydroxy-19-acetoxy-14β-sacculata-7,17E-diene 480: Colorless viscous oil. IR: ν_{max} (liquid film) 3674, 2922, 2856, 1746, 1541, 1456, 1378, 1232, 1025 cm^{-1}. ^1H NMR (400 MHz): δ_H= 0.88 (*s*,

3H, H_3-13 or H_3-14), 0.89 (*s*, 3H, H_3-14 or H_3-13), 1.64 (*bs*, 3H, H_3-20), 1.78 (*bs*, 3H, H_3-12), 2.07 (*s*, 3H, -OAc), 3.73 (*dd,* J_1 = 11 Hz, J_2 = 5 Hz, 1H, H-11b), 3.86 (*dd*, J_1 = 11 Hz, J_2 = 3 Hz, 1H, H-11a), 4.43 (*s*, 2H, H_2-19), 5.41 (*t*, *J* = 7 Hz, 1H, H-17), 5.51 (*bs*, 1H, H-7). ^{13}C NMR (75.5 MHz): δ_C= 13.9 (*q*, C-20), 15.4 (*q*, C-13), 18.5 (*t*, C-2), 20.8 (*q*, C-14), 21.0 (*q*, -OAc), 21.6 (*t*, C-16), 21.9 (*q*, C-12), 23.3 (*t*, C-6), 35.3 (*s*, C-4 or C-10), 36.1 (*s*, C-10 or C-4), 37.6 (*t*, C-3), 39.6 (*t*, C-1), 43.6 (*t*, C-15), 47.6 (*d*, C-5), 57.4 (*d*, C-9), 60.9 (*t*, C-11), 70.4 (*t*, C-19), 123.9 (*d*, C-7), 129.5 (*s*, C-18), 130.5 (*d*, C-17), 132.8 (*s*, C-8), 171.1 (*s*, -C=O). ESIMS *m/z* (%) 349 (29) $[M+H]^+$, 331 (32), 316 (8), 305 (5), 289 (100), 271 (73), 259 (28), 243 (7), 231 (7), 203 (16), 189 (27), 175 (26), 133 (47), 109 (64). HREIMS *m/z* 348.2644 (calcd for $C_{22}H_{36}O_3$ 348.2664).

11-Hydroxy-19-acetoxy-14α-sacculata-7,17E-diene 481: Colorless viscous oil. IR: ν_{max} (liquid film) 3673, 2921, 2856, 1745, 1541, 1456, 1377, 1231, 1025, 845 cm^{-1}. ^{1}H NMR (400 MHz): δ_H= 0.88 (*s*, 3H, H_3-13), 0.87 (*s*, 3H, H_3-14), 1.65 (*bs*, 3H, H_3-20), 1.78 (*bs*, 3H, H_3-12), 2.08 (*s*, 3H, -OAc), 3.73 (*dd*, J_1 = 11 Hz, J_2 = 5 Hz, 1H, H-11b), 3.85 (*dd*, J_1 = 11 Hz, J_2 = 3 Hz, 1H, H-11a), 4.45 (*s*, 2H, H_2-19), 5.45 (*t*, *J* = 7 Hz, 1H, H-17), 5.53 (*bs*, 1H, H-7). ^{13}C NMR (75.5 MHz): δ_C= 13.8 (*q*, C-20), 15.9 (*q*, C-13), 18.5 (*t*, C-2), 21.0 (*q*, -OAc), 21.9 (*q*, C-12), 22.8 (*t*, C-16), 23.1 (*t*, C-6), 29.0 (*q*, C-14), 35.6 (*s*, C-4 or C-10), 36.2 (*s*, C-10 or C-4), 32.2 (*t*, C-15), 37.0 (*t*, C-3), 40.0 (*t*, C-1), 52.1 (*d*, C-5), 57.8 (*d*, C-9), 60.9 (*t*, C-11), 70.3 (*t*, C-19), 124.2 (*d*, C-7), 129.6 (*s*, C-18), 130.8 (*d*, C-17), 132.8 (*s*, C-8), 171.1 (*s*, -C=O). ESIMS *m/z* (%) 348 (2) $[M^+]$, 331 (3), 318 (3), 305 (2), 288 (10), 271 (5), 258 (29), 243 (6), 219 (12), 189 (22), 175 (30), 133 (46), 109 (100), 81 (74). HREIMS *m/z* 348.2654 (calcd for $C_{22}H_{36}O_3$ 348.2664).

Synthesis of 5Z,9E,13E-3-ethylcarboxy-geranylgeranylacetone 486.

To a cooled solution (0 °C) of 2*Z*,6*E*,10*E*-geranylgeraniol **484** (527 mg, 1.82 mmol) in dry ether (31 ml) and pyridine (0.2 ml) was added a solution of PBr_3 (0.24 ml, 2.48 mmol) in dry ether (1.0 ml). The reaction mixture was stirred for 2 h at 0 °C then at r.t. for 12 h. Usual work-up yielded 597 mg (97%) of crude bromide **485**, which was used in the next step without purification.

To a solution of ethyl acetoacetate (0.27 ml, 2.10 mmol) in dry toluene (4.2 ml), sodium (48 mg, 2.09 equiv.) was added, under Ar atmosphere. After complete dissolving of sodium, the solution of 2*Z*,6*E*,10*E*-geranylgeranyl bromide **485** (543 mg, 1.54 mmol) in dry toluene (2.6 ml) was added.

The reaction mixture was refluxed for 2 h and then quenched by addition of 10 ml of water. Usual work-up yielded a crude residue (1.06 g), which was submitted to flash chromatography on silica gel (30 g). Elution with an increasing gradient of EtOAc in petr. ether gave 5*Z*,9*E*,13*E*-3-ethylcarboxy-geranylgeranylacetone **486** (538.2 mg, 87%) as colorless oil. IR: ν_{max} (liquid film) 1730, 1710, 1440, 1230, 1140, 840 cm^{-1}. ^1H NMR (400 MHz): δ_H= 1.24 (*t*, *J* = 7 Hz, 3H), 1.58 (*s*, 3H) and 1.59 (*s*, 6H), 1.66 (*s*, 6H), 2.03 (*m*, 12H), 2.19 (*s*, 3H), 2.52 (*t*, *J* = 7 Hz, 2H), 3.39 (*t*, *J* = 7 Hz, 1H), 4.15 (*q*, *J* = 7 Hz, 2H), 5.00 (*t*, *J* = 7 Hz, 1H), 5.09-5.02 (*m*, 3H). ^{13}C NMR (100 MHz): δ_C = 14.2 (*q*), 16.0 (*q*), 16.1 (*q*), 17.7 (*q*), 23.5 (*q*), 25.7 (*q*), 26.5 (*t*), 26.7 (*t*), 26.8 (*t*), 26.8 (*t*), 29.1 (*q*), 32.0 (*t*), 39.8 (*t*), 60.1 (*t*), 61.3 (*d*), 120.4 (*d*), 123.9 (*d*), 124.3 (*d*), 124.5 (*d*), 131.3 (*s*), 135.6 (*s*), 138.6 (*s*), 169.6 (*s*), 203.1 (*s*). HR-ESIMS. 425.3031 ([*M*+Na]$^+$, $C_{26}H_{42}NaO_3^+$; calc. 425.3026).

Synthesis of 5Z,9E,13E-geranylgeranylacetone 487.

5*Z*,9*E*,13*E*-3-Ethylcarboxy-geranylgeranylacetone **486** (727 mg, 1.81 mmol) was dissolved in EtOH (4.0 ml) and 8.5 ml of a 10% KOH/EtOH solution (6.0 ml) were added. The reaction mixture was refluxed for 2 h. After the usual work-up, a crude residue (597 mg) was obtained and purified on a silica gel column (15 g) (petr. ether–EtOAc, 7:3) to give 382 mg (64%) of 5*Z*,9*E*,13*E*-geranylgeranylacetone **487** as colorless oil. IR ν_{max} (liquid film) 1720, 1440, 1360, 1216, 1110, 850 cm^{-1}. ^1H NMR (400 MHz): δ_H = 1.57 (*s*, 9H), 1.66 (*s*, 6H), 1.96-1.95 (*m*, 4H), 2.08-2.06 (*m*, 8H), 2.10 (*s*, 3H), 2.26-2.23 (*m*, 2H), 2.42 (*t*, *J* = 7 Hz, 2H), 5.10-5.03 (*m*, 4H, m). ^{13}C NMR (100 MHz): δ_C = 16.0 (*q*), 16.0 (*q*), 16.0 (*q*), 17.5 (*q*), 17.7 (*q*), 22.3 (*t*), 23.4 (*t*), 25.7 (*q*), 26.5 (*t*), 26.7 (*t*), 26.8 (*t*), 29.9 (*q*), 31.8 (*t*), 31.9 (*t*), 39.8 (*t*), 123.3 (*d*), 124.0 (*d*), 124.2 (*d*), 124.4 (*d*), 131.3 (*s*), 135.0 (*s*), 135.4 (*s*), 136.6 (*s*), 207.8 (*s*). HR-ESIMS. 353.2819 ([*M*+Na]$^+$, $C_{23}H_{38}NaO^+$; calc. 353.281).

Synthesis of methyl-(2Z,6Z,10E,14E)- and (2E,6Z,10E,14E)-geranylfarnesoates 482 and 483.

A solution of sodium methoxide in methanol, prepared by dissolving of 64.0 mg (2.79 equiv.) of sodium metal in 2.7 ml of methanol, was slowly added to a stirred solution of 5*Z*,9*E*,13*E*-geranylgeranylacetone **487** (306 mg, 0.93 mmol) and trimethylphosphonoacetate (0.45 ml, 2.79 mmol) in benzene (15.0 ml). After refluxing for 3 h, the mixture was cooled, treated with ice-water (15.0 ml) and extracted with Et_2O (3×10 ml). After usual work-up the solvent was removed *in vacuum* to give a mixture (1:3 according to ^1H NMR) of compounds **482** and **483** (347 mg, 97%). This mixture

was separated by semipreparative normal phase HPLC. Elution was performed with 1% EtOAc in hexane.

Methyl-(2*Z*,6*Z*,10*E*,14*E*)-geranylfarnesoate 482: Colorless viscous oil. IR ν_{max} (liquid film): 1728, 1640, 1440, 1380, 1220, 1150, 840, cm^{-1}. ^1H NMR (400 MHz): δ_H = 1.58 (*s*, 9H), 1.67 (*s*, 6H), 1.87 (*s*, 3H), 1.97-1.95 (*m*, 4H), 2.04 (*b.s*., 8H), 2.18-2.13 (*m*, 2H), 2.62 (*t*, *J* = 7.8 Hz, 2H), 3.66 (*s*, 3H), 5.16-5.5.08 (*m*, 4H), 5.64 (*s*, 1H). ^{13}C NMR (75.5 MHz): δ_C = 16.1 (*q*), 17.8 (*q*), 23. 5 (*q*), 25.5 (*q*), 25.8 (*q*), 26.7 (*q*), 26.8 (*t*), 26.9 (*t*), 29.8 (*t*), 32.0 (*t*), 33.7 (*t*), 33.8 (*t*), 39.7 (*t*), 39.8 (*t*), 50.8 (*q*), 115.9 (*d*), 124.27 (*d*), 124.3 (*d*), 124.4 (*d*), 124.5 (*d*), 131.3 (*s*), 135.0 (*s*), 135.3 (*s*), 136.0 (*s*), 160.5 (*s*), 166.8 (*s*). HR-ESIMS: 409.3079 ([*M*+Na]$^+$, $C_{26}H_{42}NaO_2^+$; calc. 409.3077).

Methyl-(2*E*,6*Z*,10*E*,14*E*)-geranylfarnesoate 483: Colorless viscous oil. IR ν_{max}: 1726, 1648, 1438, 1222, 1156, 856 cm^{-1}. ^1H NMR (400 MHz): δ_H (selected peaks) = 1.58 (*s*, 9H), 1.67 (*s*, 6H), 1.95-2.07 (*m*, 10H), 2.14 (*b.s*, 8H), 3.67 (*s*, 3H), 5.08-5.11 (*m*, 4H), 5.66 (*s*, 1H). ^{13}C NMR (100 MHz): δ_C = 16.0 (*q*), 16.0 (*q*), 17.7 (*q*), 18.8 (*q*), 23.4 (*q*), 25.7 (*q*), 25.8 (*t*), 26.5 (*t*), 26.6 (*t*), 26.8 (*t*), 29.7 (*t*), 32.0 (*t*), 39.7 (*t*), 41.2 (*t*), 50.8 (*q*), 115.2 (*d*), 123.6 (*d*), 124.0 (*d*), 124.2 (*d*), 124.4 (*d*), 131.2 (*s*), 135.0 (*s*), 135.4 (*s*), 136.3 (*s*), 160.1 (*s*), 167.3 (*s*). HR-ESIMS: 409.3081 ([*M*+Na]$^+$, $C_{26}H_{42}NaO_2^+$; calc. 409.3077).

Superacidic cyclisation of methyl-(2Z,6Z,10E,14E)-geranylfarnesoate 482.

A solution of methyl-(2*Z*,6*Z*,10*E*,14*E)*-geranylfarnesoate **482** (150 mg, 0.39 mmol) in *i*-$PrNO_2$ (5.0 ml), cooled at -78°C, was treated with a cooled at the same temperature solution of FSO_3H (390 mg, 3.90 mmol) in *i*-$PrNO_2$ (0.9 ml), under stirring. After 15 min, the reaction was stopped by adding a solution of Et_3N (0.5 ml) in light petroleum ether (0.5 ml). The usual work up gave 147 mg of a crude residue, which was used in the next step without any purification. The residue (147 mg) was dissolved in EtOH (1.0 ml) and a 10% KOH/EtOH solution (3.0 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 142 mg of crude reaction product, which was chromatographed on a silica gel (4.5 g) column. Elution with a light petroleum ether/EtOAc gradient gave, in order of increasing polarity, 39.2 mg (26%) of ester **344**, which showed spectral data (IR, ^1H

and ^{13}C NMR) identical with those reported in literature [103] and 101.5 mg (70.2%) of acid containing fraction.

Methyl-19α-scalar-16-enoate 344: Colorless viscous oil. ^{1}H NMR (300 MHz): δ_H (selected peaks) = 0.79 (*s*, H_3-20, 3H), 0.83 (*s*, H_3-21 and H_3-22, 6H), 0.89 (*s*, H_3-23, 3H), 0.91 (*s*, H_3-24, 3H), 1.60 (*s*, H_3-25, 3H), 2.47 (*b.s*, H-18, 1H), 3.69 (*s*, OMe, 3H), 5.58 (*b.s*, H-16, 1H). ^{13}C NMR (75.5 MHz): δ_C = 16.5 (*q*), 17.0 (*q*), 17.4 (*q*), 18.2 (*t*), 18.6 (*t*), 21.3 (*q*), 22.4 (*q*), 22.6 (*t*), 22.9 (*t*), 33.3 (*q*), 33.4 (*s*), 36.4 (*s*), 37.4 (*s*), 37.5 (*s*), 39.2 (*t*), 39.7 (*t*), 41.6 (*t*), 42.1 (*t*), 46.7 (*d*), 51.4 (*q*), 56.1 (*d*), 60.8 (*d*), 61.9 (*d*), 124.6 (*d*), 128.5 (*s*), 174.8 (*s*). Anal. Calc. for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.68, H 10.97.

The acid fraction (101.5 mg) was treated with a saturated solution of CH_2N_2 in Et_2O (3.0 ml). After 20 min, the solvent was removed i*n vacuum* and residue was purified on a column with silica gel (3 g, light petroleum ether as eluent) to give 100.6 mg of a mixture containing the ester **488**, which was further submitted to HPLC purification [semipreparative Nova-Pack C-18 column, MeOH/H_2O (95:5), flow rate 1.5 ml/min, affording pure ester **488** (58.5 mg, 39%), which showed spectral data (IR, ^{1}H and ^{13}C NMR) identical with those reported in literature [114].

Methyl-15α-cheilantha-12,17Z-dienoate 488: Colorless viscous oil. IR ν_{max} (liquid film) 1726, 1658, 1380, 1238, 1152, 859 cm^{-1}. ^{1}H NMR (300 MHz): δ_H (selected peaks) = 0.84 (*s*, H_3-20, 3H), 0.88 (*s*, H_3-23, 3H), 0.887 (*s*, H_3-21, 3H), 0.893 (*s*, H_3-22, 3H), 1.71 (*s*, H_3-24, 3H), 1.91 (*s*, H_3-25, 3H), 2.53 (*ddd*, J_1 = 12 Hz, J_2 = 12 Hz, J_3 = 6 Hz, H_2-16, 1H) and 2.75 (*ddd*, J_1 = 12 Hz, J_2 = 12 Hz, J_3 = 4 Hz,, 1H), 3.67 (*s*, OMe, 3H), 5.23 (*b.s*, H-12, 1H), 5.63 (*b.s*, H-18, 1H). ^{13}C NMR (75.5 MHz): δ_C = 15.6 (*q*), 18.5 (*t*), 18.6 (*t*), 21.9 (*q*), 23.1 (*t*), 23.2 (*q*), 23.4 (*q*), 25.3 (*q*), 30.4 (*t*), 33.1 (*s*), 33.6 (*q*), 35.5 (t), 37.1 (*t*), 37.2 (*s*), 37.2 (*s*), 40.1 (*t*), 42.0 (*t*), 47.2 (*d*), 50.7 (*q*), 54.9 (*d*), 56.5 (*d*), 115.8 (*d*), 119.7 (*d*), 136.1 (*s*), 160.3 (*s*), 166.2 (*s*). Anal. Calc. for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.83, H 10.87.

Superacidic cyclisation of methyl 2E,6Z,10E,14E-geranylfarnesoate 483.

A solution of methyl 2*E*,6*Z*,10*E*,14*E*-geranylfarnesoate **483** (210 mg, 0.54 mmol) in *i*-$PrNO_2$ (7.0 mL), cooled at -78°C, was treated with a cooled at the same temperature solution of FSO_3H (270

mg, 2.70 mmol) in *i*-$PrNO_2$ (1.2 ml), under stirring. After 15 min, the reaction was stopped by adding a solution of Et_3N (2.5 ml) in light petroleum ether (2.5 ml). The usual work up gave ~207 mg of a crude residue, which was used in the next step without purification. The residue (207 mg) was dissolved in EtOH (1.2 ml) and a 5% KOH/EtOH solution (4.5 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 203 mg of crude reaction product, which was chromatographed on a silica gel (5 g) column. Elution with a light petroleum ether/EtOAc gradient gave, in order of increasing polarity, 52.5 mg (25%) of ester **343**, which showed spectral data (IR, ^1H and ^{13}C NMR) identical with those reported in literature [103][114] and 128.2 mg of acid fraction, to which was added a saturated solution of CH_2N_2 in Et_2O (1.0 ml). After 20 min, the solvent was removed *in vacuum* to give 133.0 mg of residue, which was purified on a silica gel column (0.5 g), (light petroleum ether as eluent) to give 132.3 mg (63%) of methyl ester **489**.

Methyl-19β-scalar-16-enoate 343: Colorless crystals, mp 166–168°C (from light petr. ether, lit. [103] mp 167–169°C (from petr. ether)]. ^1H NMR (400 MHz): δ_H (selected peaks) = 0.80 (*s*, H_3-20, 3H), 0.83 (*s*, H_3-21 and H_3-22, 6H), 0.91 (*s*, H_3-23, 3H), 0.92 (*s*, H_3-24, 3H), 1.59 (*b.s*, H_3-25, 3H), 2.89 (*b.s*, H-18, 1H), 3.66 (*s*, OMe, 3H), 5.51 (*b.s*, H-16, 1H). ^{13}C NMR (100 MHz): δ_C = 15.4 (*q*), 16.4 (*q*), 16.9 (*q*), 17.5 (*q*), 18.2 (*t*), 18.6 (*t*), 21.2 (*q*), 21.4 (*t*), 22.6 (*t*), 33.2 (*q*), 33.3 (*s*), 36.3 (*s*), 37.4 (*s*), 37.7 (*s*), 39.9 (*t*), 41.8 (*t*), 41.9 (*t*), 42.1 (*t*), 51.0 (*q*), 54.8 (*d*), 56.5 (*d*), 61.3 (*d*), 62.7 (*d*), 124.1 (*d*), 128.7 (*s*), 174.4 (*s*). Anal. Calc. for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.72, H 10.83.

Methyl-24α,15α-23(8→14)abeocheilantha-8(9),17E-dienoate 489: Colorless crystals, mp 109–111°C (from petr. ether). IR ν_{max} (liquid film) 1722, 1648, 1436, 1379, 1225, 1151, 865 cm^{-1}. ^1H NMR (400 MHz): δ_H (selected peaks) = 0.83 (*s*, H_3-20, 3H), 0.85 (*d*, *J* = 7 Hz, H_3-24, 3H), 0.87 (*s*, H_3-21, 3H), 0.96 (*s*, H_3-22, 3H), 1.04 (*s*, H_3-23, 3H), 2.17 (*b.s*, H_3-25, 3H), 3.67 (*s*, OMe, 3H), 5.68 (*b.s*, H-18, 3H). ^{13}C NMR (100 MHz): δ_C = 14.7 (*q*), 19.2 (*q*), 19.2 (*t*), 19.4 (*t*), 19.8 (*q*), 20.0 (*t*), 21.8 (*q*), 26.1 (*t*), 26.6 (*q*), 27.2 (*t*), 33.2 (*q*), 33.2 (*s*), 34.1 (*t*), 34.7 (*d*), 35.5 (*t*), 37.0 (*t*), 38.3 (*s*), 39.0 (*s*), 41.6 (*t*), 50.6 (*q*), 51.5 (*d*), 114.6 (*d*), 130.8 (*s*), 137.3 (*s*), 162.0 (*s*), 167.3 (*s*). Anal. Calc. for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.84, H 10.92.

Synthesis of methyl 13Z,17Z- and 13Z,17E-bicyclogeranylfarnesoates 490 and 491.

A solution of sodium methoxide in methanol [105.0 mg (4.56 equiv.) of sodium metal in 2.7 ml of methanol] was slowly added to a stirred solution of *13Z*-bicyclogeranylgeranylacetone **492** (500.0 mg, 1.52 mmol) and trimethylphosphonoacetate (830.1 mg, 4.56 mmol) in benzene (35 ml). After refluxing 2 h, the mixture was cooled, treated with ice-water and extracted with Et_2O. After usual work-up the solvent was removed in vacuum and the residue (491.1 mg) was chromatographed on SiO_2·$AgNO_3$ (18 g) column by elution with light petroleum ether/Et_2O gradient giving, in order of increasing polarity 78.5 mg of 13*Z,*17*Z*-ester **490**, 124.3 mg of mixture of esters **490** and **491** and 315.1 mg of 13*Z,* 17*E*-ester **491**.

(+)-Methyl-13*Z*,17*Z*-bicyclogeranylfarnesoate 490: Colorless viscous liquid; $[\alpha]_D$ +5.2° (c 0.21, $CHCl_3$); IR ν_{max} (liquid film) 840, 890, 1150, 1224, 1380, 1438, 1635, 1730 cm^{-1}; ^{1}H-NMR (300 MHz, selected values) δ_H: 0.67 (3H, s, H_3-22), 0.80 (3H, s, H_3-20), 0.87 (3H, s, H_3-21), 1.68 (3H, bs, H_3-24), 1.87 (3H, bs, H_3-25), 3.67 (3H, s, OMe), 4.57 (1H, bs, H-23a), 4.83 (1H, bs, H-23b), 5.16 (1H, m, H-14), 5.65 (1H, bs, H-18). Anal. Calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; Found: C 80.56, H 10.78.

(+)-Methyl-13Z,17E-bicyclogeranylfarnesoate 491: Colorless viscous liquid; $[\alpha]_D$ +14.7° (c 0.31, $CHCl_3$); IR ν_{max} (liquid film) 889, 1150, 1224, 1382, 1440, 1648, 1724 cm^{-1}; ^{1}H-NMR (300 MHz, selected values) δ_H: 0.67 (3H, s, H_3-22), 0.80 (3H, s, H_3-20), 0.87 (3H, s, H_3-21), 1.67 (3H, bs, H_3-24), 2.15 (3H, bs, H_3-25), 3.68 (3H, s, OMe), 4.56 (1H, bs, H-23a), 4.85 (1H, bs, H-23b), 5.07 (1H, m, H-14), 5.66 (1H, bs, H-18). Anal. calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; Found: C 80.63, H 10.79.

Superacidic cyclisation of (+)-methyl-13Z,17Z-bicyclogeranylfarnesoate 490.

A solution of (+)-methyl-13*Z,*17*Z*-bicyclogeranylfarnesoate **490** (40.0 mg, 0.103 mmol) in *i*-$PrNO_2$ (0.7 ml), cooled at -78 °C, was treated with FSO_3H (52.0 mg, 0.52 mmol) in *i*-$PrNO_2$ (0.3 ml), under stirring. After 15 min., the reaction was stopped by adding a solution of Et_3N (1.0 ml) in

light petroleum ether (1.0 ml). The usual work up gave 39.4 mg of a crude residue, which was used in the next step without any purification. The residue (39.4 mg) was dissolved in EtOH (0.8 ml) and 10% KOH/EtOH solution (2.5 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 38.7 mg of crude reaction product, which was chromatographed on a SiO_2 (1.0 g) column. Elution with a light petroleum ether/Et_2O gradient gave, in order of increasing polarity, 10.4 mg (26%) of ester **344**, which showed spectral data (MS, IR, ^{1}H- and ^{13}C-NMR) identical with those reported in literature [103] and 25.2 mg (63%) of acid-containing fraction.

(-)-Methyl-19α-scalar-16-enoate 344: Colorless viscous liquid; $[\alpha]_D$ -22.6° (c 0.20, $CHCl_3$), lit. [103] $[\alpha]_D$ -26.5° (c 2.3, $CHCl_3$); ^{1}H-NMR (300 MHz, selected values) δ_H: 0.79 (3H, s, H_3-20), 0.83 (6H, s, H_3-21 and H_3-22), 0.89 (3H, s, H_3-23), 0.91 (3H, s, H_3-24), 1.60 (3H, s, H_3-25), 2.47 (1H, bs, H-18), 3.69 (3H, s, OMe), 5.58 (1H, bs, H-16); ^{13}C-NMR (75.5 MHz) δ_C: 174.8, 128.5, 124.6, 61.9, 60.8, 56.1, 51.4, 46.7, 42.1, 41.6, 39.7, 39.2, 37.5, 37.4, 36.4, 33.4, 33.3, 22.9, 22.6, 22.4, 21.3, 18.6, 18.2, 17.4, 17.0, 16.5. The acid fraction (25.2 mg), was treated with a saturated solution of CH_2N_2 in Et_2O (2.0 ml). After 20 min., the solvent was removed *in vacuum* and residue was purified on a column with SiO_2 (0.5 g) (light petroleum ether as eluent) to give 24.5 mg of mixture containing the ester **488**, which was further submitted to HPLC purification [semipreparative Nova-Pack C-18 column, MeOH/H_2O (95:5), flow rate 1.5 ml/min, affording pure ester **488** (15.6 mg).

(+)-Methyl-15α-cheilantha-12,17Z-dienoate 488: Colorless viscous liquid; $[\alpha]_D$ +54.1° (c 0.2, $CHCl_3$); IR ν_{max} (liquid film) 857, 1155, 1236, 1382, 1443, 1660, 1724 cm^{-1}; ^{1}H- and ^{13}C-NMR data (see Table 3.2); EIMS *m/z* (%) 386 (M^+, 5), 371 (5), 273 (8), 259 (15), 220 (98), 205 (100), 177 (58), 145 (72), 105 (88), 73 (91). HREIMS: 386.3195, calcd. for $C_{26}H_{42}O_2$ 386.3185.

Superacidic cyclisation of (+)-methyl 13Z,17E-bicyclogeranylfarnesoate 491.

Using the above described procedure, (+)-methyl 13*Z*,17*E*-bicyclogeranylfarnesoate **491** (60.0 mg, 0.155 mmol) in *i*-$PrNO_2$ (1.0 ml) was cooled at -78°C and treated with FSO_3H (80.2 mg, 0.80 mmol) in *i*-$PrNO_2$ (0.4 ml), under stirring. After 30 min., the reaction was stopped by adding a solution

of Et_3N (1.5 ml) in petroleum ether (1.5 ml). The usual work up gave 58.3 mg of a crude residue, which was used in the next step without any purification. The residue (58.3 mg) was dissolved in EtOH (1.0 ml) and 10% KOH/EtOH solution (3.0 ml) was added. The reaction mixture was refluxed for 2 h. The usual work-up yielded 56.4 mg of crude reaction product, which was chromatographed on SiO_2 (1.2 g) column by elution with light petroleum ether/Et_2O gradient giving, in order of increasing polarity, 14.8 mg (25%) of ester **343**, which showed spectral data (MS, IR, ^{1}H- and ^{13}C-NMR) identical with those described in literature [103] and 37.8 mg (63%) of acid-containing fraction.

(-)-Methyl-19β-scalar-16-enoate 343: Colorless crystals, m.p. 170-171.5°C (from light petroleum ether), [lit. [103] m.p. 167-169 °C (from light petroleum ether), lit. [104] m.p. 165-169 °C (from light petroleum ether)]; $[\alpha]_D$ +62.4° (c 0.43, $CHCl_3$) [lit. [103] $[\alpha]_D$ +65.7° (c 3.6, $CHCl_3$)]; ^{1}H-NMR (400 MHz, selected values) δ_H: 0.80 (3H, s, H_3-20), 0.83 (6H, s, H_3-21 and H_3-22), 0.91 (3H, s, H_3-23), 0.92 (3H, s, H_3-24), 1.59 (3H, bs, H_3-25), 2.89 (1H, bs, H-18), 3.66 (3H, s, OMe), 5.51 (1H, bs, H-16); ^{13}C-NMR (100 MHz) δ_C: 173.4, 128.9, 124.0, 62.6, 61.2, 56.5, 54.8, 51.0, 42.2, 41.9, 41.8, 39.9, 37.7, 37.4, 36.3, 33.3 (2C), 22.6, 21.4, 21.2, 18.6, 18.2, 17.5, 16.9, 16.4, 15.4. To an aliquot of the above acid-containing fraction (20.0 mg, 0.054 mmol) in Et_2O (0.5 ml) was added a saturated solution of CH_2N_2 in Et_2O (1.0 ml). After 20 min., the solvent was removed *in vacuum* to give 20.4 mg of residue, which was purified on a SiO_2 column (0.5 g), (light petroleum ether as eluent) to give 18.9 mg (91%) of methyl ester **489**.

(+)-Methyl-24α,15α-23(8→14)abeocheilantha-8(9),17E-dienoate 489: Colorless crystals, m.p. 110-111 °C (from light petroleum ether); $[\alpha]_D$ +22.3° (c 0.31, $CHCl_3$); IR ν_{max} (liquid film) 865, 1151, 1225, 1379, 1436, 1648, 1722 cm^{-1}; ^{1}H- and ^{13}C-NMR data (see Table 3.1). Anal. calcd for $C_{26}H_{42}O_2$: C 80.77, H 10.94; found: C 80.81, H 10.84.

Horner olefination of the mixture of ketones 506. Mixture of isomeric methylbicyclogeranylfarnesoates 507 and 508.

The mixture of ketones **506** (4.3 g, 12.95 mmol), obtained from 5 g of sclareol **247** according to the known methodology, was dissolved in 230 ml of dry benzene, trimethylphosphonoacetate (6.33 ml, 39.13 mmol) was added, followed by a solution of NaOMe obtained from 0.9 g (39.13 mmol) of Na dissolved in 23 ml of methanol. The reaction mixture was refluxed under nitrogen for 2 hours. Usual work-up , followed by flash chromatography on Si gel provided 4.578 g (11.87 mmol) of the mixture of esters **507** and **508** which was identified by TLC comparison with an authentic sample of pure E-isomer **508**.

Superacidic cyclization of the mixture of isomeric methylbicyclogeranylfarnesoates 507 and 508.

The mixture of esters **507** and **508** (3.978 g, 10.31 mmol) was dissolved in 35 ml dichloromethane and thermostated at -78 ºC. To this cooled solution, a solution of 2.96 ml (51.53 mmol) of fluorosulfonic acid in 10 ml of 2-nitropropane, chilled at the same temperature was added dropwise. The reaction mixture was stirred at -78 ºC for 25 minutes, then quenched with a solution of triethylamine (16 ml, 155 mmol) in hexane (16 ml). Usual work-up gave the crude reaction product, that was hydrolyzed by refluxing for two hours with a solution of 2.073 g NaOH (51.81 mmol) in 20 ml ethanol. Usual work-up and separation of the acidic part gave the crude mixture of scalaranic esters **343** and **344** in the neutral part, which was submitted to flash chromatography on Si gel. Elution with 3% EtOAc in petroleum ether gave 1.8 g (4.66 mmol) of pure ester **343** which was identified by TLC comparison with an available sample.

Superacidic cyclisation of *E,E,E,E*-8-phenylsulfonyl-geranylfarnesyl tetrahydropyranyl ether 509.

A solution of *E,E,E,E*-8-phenylsulfonylgeranylfarnesyl tetrahydropyranyl ether **509** (85 mg, 0.146 mmol) in *i*-$PrNO_2$ (1.4 mL), cooled at -78°C, was treated with a cooled at the same temperature solution of FSO_3H (37 mg, 0.37 mmol) in *i*-$PrNO_2$ (0.1 mL), under stirring. After 15 min, the reaction was stopped by adding a solution of Et_3N-hexane (1:1) (1.0 mL) in light petroleum ether (2.5 mL). The usual work-up yielded crude reaction product (100 mg), which was chromatographed on a silica gel column (4 g). Elution with a light petroleum ether/EtOAc gradient gave, in order of increasing

polarity, 13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesyl tetrahydropyranyl ether, (9 mg, 8%) and 13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesol **463** (21 mg, 25%).

13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesyl tetrahydropyranyl ether: Colorless oil. IR liquid film, (ν, см$^{-1}$): 2927, 2854, 1446, 1378, 1304, 1146, 1086. ^{1}H NMR (300 MHz, δ_H, J/Hz): 0.80 (3H, *s*, H_3-21), 0.87 (3H, *s*, H_3-23), 1.05 (3H, *s*, H_3-22), 1.52 (3H, *s*, H_3-24), 1.57 (3H, *s*, H_3-20), 1.63 (3H, *s*, H_3-25), 3.15-3.30 (2H, m, H_2-5"), 3.38 (1H, *dd*, J_1 = 6.9, J_2 = 11.2, H_A-19), 3.44 (1H, *dd*, J_1 = 3.8, J_2 = 11.2, H_B-19), 3.60-3.67 (1H, *m*, H-12), 4.80-4.86 (1H, *m*, H-1"), 5.21 (1H, *t*, *J* = 5.6, H-14), 5.32 (1H, *m*, H-18), 7.54-7.88 (5H, *m*, Ar-H). ^{13}C NMR (75.5 MHz, δ_C, ppm): 15.5 (q, C-25), 16.7 (t, C-2), 19.6 (t, C-4"), 19.7 (t, C-6), 20.1 (q, C-21), 20.4 (q, C-24), 21.1 (q, C-23), 24.4 (t, C-11), 26.7 (q, C-20), 24.5 (t, C-3"), 26.8 (t, C-15), 29.5 (t, C-2"), 33.0 (q, C-22), 33.1 (t, C-7), 33.2 (s, C-4), 34.9 (t, C-1), 38.8 (s, C-10), 45.5 (t, C-16), 46.3 (t, C-3), 50.8 (d, C-5), 52.3 (d, C-12), 59.7 (t, C-19), 63.3 (t, C-5"), 97.1 (d, C-1"), 120.4 (d, C-18), 127.7 (d, C-14), 128.5 (s, C-8), 129.1 (d, C-2' and C-6'), 129.3 (d, C-3' and C-5'), 133.8 (s, C-9), 134.6 (s, C-13), 135.3 (s, C-17), 135.6 (d, C-4'), 139.8 (s, C-1'). Found (%):C 74.24; H 9.28. $C_{36}H_{54}SO_4$. Calculated (%):C 74.18; H 9.34.

13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesol 463: Colorless oil. IR liquid film, (ν, см$^{-1}$): 3449, 2931, 2856, 1447, 1380, 1304, 1145, 1085, 895. ^{1}H NMR (300 MHz, δ_H, J/Hz): 0.84 (3H, *s*, H_3-21), 0.88 (3H, *s*, H_3-23), 1.08 (3H, *s*, H_3-22), 1.52 (3H, *s*, H_3-24), 1.57 (3H, *s*, H_3-20), 1.64 (3H, *s*, H_3-25), 3.33 – 3,49 (2H, *m*, H_2-19), 3.98 (1H, *d*, *J* = 9.8, H-12), 5.19-5.24 (1H, *m*, H-14), 5.27-5.35 (1H, *m*, H-18), 7.53-7.89 (5H, *m*, Ar-H). ^{13}C NMR (75.5 MHz, δ_C, ppm): 14.1 (q, C-25), 16.4 (t, C-2), 18.7 (t, C-6), 19.8 (q, C-21), 20.0 (q, C-24), 21.6 (q, C-23), 24.9 (t, C-11), 25.2 (q, C-20), 27.7 (t, C-15), 32.3 (q, C-22), 32.4 (t, C-7), 33.3 (s, C-4), 34.4 (t, C-1), 38.8 (s, C-10), 44.3 (t, C-16), 46.0 (t, C-3), 51.3 (d, C-5), 52.2 (d, C-12), 59.4 (t, C-19), 118.4 (d, C-18), 122.6 (d, C-14), 126.9 (s, C-8), 129.3 (d, C-2' and C-6'), 129.5 (d, C-3' and C-5'), 131.4 (s, C-9), 132.3 (s, C-13), 133.3 (s, C-17), 137.2 (d, C-4'), 140.0 (s, C-1'). Found (%): C, 74.72; H,9.24. $C_{31}H_{46}SO_3$. Calculated (%):C 74.65; H 9.30.

Deprotection of 13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesyl tetrahydropyranyl ether.

13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesyl tetrahydropyranyl ether (21 mg, 0.036 mmol) was dissolved in methanol (1.5 mL) and PTSA (1 mg, 0.006 mmol) was added at room

temperature in nitrogen atmosphere. The mixture was stirred at room temperature for 12 h and work up as usual. The crude product (18 mg) was purified by chromatography on silica gel column (0.3 g). Using petroleum ether/EtOAc gradient chromatography the 13*E*,17*E*-12-phenylsulfonylbicyclogeranylfarnesol **463**, (15.1 mg, 85%) was obtained, which showed spectral data (IR, ^{1}H and ^{13}C NMR) identical with those obtained from the cyclization mixture.

Superacid Cyclization of Aliphatic Sesquiterpenoids in Ionic Liquids. General Method.

Solutions of **2**, **10**, **511**, **512** in the appropriate volume of ionic liquids **513** or **514** and CH_2Cl_2 were cooled to the temperatures listed in Table 3.3, stirred, and treated with the corresponding volume of fluorosulfonic acid (5 equiv.) in CH_2Cl_2 cooled to the same temperature. The mixtures were stirred for the times shown in Table 3.3, treated with Et_3N (0.75 equiv.), and extracted with hexane (3 × 25 mL). The hexane extract was washed successively with water, H_2SO_4 solution (10%), water, saturated NaHCO3 solution, and water, dried over anhydrous Na_2SO_4, and filtered. Solvent was removed *in vacuum*. The reaction products were chromatographed over Si-gel. Table 3.3 lists the results.

(±)-Drimenol 515 from 10: IR spectrum (ν, cm^{-1}): 3627, 3450, 1664, 1030, 834. ^{1}H NMR spectrum (δ, ppm): 0.80 (3H, s), 0.86 (6H, s), 1.76 (3H, s), 2.20 (1H, br.s), 3.67 (2H, m), 5.38 (1H, m). Compound **515** was identified by comparison of the spectral properties with those in the literature [107].

(±)-Driman-8a,11-diol 11-Monoacetate 516 from 511: IR spectrum (ν, cm^{-1}): 3585, 3485, 1735, 1240, 1030. ^{1}H NMR spectrum (δ, ppm): 0.78 (3H, s), 0.83 (3H, s), 0.85 (3H, s), 1.17 (3H, s), 2.02 (3H, s), 3.44 (2H, m). Compound **516** was identified by comparison of the spectral properties with those in the literature [107].

(±)-Drimenylphenylsulfone 517 from 512: IR spectrum (ν, cm^{-1}): 1320, 1145. ^{1}H NMR spectrum (δ, ppm): 0.68 (3H, s), 0.83 (3H, s), 0.86 (3H, s), 1.70 (3H, s), 2.63 (1H, br.s), 3.12 (2H, d, J = 5), 5.48 (1H, br.s), 7.52-7.93 (5H, m). Compound **517** was identified by comparison of the spectral properties with those in the literature [161].

(±)-Methyldrim-7-en-11-oate 518 from 2: IR spectrum (ν, cm^{-1}): 1730, 1640, 1380, 1362, 860. ^{1}H NMR spectrum (δ, ppm): 0.90 (6H, s), 0.95 (3H, s), 1.58 (3H, s), 2.88 (1H, br.s), 3.63 (3H, s), 5.46 (1H, m). Compound **518** was identified by comparison of the spectral properties with those in the literature [162].

(±)-β-Cyclofarnesoic Acid 520 from 2: IR spectrum (ν, cm^{-1}): 1244, 1423, 1635, 1685, 2866, 2927, 2958, 3411, 3469. ^{1}H NMR spectrum (δ, ppm): 1.00 (6H, s), 1.39-1.45 (2H, m), 1.52-1.59 (2H, m), 1.61 (3H, s), 1.91 (2H, t, J = 6), 2.1-2.19 (5H, m), 2.21 (3H, d, J = 1.2), 5.73 (1H, d, J = 1.2). ^{13}C NMR spectrum (75 MHz, δ, ppm): 19.39, 19.60, 19.96, 27.14, 28.71, 32.91, 35.18, 39.90, 41.91, 114.69, 128.17, 136.17, 164.02, 172.38.

(±)-Methyl-β-cyclofarnesoate 519 from 2: IR spectrum (ν, cm^{-1}): 1028, 1070, 1147, 1221, 1358, 1383, 1435, 1647, 1720, 2866, 2935. ^{1}H NMR spectrum (δ, ppm): 0.99 (6H, s), 1.39-1.41 (2H, m), 1.51-1.59 (2H, m), 1.60 (3H, s), 1.91 (2H, t, J = 6), 2.1-2.19 (4H, m), 2.20 (3H, d, J = 1.2), 3.69 (3H, s), 5.70 (1H, d, J = 1.2). ^{13}C NMR spectrum (75 MHz, δ, ppm): 19.05, 19.59, 19.93, 27.17, 28.69, 32.89, 35.15, 39.89, 41.60, 50.95, 114.71, 128.04, 136.26, 161.18, 167.52.

3.4 Conclusions to chapter 3

A very selective process of directed cyclization of a linear sesquiterpenic farnesol derivative has been shown to occur with the formation of a monocyclic structure with the pendant terminal isoprenyl unit [124]. A selective protonation of the internal double bond of the substrate, followed by a single cyclization event was achieved, due to the inhibition of the terminal isoprenyl unit by an additional acetoxy- functional group at the ω- end of the linear structure.

A biomimetic synthetic route to compounds of sacculatane structure has been elaborated [125]. The proposed synthesis of sacculatane compounds involves 10 synthetic steps starting with geranyllinalool **441**, and could be used in the synthesis of diverse members of sacculatane family. The specific value of this example is given by the unique reaction mechanism, which proves the principle of functional group involvement into directing cyclisation selectivity.

A totally different cyclization mechanism was demonstrated by the low temperature superacidic cyclization of sesterterpenic open chain substrates with cis-configured internal double bonds [146], [147]. These structural features resulted in a controlled suspension of the cyclization casade to tricyclic products of cheilanthane family. These results provide an additional support of a biogenetical relationship between long chain polyprenols found in plants and polycyclic compounds isolated from different natural sources, including fossil sediments. This effect of the double bond configuration was also confirmed in the case of bicyclic optically active sesterterpenic substrates [152].

The configuration of internal Δ^{13}-double bond does not influence the mode of C/D rings junction in the tetracyclic scalarane sesterterpenes: the 13-*cis*- isomers give the same C/D trans-fusion as in the case of 13-*trans*- isomers cyclisation. For the synthesis of scalaranic compounds this is a very important finding and we explore it for the elaboration of a practical procedure aiming both scalaranes and cheilanthanes [155].

A heteroatomic functional group, intercalated into the linear chain of higher terpenoids, strongly influences the superacidic cyclization of such substrates, inhibiting in fact the propagation of cyclization cascade. It was demonstrated on the example of the corresponding phenylsulfone **509**, which under treatment with fluorosulfonic acid at low temperature cyclized to the bicyclic sulfone **463** [120],[121].

Basing on these results, we can conclude that heteroatomic functional groups, properly placed within the linear terpenic chain can direct the biomimetic cyclization processes in a predictable way: functional groups at the terminal extremity promote the selective initiation of the cyclization sequence from an internal double bond, while functional groups intercalated in the chain selectively suspend the cyclization sequence.

It was demonstrated for the first time that ionic liquids can be used successfully for superacid cyclization of terpene esters and phenylsulfones, i.e., compounds containing functional groups that are stable in the acidic medium [159],[160].

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

As it was pointed out in the introductory part of this work, the impressive diversity of terpenoids structures is due not only to cyclizations but rearrangements too. In fact, this kind of transformations represent the most intriguing and fascinating from mechanistic point of view and most challenging from the point of view of biomimetic synthesis. The major difficulty connected to *in vitro* reproduction of biosynthetic pathways based on rearrangements, stems on the multitude of reaction possibilities that can be potentially viable and an exact prediction of the real reactivity based on rearrangement processes is not always an easy task. On the other hand, this specific feature of terpene reactivity provides a broad field to the synthetic chemist's creativity and imagination. Inspired examples of synthetic rearrangement processes are characterized first of all by the amplitude of functional group migration paths and reaction conditions which ensure high selectivity of rearranged product and its overall yield. The most relevant examples of synthetic schemes based on rearrangement processes as key transformations are provided below to show our approach towards several structural families of terpenes.

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

Austrodoric acid **521** and austrodoral **522** (Figure 4.1) are two related nor-sesquiterpenes recently from the skin extract of Antarctic dorid nudibranch *Austrodoris kerguelenensis* [163]. They possess a bicyclic structure with the unprecedented carbon backbone, which could biogenetically arise from a drimanic-like framework by a ring contraction process.

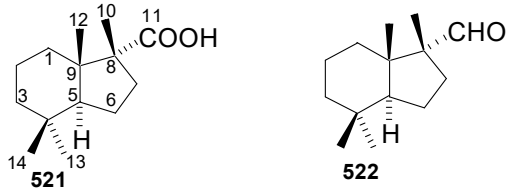


Figure 4.1**.** The structure of austrodoric acid **521** and austrodoral **522**.

The relative stereochemistry of natural nor-sesquiterpenes **521** and **522** was established on the basis of spectral data, whereas their absolute stereochemistry remained undetermined. A role of stress metabolites was suggested for these molecules that were detected in high levels in some selected specimens of *A. kerguelenensis*, which were kept in captivity in aquarium [163]. However, the biological activities of both compounds could not be evaluated due to their degradation during work-up. With the aim at both obtaining larger amounts of such molecules to test their biological potential and determining their absolute stereochemistry, a synthetic study towards this rearranged skeleton has been carried out [164],[165].

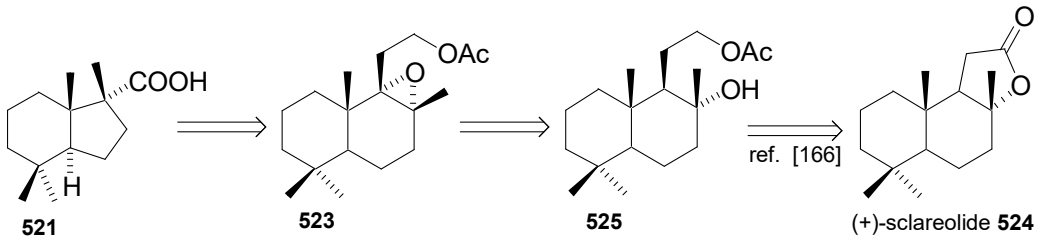


Figure 4.2. Retrosynthetic analysis of austrodoric acid **521**.

As shown in Figure 4.2, the key step of our retrosynthetic analysis is the ring contraction of the homo-drimanic epoxide **523** followed by the cleavage of the side chain to give the desired final product. The key intermediate **523** could be easily obtained from commercial (+)-sclareolide **524**, via the acetate **525**.

Preparation of compound **523** was carried out as shown in Figure 4.3, starting from compound **525**, which was obtained from commercial (+)-sclareolide **524** according to the literature procedure [167]. Selective dehydration of acetate **525** to the corresponding tetra-substituted olefin **526** was performed with iodine in refluxing benzene. As has been reported [168], the direction of this kind of dehydration strongly depends on the refluxing temperature conditions. Therefore, we have investigated this reaction using an oil heating bath adjusted at different temperatures: from 85 ºC (minimum refluxing rate) to 127 ºC (the maximum refluxing rate). As expected, at the minimum refluxing rate a mixture of isomeric dehydrated compounds was obtained, while dehydration performed at the maximum refluxing rate (heating bath temperature 127 ºC) gave the thermodynamically more favored isomer **526** almost exclusively (90% yield). Treatment of compound **526** with *m*-CPBA at 0 ºC for 2 h gave a mixture of the corresponding epoxides **523** and **527** (ratio

3:1 by ^{1}H NMR). Unfortunately, the separation of this mixture proved impossible by flash chromatography.

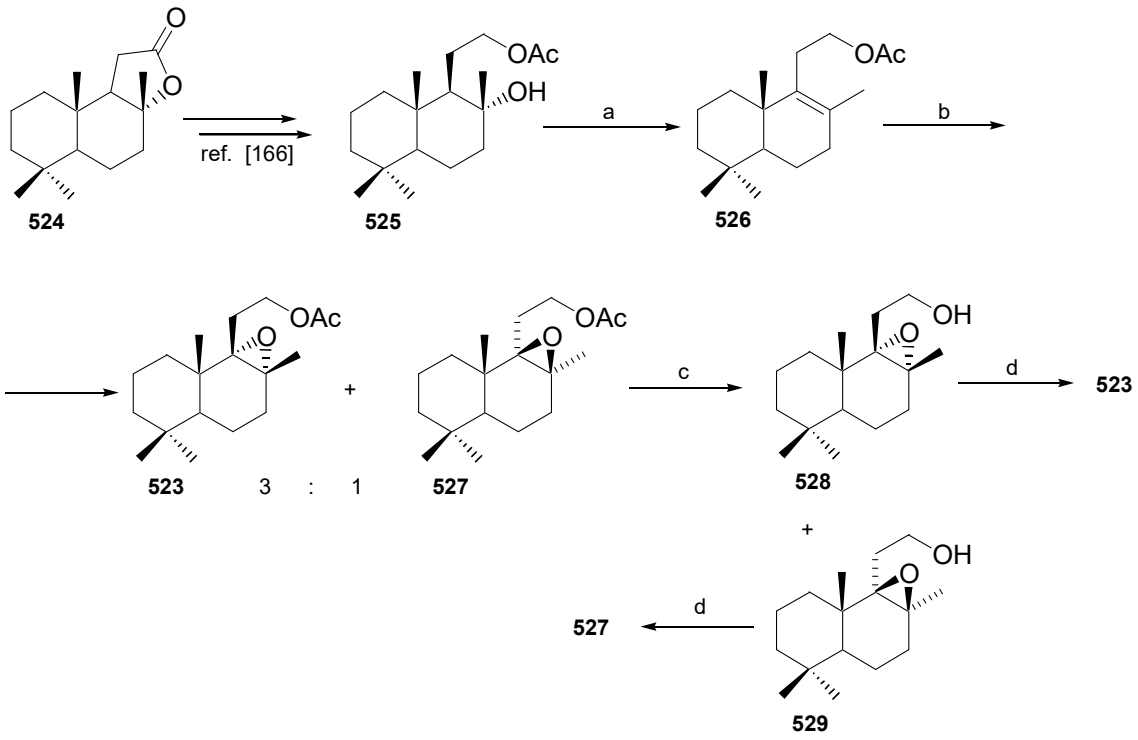


Figure 4.3. Synthesis substrates for ring contraction towards austrodoric acid. Reagents and conditions: (a) I_2/Ph-H, reflux, 90%; (b) *m*-CPBA, 0 ºC, 90%; (c) K_2CO_3, MeOH, r.t., 2 h., 89%; (d) Ac_2O/Py, r.t., 97%.

We decided to hydrolyze the mixture and separate the corresponding epoxy-alcohols **528** and **529** by silica-gel column chromatography (ethyl acetate/light petroleum ether gradient). Acetylation of the individual epoxyalcohols **528** and **529** provided pure epoxyacetates **523** (97% yield) and **527** (97% yield). Epoxide **523** was considered as the precursor for the subsequent steps, as shown in Figure 4.4. The ring contraction reaction that has been reported to occur with different reagents [89],[169],[170] was in this case performed by using a complex Lewis acid, *tris*-(p-bromo-phenyl)-aminiumhexachloroantimonate ($RSbCl_6$), which has efficiently promoted this kind of isomerization in related epoxides [171]. Treatment of epoxide **523** with a catalytic amount of tris-(p-bromo-phenyl)-aminium-hexachloro-antimonate in DCM at room temperature provided a mixture of isomerization

products that was subjected to chromatography on a silica-gel column. Pure rearranged acetoxy-ketone **530** was obtained by elution with 3% ethylacetate in benzene.

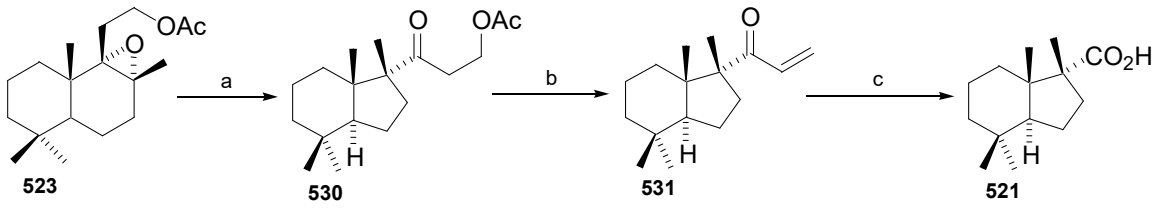


Figure 4.4. Synthesis of austrodoric acid **521**. Ring contraction and end game. Reagents and conditions: (a) *tris*-(p-bromo-phenyl)-aminiumhexachloroantimonate ($RSbCl_6$), r.t., 45%; (b) NaH/THF, 52%; (c) $OsO_4/NaIO_4$, 70%.

The next objective was the cleavage of the side chain of the acetoxy-ketone **530**. The formation of the silyl enolether derivative of **530**, which could be submitted to a subsequent oxidative degradation, was examined [172]. But the treatment of **530** with tert-butyldimethylsilyl chloride in the presence of sodium hydride (6 equiv.) did not give the expected silyl enolether, the α,β-unsaturated ketone **531** being the predominating reaction product. The explanation for this reaction course can most probably be found on examining the steric hindrance around the oxygen atom of the ketone functionality. Under these circumstances, the formation of a bulky TBDMS enolether did not occur. On the contrary, the anion formed under the action of sodium hydride was stabilized by the elimination of the acetate group.

However, having the keto-olefin **531** in our hands, we decided to carry out the double bond hydroxylation followed by an oxidative degradation of diol derivative. This was achieved in a one-pot procedure, employing a catalytic amount of osmium tetraoxide for double bond hydroxylation, along with an excess of sodium periodate as both co-oxidant and reagent for oxidative cleavage of the arising hydroxyketone. The reaction mixture was stirred for 12 h in *tert*-butanol at 45 °C, at the end of this period the initial keto-olefin **531** was consumed. Usual work-up followed by flash chromatography of crude reaction mixture provided pure austrodoric acid **521**. Spectral data (^1H NMR, ^{13}C NMR, IR, MS) of synthetic product were identical with those of natural sample isolated from the nudibranch *A. kerguelenensis*, whereas the specific rotation value was slightly different: $[\alpha]_D$ synth. -2 (c 0.15, $CHCl_3$); $[\alpha]_D$ nat. -16 (c 0.1, $CHCl_3$) [163]. However, the absolute stereochemistry of natural austrodoric acid was definitively established as that reported by comparing the CD curve

with that of synthetic product. Identical profiles were obtained for both natural and synthetic samples (CD synthetic sample $[\eta]_{214}$ (n-hexane) -470; CD natural sample $[\eta]_{212}$ (n-hexane) -310).

In order to establish the absolute stereochemistry of austrodoral **522** and also to provide larger amounts of this compound for evaluating its biological activity, we planned synthetic studies towards this aldehyde. Unfortunately, the conversion of austrodoric acid **521**, or the corresponding methyl ester into austrodoral **522** did not occur as expected, most probably due to steric hindrance of the tertiary carboxyl group. Therefore, with the aim at obtaining the aldehyde **522** we decided to explore two different approaches starting from the easily available drimanic substratum **532**. We report here the results of this investigation [173].

The retrosynthetic analysis (Figure 4.5) assumed two different pathways (a) and (b), both starting from the drimane oxyacetate **532** easily available from the commercial (+)-sclareolide **524** by a known procedure [174]. According to the approach (a), oxyacetate **532** should be transformed into albicanol **533** as reported in the literature [175] and subsequently degraded to *nor*-drimane epoxide **534** to give the desired aldehyde **522** after ring contraction step. In the approach (b) aldehyde **522** should be obtained by ring contraction of drimane epoxide **535** formed from oxyacetate **532** via drimenol acetate **536**.

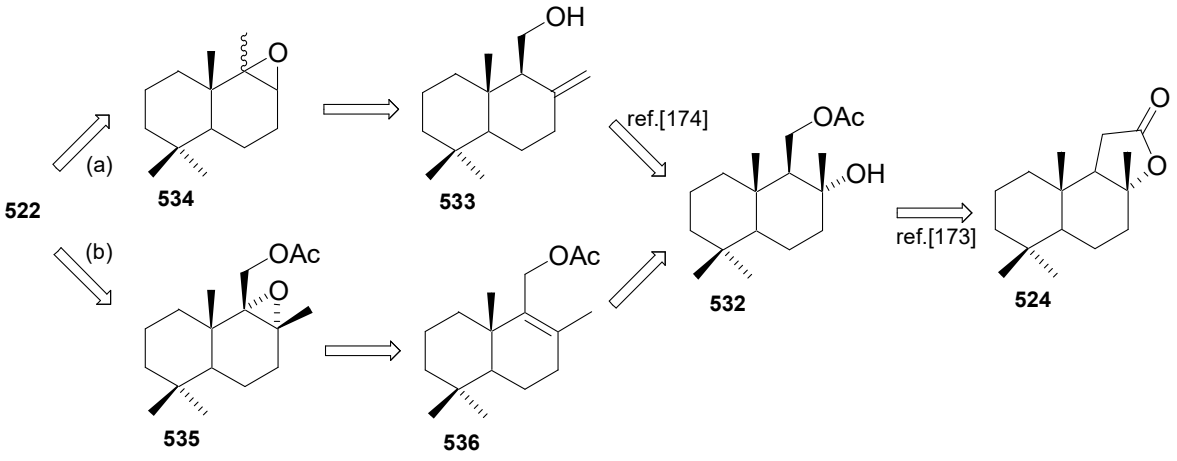


Figure 4.5. Retrosynthetic scheme towards austrodoral **522**.

The approach (a) was considered first. Albicanol **533**, which was obtained according to the literature procedure [175], was submitted to mesylation to give derivative **537** that was subsequently reduced providing the hydrocarbon sesquiterpene **538** (Figure 4.6). The hydroxylation of the double

bond and the cleavage of the resulting diol was performed by osmium tetraoxide/sodium periodate in one pot procedure, as reported in the literature [176]. Ketone **539** was reduced by sodium borohydride affording a mixture of epimeric alcohols **540a** and **540b** (ratio **540a**/**540b**, 2:1).

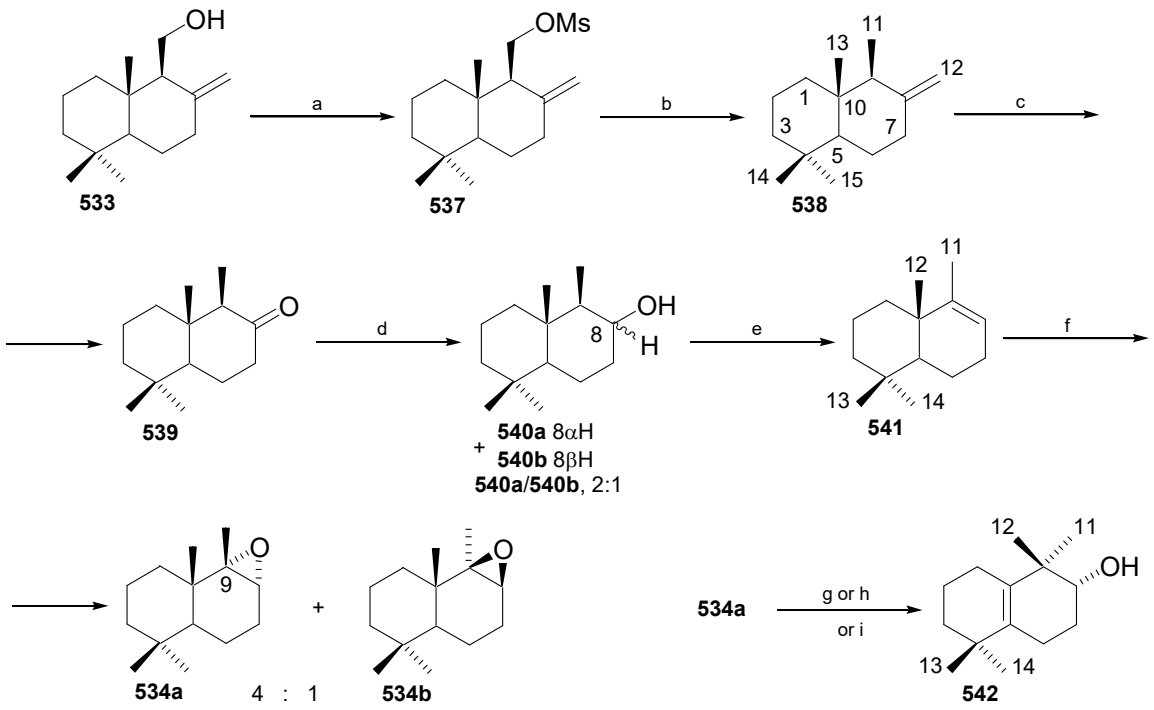


Figure 4.6. Synthetic pathway leading to rearranged compound **542** without ring contraction. Reagents and conditions: (a) MsCl/Py, DMAP, 0 ºC, 4 h, 84%; (b) $LiAlH_4$, Et_2O, reflux, 4 h, 93%; (c) OsO_4, $NaIO_4$/*t*-BuOH, r.t., 48 h, 93%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -50 ºC, 1 h, 96%; (e) DEAD, Ph_3P/THF, reflux, 4 h, 88%; (f) *m*-CPBA, Na_2HPO_4, $CHCl_3$, 0°C, 2h, 87%; (g) $BF_3 \cdot Et_2O$, C_6H_6, r.t., 40 min.; (h) $BF_3 \cdot Et_2O$, $MeNO_2$, -23 ºC, 40 min.; (i) FSO_3H, *i*-$PrNO_2$, -78 ºC, 15 min, then Et_3N.

This unresolved mixture was subjected to dehydration under the action of diethylazadicarboxylate in refluxing tetrahydrofuran [176], to give as main product (+)-*nor*-sesquiterpene **541**, which was identified by comparison of spectral data with those reported in the literature for the racemic form obtained as intermediate in the synthesis of fungitoxic sesquiterpene hydroquinones [177]. According to literature procedure [177], compound **541** was subsequently treated with buffered *m*-chloroperoxybenzoic acid to give a mixture of diastereoisomeric epoxides **534a** and **534b** (ratio **534a**/**534b**, 4:1). This mixture was submitted without purification to the

following key step involving the skeleton rearrangement by using different acid promoters in different conditions [89], [178], [179]. By analogy with synthesis of austrodoric acid **521** [165], it was expected that the epoxides **534a** and **534b** after opening would provide the contraction product, aldehyde **522**, but the secondary alcohol **542** was obtained as main reaction product.

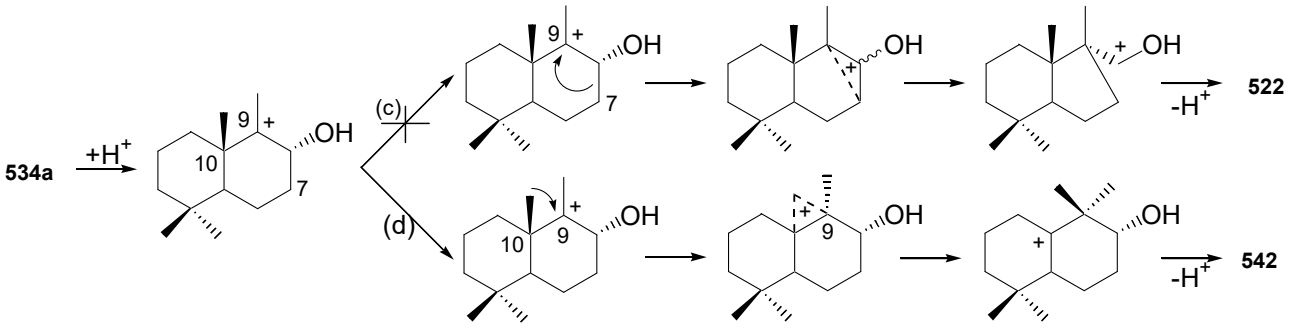


Figure 4.7. Probable reaction mechanism of compound **542** formation.

The formation of compound **542** could be rationalized in terms of stabilization of carbocation at C-9, which was formed by opening of epoxide ring of the main α-epoxide **534a** (Figure 4.7). The expected interaction between the carbonium ion at C-9 and the β-carbon C-7 depicted in pathway (c) did not occur, whereas the stabilization of carbocation at C-9 was obtained by migration of β- methyl group at C-10, pathway (d). The *R* absolute stereochemistry at C-8 required by the course of reaction was suggested by the equatorial orientation of H-8 (^{1}H-NMR, dd, *J*=9, 3 Hz) and confirmed by applying the advanced Mosher method [180],[181] on alcohol **542**. According to MTPA determination rule, the observed values in the ^{1}H NMR chemical shifts of the corresponding *S*-ester and *R*-ester were in agreement with such absolute configuration.

These results prompted us to consider the approach (b) (Figure 4.5) that employs as key step the ring contraction of drimanic epoxide **535** with the subsequent cleavage of the side chain. We used as initial substratum the readily available oxyacetate **532** [174] (Figure 4.8). In order to generate the tetrasubstituted double bond between C-8 and C-9, we tried the dehydration of **532** by iodine in refluxing benzene, using the same conditions as those used for the synthesis of austrodoric acid **521** [165]. But in this case the dehydration reaction did not occur. Although different refluxing conditions were investigated, the desired tetrasubstituted acetate was not formed. At lower refluxing temperatures (heating bath temperature from 85 ºC to 110 ºC) the initial substratum remained intact and at the maximum refluxing rate (127 ºC) a complex mixture of substances was formed. So, we decided to

conduct the dehydration reaction on a different drimane substratum, the hydroxy aldehyde **543** [182], which was prepared starting from 8,11-drimane diol **544** by Swern oxidation.

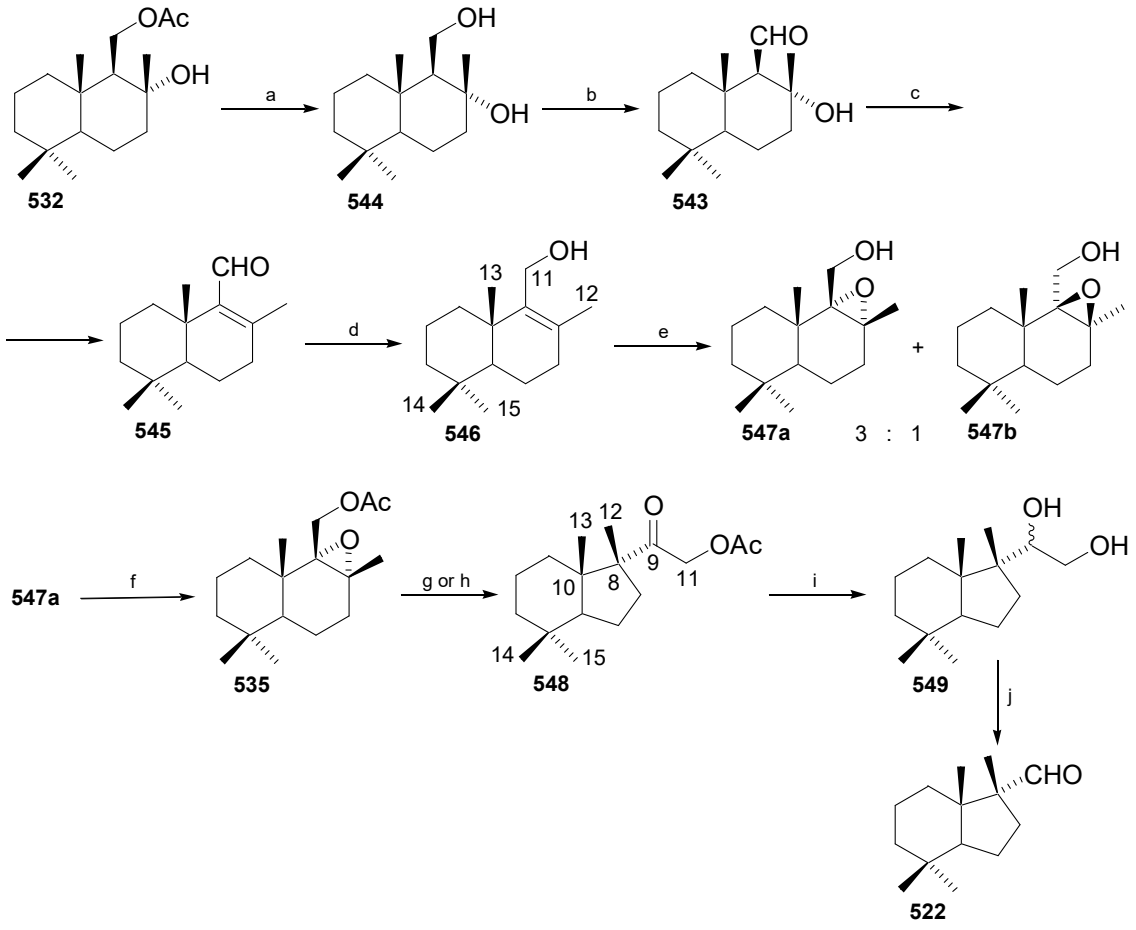


Figure 4.8. Synthesis of austrodoral **522**. Reagents and conditions: (a) NaOH/EtOH, reflux, 97%; (b) Swern oxidation; (c) I_2/C_6H_6, reflux; (d) $NaBH_4$ / EtOH, 83 % after 3 steps; (e) *o*-PPA / Et_2O, 75%, (f) Ac_2O/Py, 89 %; (g) $RSbCl_6$ (cat.), 87 %; (h) FSO_3H (cat.), 100%; (i) $LiAlH_4/Et_2O$, 98%; (j) $NaIO_4$/THF-H_2O, quant.

It has been already reported that aldehyde **543** can be easily dehydrated into the corresponding α,β-unsaturated aldehyde **545** [183] under the action of *p*-toluensulfonic acid in refluxing toluene [184], with a moderate yield of 58%. With the aim at increasing the yield for this step, we decided to use iodine in refluxing benzene as an alternative dehydration agent. Refluxing **543** for two hours at 95 ºC (heating bath temperature) with iodine in benzene provided compound **545** almost quantitatively. Reduction of **545** by sodium borohydride at 0 ºC in ethanol afforded bicyclofarnesol

546 [185]. The overall yield of compound **546** was 83% after 3 steps. The subsequent epoxidation of **546** with a solution of monoperfthalic acid in diethyl ether provided a mixture of isomeric epoxyalcohols **547a** and **547b** (ratio **547a**/**547b**, 3:1). After chromatographic separation, compound **547a** was acetylated to the corresponding derivative **535**. This compound was the substratum for the ring contraction reaction that was first carried out with *tris*-(*p*-bromo-phenyl)-aminium-hexachloro-antimonate ($RSbCl_6$), the same reagent used in the synthesis of austrodoric acid **521** [165]. Treatment of **535** with a catalytic amount of $RSbCl_6$ in dichloromethane at room temperature provided the desired acetoxy-ketone **548** (yield 87%). However, in order to improve the yield of the ring contraction step, we decided to carry out the ring contraction reaction with fluorosulfonic acid (FSO_3H), an agent that we have employed broadly in our laboratories to perform acid induced isomerizations of terpenoids at low temperatures. Treatment of **535** with a catalytic amount of FSO_3H in 2-nitropropane at –78 ºC provided quantitatively acetoxy-ketone **548**. The subsequent conversion of compound **548** to austrodoral **522** comprised the reduction with lithium aluminium hydride and the cleavage of resulting mixture of diols **549** by sodium periodate. Spectral data of synthetic austrodoral **522** (^1H NMR, ^{13}C NMR, MS, $[\alpha]_D$) were identical with those of the natural product [163]. Synthetic austrodoral **522** has been submitted to a preliminary evaluation of biological activity by assaying ichthyotoxicity in the *Gambusia affinis* test [186],[187]. It resulted to be very toxic at 10 ppm.

4.2 Rearangement processes involving functional group migrations.

Examples of deeper skeletal rearrangements are present in diverse synthetic applications of terpenoids, in spite of the difficulties connected to control a cascade of events affecting reaction course and selectivity. They represent a generally accepted biosynthetic pathway to diverse natural compounds and their mimicking also provides an efficient synthetic tool. In particular, the ring contraction reaction that we have successfully exploited [164],[165] for the synthesis of austrodoric acid includes a relevant bio-mimetic approach. The key step of the synthesis was a ring contraction of the homodrimanic substrate **523** under the action of a Lewis acid (Figure 4.9).

The relatively moderate yield of target perhydrindane **530** (cca. 45 %) made us to deeper investigate the secondary products obtained on the acid induced rearrangement of the epoxide **523**. This incursion into the reaction peculiarities led to the identification of several products having the

bicyclic core of halimanes **550**. We have investigated this alternative rearrangement pathway in order to reveal the possibilities to control the selectivity in these rearrangements [188].

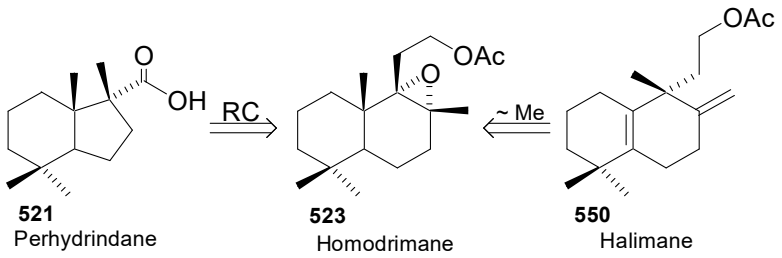


Figure 4.9. Possible rearrangement pathways of homodrimanic epoxide **638**.

Terpenoids of halimanic structure are widely distributed in natural sources [189]. Biosynthetically, they are considered intermediates between labdanes and clerodanes [190], since all arise from enzymatic cyclisation of geranylgeranyl diphosphate to labda-13-en-8-yl diphosphate cation, which can deprotonate to labdadienyl diphosphate or suffer rearrangements to halimanes and clerodanes.

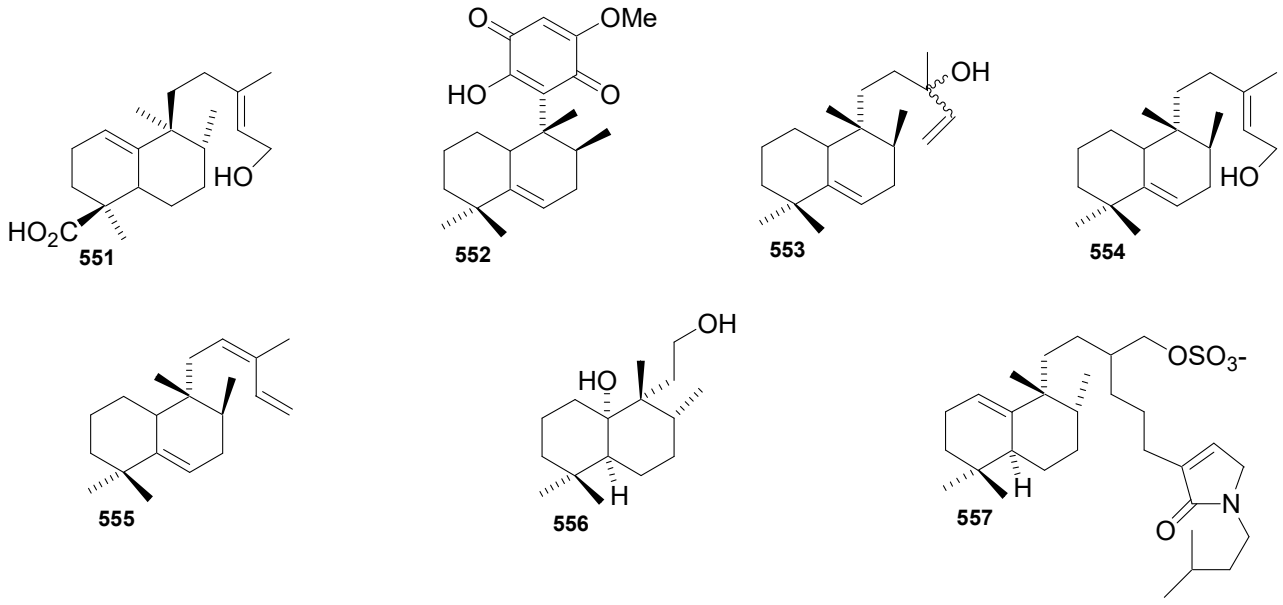


Figure 4.10. Representatives of halimane family of diterpenoids.

From the practical point of view, labdanes are more accessible from different plant sources. But the deeper the skeleton rearrangement of the bicyclic core, the harder to find reliable sources of

corresponding compounds. Halimanes follow this regularity and to date there are not so many readily available representatives. The most relevant is *ent*-halimic acid **551** (Figure 4.10), the main component of *Halimium viscosum*, which was extensively studied as a template for the synthesis of other related terpenes of *ent*-series [191]. As regarding normal halimanes (non-*ent*), their presence was reported only in scarce amounts either in plants or animals [192],[193],[194],[195],[196]. That's why efforts have been undertaken to devise synthetic approaches for reliable production of halimanes of relevant biological activity.

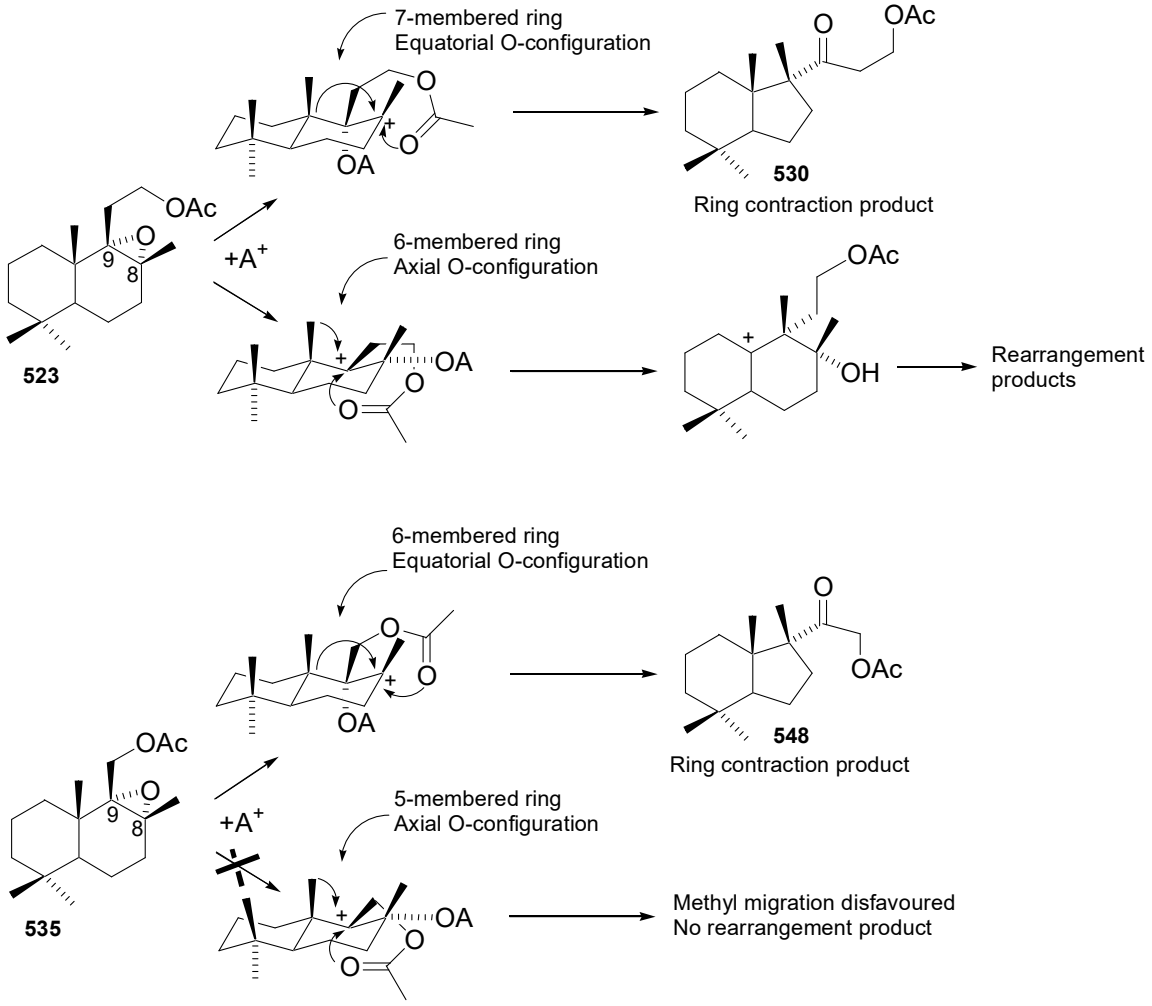


Figure 4.11. Lateral chain assistance of C-8/C-9 epoxide opening in homo- and drimanic substrates.

Among them, one can mention cytotoxic compounds like mamanuthaquinone **552** [197] or antitubercular isotuberculosinol **553** and tuberculosinol **554** [198]. Recent examples of isolated halimanes include tuberculosene **555**, a *Mycobacterium Tuberculosis* halimanic metabolite, which is also regarded as potential inhibitor of macrophage phagocytosis [199],[200]. Current concern about

the tuberculosis danger will stimulate research in this area, including elaboration of alternatives to antibiotic therapies. Besides, interesting compounds with halimanic bicyclic core possessing either degraded lateral chain like euplectellodiol **556** [201] or an additional isoprene residue as of irregularasulfate **557** [202] are also known. Therefore, facile methods for generation of different halimanic compounds in optically active form can contribute to progress in this area.

Most of the reported synthetic methods for halimanes synthesis rely on a *exo*-selective Diels-Alder reaction. Despite the known availability of enantioselective Diels-Alder reactions, all the examples based on this strategy relate to racemic material only [197],[198],[203].

We present below a biomimetic synthesis of optically active halimanic compounds, making use of a rearrangement reaction of the homodrimanic epoxide **523**. It was observed previously, that a similar treatment of the drimanic derivative **535** (Figure 4.8) has led to exclusive formation of perhydrindanic ketone **548** in a quantitative yield [173]. Such a difference in reaction yields on substrates differing only by a single CH_2- group could be only interpreted on the basis of the lateral chain involvement in the stabilization of reaction intermediates. In fact, participation of lateral chains in the stabilization of cyclic carbonium species is a well know effect in different acid induced cyclizations of terpenoids [1], and a possible explanation for the particular case of substrates **523** and **535** could be also thought. Opening of the epoxy-ring in both substrates (Figure 4.11) can follow two possible directions: either at C-8 or C-9 atoms. Basing on the direct substituents character on these atoms, the stability of both is relatively equal. But, if the participation of the lateral chain OAc-group is considered, some differences could be observed.

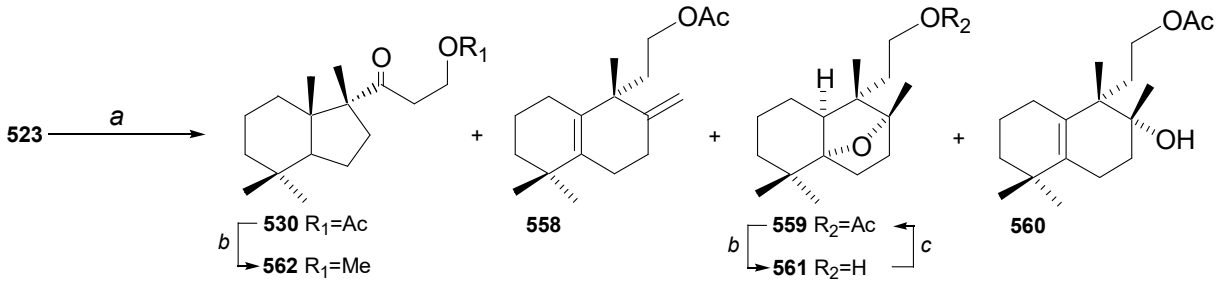


Figure 4.12. Acid-induced rearrangements of homodrimanic epoxide **523**. Reagents and conditions: (a) see Table 4.1; (b) K_2CO_3/MeOH, r.t.; (c) Ac_2O/Py, r.t.

In our opinion, the main factors that cause the stabilization effect of the lateral –OAc group are the ring size and the position of the =O atom in the transition state. A five- or six- membered

transition state, along with equatorial position of oxygen atom should be considered favorable. On comparing substrates **523** and **535**, one can conclude that for drimanic substrate C-8 epoxide opening has both these conditions favorable. For the homodrimanic epoxide, C-8 epoxide opening is favored by equatorial =O disposal, but the 7-membered transition state is not favorable. On the other hand, C-9 opening is favored by the 6-membered transition state but disfavored by the axial disposal of the oxygen atom. Consequently, the rearrangement of **535** is highly selective in providing the hydrindanic compound **548**, while isomerization of **523** occurs with less selectivity and provides opportunities for an alternative reaction course.

We have investigated the reaction of epoxide **523** with different acids. All experiments led to similar reaction products, consisting of mixtures of several compounds (Figure 4.12). But the product composition was affected by inducing acid nature and reaction conditions. It was established, that the yield of ring contraction product **530** was highest on treatment of **523** with fluorosulfonic acid at -78 ºC for 15 min, followed by Et_3N-quenching. Performing the rearrangement reaction at higher temperatures under the action of milder acids increased the yield of halimanic derivatives **558**-**560**. Formation of **560** was detected in lower yields.

Table 4.1. Isomerization experiments of substrate **523**.

N/o	Solvent	Reaction temperature, ºC	Reaction duration, min	Reaction product distribution, %				Acid
				530	558	559	560	
1	DCM	22	60	45	35	20	n.d.	*R-$SbCl_6$
2	2-NO_2-Pr	22	15	44	27	29	n.d.	$BF_3 \cdot Et_2O$
3	$MeNO_2$	0	20	47	18	35	n.d.	$BF_3 \cdot Et_2O$
4	DCM	-20	35	45	18	37	n.d.	$BF_3 \cdot Et_2O$
5	$MeNO_2$	-25	15	50	33	17	n.d.	$BF_3 \cdot Et_2O$
6	$MeNO_2$/2-NO_2-Pr (1:1)	-50	15	50	n.d.	28	22	$BF_3 \cdot Et_2O$
7	$MeNO_2$/2-NO_2-Pr (1:1)	-78÷-40	45	55	n.d.	18	27	$BF_3 \cdot Et_2O$
8	2-NO_2-Pr	-78	15	65	n.d.	35	n.d.	FSO_3H

*R=*tris*-(*p*-bromophenylaminium) cation

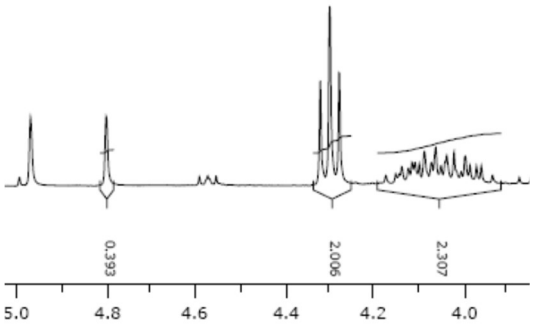
The results of all isomerization experiments are presented in the Table 4.1. The relative ratio between reaction products was determined on the basis of ^{1}H NMR data of crude reaction mixtures,

by integration of selective proton signals (Figure 4.13). Separation of individual compounds posed some difficulties due to similar chromatographic behavior of perhydrindane **530** and oxide **558**. It was relatively easy to isolate unpolar diene **559** and polar hydroxiacetate **560** by column chromatography.

In order to resolve the mixture of **530** and **558** which eluted together, a hydrolysis of the mixture was performed. Standard condition for removal of acetate group (K_2CO_3-MeOH) led to the oxi-alcohol **561** derived from **559**, along with the unexpected methyl ether **562** derived from **530**. The obtained products have been separated by column chromatography and **561** was re-acetylated to regenerate the acetate **559**.

Structural assignment was performed on the basis of extensive NMR experiments (^1H, ^{13}C, DEPT, HSQC, HMBC, COSY, NOESY) on pure compounds (see Table 4.2), as well as on the basis of IR and MS data.

Explanation of these results can be made on mechanistic grounds (Figure 4.11). In order for the substrate **523** to form a ring contracted product, the acid attack on the epoxy-group shall lead to formation of C-8 carbonium ion. It is stabilized by three alkyl groups and by neighboring acetoxy-group. Following rupture of C-9 – C-10 bond and formation of the new C-10 – C-8 bond occurs through the tri-centered cation and after proton expulsion provides the ring contracted perhydrindane **530**.



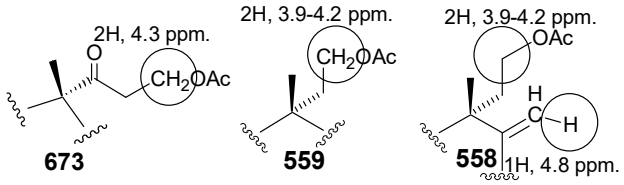


Figure 4.13. Determination of the isomeric product distribution by integration of selective NMR peaks (Table 4.1, entry 3). Peak at 4.8 ppm corresponds to one proton of **558**, the triplet at 4.3 ppm – to two protons of **530** and the multiplet 3.9-4.2 represents additive signals from two CH_2-groups of compounds **558** and **559**.

The other reaction pathway involves carbonium ion formation at C-9, which is also facilitated by three alkyl substituents, but less likely stabilized by acetoxy- group. Instead, it is facilitated by the equatorial disposal of the –OH group and by a facile methyl migration from C-10 to C-9, to give the intermediate carbocation. It can transform either by a following hydride shift and cyclisation through the C-8 - O- atom into oxide **559**, or by deprotonation to **560** which dehydrate into **558**.

Table 4.2. Assignment of NMR spectra for compounds **558-562**.

Carbon atoms	Compounds									
	558		**559***		**560**		**561**		**562**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	26.97	2.02 2.25	24.73		26.44	1.93	24.72	1.31 1.46	33.54	0.89 1.61
2	19.32	1.66	22.43		19.78	1.58	22.45	1.46 1.55	20.05	1.47 1.56
3	39.15	1.44	37.91		39.70	1.40	36.14	1.16 1.26	41.1	0.93 1.37
4	34.67	-	35.60		34.28	-	35.64		33.18	-
5	140.97	-	90.29		134.85	-	90.38		52.50	1.38
6	21.86	2.14	23.22		22.71	2.09	23.20	1.69	21.78	1.38 1.66
7	34.94	1.45 1.55	34.71		33.42	1.74 1.59	34.77	1.90 1.25	31.71	1.22 2.22
8	125.96	-	88.73		73.91	-	89.01		61.43	-
9	35.95	-	42.23		44.65	-	42.33		47.05	-
10	151.94	-	48.98		132.00	-	48.73	1.82	215.21	-
11	37.04	1.69	39.40		35.35	1.89 1.77	43.99	1.52 1.62	41.3	2.7
12	62.09	4.02 4.09	61.97	4.06 4.14	63.67	4.15 4.17	59.72	3.69	68.2	3.54 3.66
13	105.26	4.85 5.02	16.69	1.27	24.41	1.13	17.54	1.29	20.29	1.18
14	26.66	1.10	17.49	0.78	20.71	0.98	17.42	0.77	16.1	0.87
15	28.16	1.04	26.00	1.01	28.50	0.96	26.02	1.01	21.66	0.86
16	27.96	1.03	21.36	1.10	28.42	0.99	21.38	1.10	33.80	0.84
O=C-	171.09	-	171.24	-	171.15	-				
C(O)Me	21.05	2.04	21.12	2.04	21.15	2.02				
-O-Me									58.84	3.32

* No 2D experiments performed. Structure assigned on the basis of related **561**.

Triterpenes are one of the most structurally diverse groups of natural products, with more than 100 skeleta described as natural products [204],[205],[206]. Interest in the biological activities of triterpenoids is permanently fueled by their relevant anti-inflammatory [207], antitumor [208], anti-HIV [209],[210] and insecticidal [211] activities and for treatment of metabolic and vascular diseases as well [212].

In the continuation of our efforts directed to the synthesis of complex terpenes basing on random biomimetic concept, we have investigated the reactivity of the bicyclic triterpenic adduct **467**, which contains two heteroatomic functional groups intercalated in the linear chain [123].

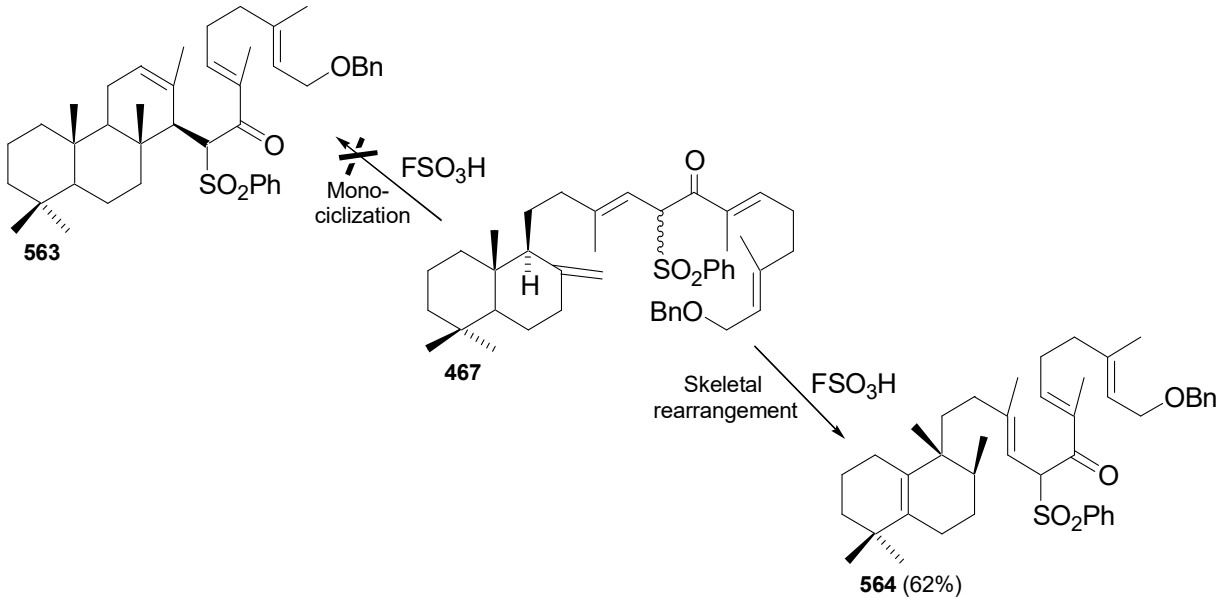


Figure 4.14. Total inhibition of the double bonds in the polyenic chain by the intercalated phenylsulfonyl functional group.

The superacidic treatment of the bicyclic sulfone **467** was addressed in the context of the results obtained with a similar substrate **509**, having a phenylsulfonyl functional group intercalated into the linear isoprenic chain [120],[121]. If expecting only one cyclization event, initiated from the exo-methylenic double bond and de-activation of the last two double bonds in the chain, a tricyclic compound **563** with two prenyl residues of tricyclohexaprenyl family should be formed (Figure 4.14). But contrary to the expectations, superacidic treatment of sulfone **467** also resulted in a bicyclic compound, but with a rearranged carbon skeleton **564**. Its formation involves protonation of the exo-methylenic double bond, followed by a sequence of hydride and methyl shifts. All other double bonds in the lateral chain have been totally inhibited by both sulfone and ketone functional groups and no cyclization event took place. These mechanistic considerations are represented in Figure 4.15. Shortly, the functional groups at C-16 and C-17 in the side chain, are preferentially protonated, leading to dication **A**, which blocks the carbocyclization cascade. In such a manner, only the migration of proton from C-9 to C-8 takes place, producing the carbocation **B**. The latter is subjected to following conversion into the carbocation **C**, as a result of methyl group migration from C-10 to C-9. While „quenching" the carbocation **C**, removal of proton at C-5 occurs and the final product **564** is obtained.

The structure of rearranged product **564** was assigned basing on spectral data. The IR spectrum exhibited absorption bands at 1145, 1385, 1451, 1668, 1793, 2286, 2993 and 3362 cm^{-1}, suggesting the presence of carbonyl-, phenylsulfonyl- and olefinic groups.

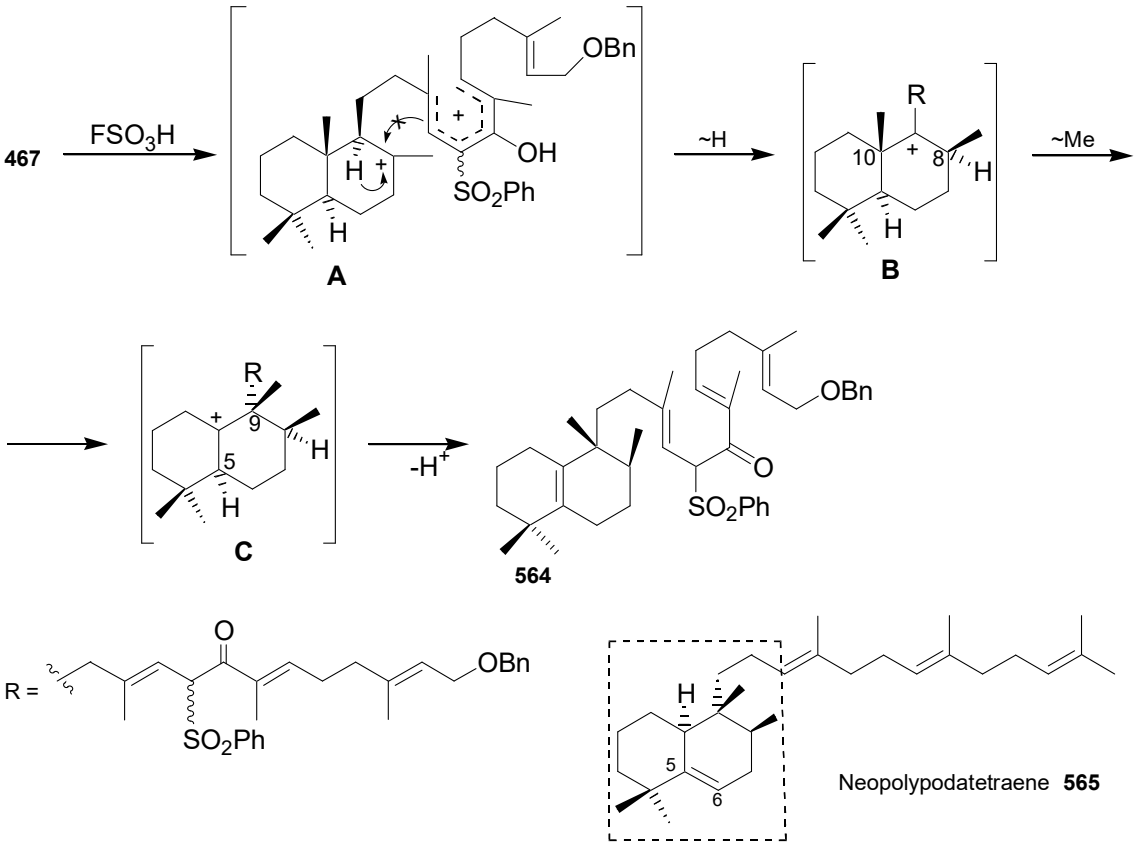


Figure 4.15. Proposed reaction course for superacid-promoted isomerization of compound **467**.

NMR characteristics of compound **564** has been obtained on the basis of its 1D (^{1}H, ^{13}C, DEPT-135°) and 2D homo- (^{1}H/^{1}H COSY-45°) and heteronuclear (^{1}H/^{13}C HSQC and ^{1}H/^{13}C HMBC) correlation spectra.

The ^{1}H NMR spectrum (table 4.3) displayed singlets of geminal dimethyl at δ_H 0.99, 1.01, (each 3H, H-28, H-29), signal of one tertiary and one secondary methyl groups at δ_H 0.86 (6H, H-30, H-27) that appears as a multiplet due to overlapping, low-field singlets of three methyls attached to double bond at δ_H 1.49, 1.66, 1.80 (each 3H, H-26, H-24, H-25), downfield signals of ether methylenes at δ_H 4.00 (*d*, *J* = 6.6 Hz, H-23) and δ_H 4.50 (s, H-1') and deshielded

signals of three sp^2 methines: δ_H 5.44 (*tq*, *J* = 6.6; 1.1 Hz, H-22), 5.74 (*br. s.*, H-14), 6.96 (*tq*, *J* = 7.2; 1.2 Hz, H-18).

Table 4.3. ^{1}H (400.13 MHz) and ^{13}C NMR (100.61 MHz) data of compound **564** in $CDCl_3$ (δ in ppm).

Position	***Compound 564***		
	δ ^{1}H	m, *J* (Hz)	δ ^{13}C [a,b]
1	1.73, 1.98	m[c]	25.9 CH_2
2	1.49-1.65	m[c]	20.0 CH_2
3	1.37, 1.48	m[c]	40.0 CH_2
4	--	--	34.6 qC
5	--	--	137.8 qC
6	1.96	m[c]	25.2 CH_2
7	1.43	m[c]	34.2 CH_2
8	1.60	m[c]	33.6 qC
9	--	--	40.6 qC
10	--	--	131.7 qC
11	1.34, 1.48	m[c]	27.2 CH_2
12	1.70, 2.00	m[c]	35.9 CH_2
13	--	--	150.8 qC
14	5.74	br. s.	119.4 qC
15	--	--	not detected
16	--	--	190.3 qC
17	--	--	132.4 qC
18	6.96	tq (7.2; 1.2)	147.0 CH
19	2.40	m	27.7 CH_2
20	2.10	m	37.8 CH_2
21	--	--	138.5 qC
22	5.44	tq (6.6; 1.1)	122.0 CH
23	4.00	d (6.6)	66.5CH_2

Table 4.3. Ctd.

24	1.66	s	16.5 CH_3
25	1.80	s	12.4 CH_3
26	1.49	s	18.4 CH_3
27	0.86	m[c]	16.1 CH_3
28	0.99	s	29.2 CH_3
29	1.01	s	27.7 CH_3
30	0.86	m[c]	21.2 CH_3
1'	4.50	s	72.3 CH_2
2'	--	--	138.4 qC
4', 6'	7.30	m[c]	127.8 CH
3', 7'	7.30	m[c]	128.4 CH
5'	7.30	m[c]	128.4 CH
1″	--	--	136.5 qC
2", 6"	8.09	dm (8.0)	132.5 CH
3", 5"	7.50	br.t. (8.0)	128.2 CH
4"	7.64	dm (7.5)	134.0 CH

[a] – degree of protonation found by DEPT sequence, [b] –HMBC experiments (J = 8 Hz), [c] – signal overlapping.

The ^{1}H NMR spectrum of compound **564** also contains the signals of two phenyl groups: one belonging to benzyl moiety, for which strong signal overlapping has been noted, at δ_H 7.26-7.35 (*m*, 4H, H-3'-7'*)* and another one, identifying phenylsulfone fragment at δ_H 7.50 (*bt*, J = 8.0 Hz, H- 3", 5" and 8.09 (*dm*, J = 8.0 Hz, H- 2", 6"). The clear substructures H-18 - H-19 -H-20; H-14 -H-26; H-22 -H-23 - H-24 -H-20 and, in contrast to the precursor **467** - H-2"- H-3", H-4", H-5"- are evident in ^{1}H/^{1}H COSY spectrum, the accurate description of all methylene protons being difficult because of severe signal overlapping (see: table 4.3). The ^{13}C NMR data (table 4.3) exhibited thirty-nine carbon signals, which were assigned by a DEPT experiment as seven methyls, eleven sp^3 methylenes, one sp^3 and nine sp^2 methines, two sp^3 and ten sp^2 quaternary carbons. The presence of α,β-unsaturated carbonyl moiety has been corroborated, as in the molecules of precursor **467**, by the ^{1}H and ^{13}C NMR data [δ_X 190.3 (C-16), 132.4 (C-17), 147.0 (C-18); δ_H 1.80 (s, 3H, H-25)]. The rearrangement of

carbon framework of **564** becomes obvious while examining its HMBC spectrum. Thus, the observed correlations from both H-6 and H-1 to two sp^2 hybridized (C-5, δ_C 137.8 and C-10, δ_C 131.7) instead of two sp^3 (C-5, δ_C 51.9 and C-10, δ_C 40.4) in the former compound **467** were indicative on $\Delta^{5,10}$ localization, which was supported also by the correlations of H_3-29/C-5, H_3-28/C-5. The logical migration of methyl H_3-30 from C-10 to C-9 position has been ascertained by H_3-30/C-10, H_3-30/C-9 and H_3-30/C-11 cross-peaks in the HMBC spectrum, while the evident substitution of two olefinic carbons (C-8, δ_C 148.5 and C-27, δ_C 106.2) in the precursor **467** by the corresponding sp^3 atoms in **564** (C-8, δ_C 33.6 and C-27, δ_C 16.1) has been proved by long-range correlations H_3-27/C-6, H_3-27/C-7 and H_3-27/C-9.

It should be noted that the polyfunctional triterpene derivative **564** can be considered a congener of natural triterpenoid neopolypodatetraene **565**, especially on considering the similarity in the bicyclic fragment. The latter has been isolated from a squalene hopene cyclase mutant of the prokaryotic bacterium *Alicyclobacillus acidocaldarius* F365A [213].

4.3. Application of the rearrangement biomimetic processes for the synthesis of some terpenic families. Experimental methods and procedures

(+)-Homodrim-8(9)-en-12-yl acetate 526.

Oxyacetate **525** (130 mg, 0.44 mmol), obtained from sclareolide **524** according to the literature procedure [167] was dissolved in dry benzene (24 mL) and I_2 (89 mg, 0.35 mmol) was added in one portion. The reaction mixture was heated at reflux on an oil bath (bath temperature 127 ºC) for 2h. Then, the reaction mixture was poured into an ice-cooled solution of $Na_2S_2O_3$ (5%, 50 mL). Separation of the organic phase and extraction of the water phase with Et_2O (3· 15 mL), provided the combined organic phase, which was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (117 mg), which was subjected to flash chromatography (FC) on a short SiO_2 column. Elution with EtOAc/light petroleum ether mixture (3:97) gave pure **526** (110 mg, 90%): R_f (10% EtOAc in light petroleum ether) 0.61; $[\alpha]_D^{25}$ +117.1 (c 1.4, $CHCl_3$); IR (liquid film, cm^{-1}) 1742; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.00 (m, 2H, H2-12), 2.40 (m, 1H, H-11a), 2.25 (m, 1H, H-11b), 2.04 (OAc), 2.03 (m, 1H, H-7a), 1.95 (m, 1H, H-7b), 1.85 (m, 1H, H-1a), 1.65 (m, 2H, H-2a and H-6a),

1.62 (s, 3H, H3-13), 1.40 (m, 3H, H-2b, H-3a and H-6b), 1.13 (m, 1H, H-3b), 1.10 (m, 2H, H-1b and H-5), 0.93 (s, 3H, H3-14), 0.88 (s, 3H, H3-15), 0.83 (s, 3H, H3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.1 ($COCH_3$), 135.6 (s, C-9), 128.9 (s, C-8), 64.1 (t, C-12), 51.7 (d, C-5), 41.7 (t, C-3), 38.6 (s, C-10), 37.0 (t, C-1), 33.7 (t, C-7), 33.3 (s, C-4), 33.3 (q, C-15), 27.1 (t, C-11), 21.7 (q, C-16), 21.0 ($COCH_3$), 19.9 (q, C-14), 19.7 (q, C-13), 18.9 (t, C-2), 18.7 (t, C-6); EIMS (m=z) 278 (M^+, 3%), 218 (71), 203 (100), 189 (18), 175 (18), 147 (31), 133 (24), 107 (27); HREIMS: found 278.2249, $C_{18}H_{30}O_2$ requires 278.2246.

Epoxidation of compound 526. 8,9-Epoxyhomodriman-12-yl acetates 523 and 527.

The tetrasubstituted acetate **526** (47 mg, 0.17 mmol) was dissolved in dry dichloromethane (0.5 mL) and treated at 0 ºC with *m*-CPBA (0.22 mmol, 58 mg containing ca. 65% of *m*-CPBA) in 0.5 mL of dichloromethane. After stirring for 1 h at 0 ºC, the reaction mixture was diluted with diethyl ether (3 mL) and treated with 5 mL of an aqueous solution of $Na_2S_2O_3$ (5%). Separation of phases, extraction of the aqueous phase with diethyl ether (3 · 10 mL) gave the crude ether extract, which was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (57 mg), which was subjected to FC on a short SiO_2 column. Elution with EtOAc/petroleum ether mixture (3:97) gave a one-spot mixture of epoxides **523** and **527** (45 mg, 90%): R_f (10% EtOAc in light petroleum ether) 0.42; ratio 3/7, 3:1 by ^{1}H NMR spectrum of the mixture (integration of H_2-12 signal : triplet at δ 4.06 in **523** and multiplet at δ 4.19 in **527**).

Hydrolysis of epoxide 523 and 527 mixture.

The mixture of epoxides (62mg, 0.21 mmol) was dissolved in methanol (1.5mL) and treated with K_2CO_3 (58 mg, 0.42mmol). After 2 h of stirring at room temperature, methanol was distilled off and the residuum was partitioned between brine (10 mL) and diethyl ether (10 mL). Separation of the ether part and extraction of the aqueous phase with diethyl ether (3 · 10 mL) gave the crude ether extract, which was washed with brine to neutral and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude product (52.0 mg), which was subjected to FC on a short SiO_2 column. Elution with 10% EtOAc/light petroleum ether gave pure epoxyalcohols **528** (32 mg, 60%) and **529** (15 mg, 29%).

Major diastereoisomer (5S,8R,9S,10S)-8,9-epoxyhomodriman-12-ol 528: R_f (30% EtOAc/light petroleum ether) 0.26; $[\alpha]_D^{25}$ +29.1 (c 0.5, $CHCl_3$); IR (liquid film, cm^{-1}) 3431, 1461, 1381; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.81 (m, 1H, H-12a), 3.66 (m, 1H, H-12b), 2.55 (br s, –OH), 2.00 (m, 1H, H-11a), 1.90 (m, 2H, H-7a and H-11b), 1.80 (m, 1H, H-7b), 1.70 (m, 1H, H-1a), 1.52(m, 2H, H2-2), 1.48 (m, 1H, H-5), 1.35 (m, 3H, H-1b), 1.30 (s, 3H, H3-13), 1.20 (m, 1H, H-6b), 1.18 (m, 1H, H-3b), 0.98 (s, 3H, H3-14), 0.84 (s, 3H, H3-15), 0.81 (s, 3H, H3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) d 72.4 (s, C-9), 63.0 (s, C-8), 61.8 (t, C-12), 42.2 (d, C-5), 41.4 (t, C-3), 38.4 (s, C-10), 34.8 (t, C-1), 33.5 (q, C-15), 32.9 (s, C-4), 29.0 (t, C-7), 27.7 (t, C-11), 21.8 (q, C-13), 21.5 (q, C-16), 18.3 (t, C-2), 17.2 (t, C-6), 17.1 (q, C-14); EIMS (m=z) 252 (M^+, 5%), 237 (20), 219 (21), 207 (43), 189 (34), 167 (77), 149 (52), 138 (59), 123 (100), 95 (87), 81 (59).

Minor diastereoisomer (5S,8S,9R,10S)-8,9-epoxyhomodriman-12-ol 529: R_f (30% EtOAc/light petroleum ether) 0.18; $[\alpha]_D^{25}$ +17.6 (c 0.6, CHCl3); IR (liquid film, cm^{-1}) 3414, 1465, 1379; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (m, 1H, H-12a), 3.75 (m, 1H, H-12b), 2.44 (br s, –OH), 2.09 (m, 1H, H-7a), 2.08 (m, 1H, H-11a), 1.82 (m, 1H, H-11b), 1.76 (m, 1H, H-1a), 1.71 (m, 1H, H-2a), 1.66 (m, 1H, H-7b), 1.54 (m, 1H, H-2b), 1.42 (m, 1H, H-3a), 1.33 (s, 3H, H_3-13), 1.32(m, 1H, H-6), 1.30 (m, 1H, H-1b), 1.20 (m, 1H, H-6b), 1.15 (m, 1H, H-3b), 1.11 (s, 3H, H_3-14), 0.83 (s, 3H, H_3-15), 0.77 (m, 1H, H-5), 0.78 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) d 72.3 (s, C-9), 64.4 (s, C-8), 61.7 (t, C-12), 53.6 (d, C-5), 41.3 (t, C-3), 38.5 (s, C-10), 38.0 (t, C-1), 35.6 (t, C-7), 33.9 (s, C-4), 33.2 (q, C-15), 31.3 (t, C-11), 21.9 (q, C-16), 21.2 (q, C-13), 19.8 (t, C-2), 17.1 (q, C-14), 16.9 (t, C-6); EIMS (m=z) 252 (M^+, 2%), 234 (6), 207 (22), 179 (18), 167 (50), 123 (67), 95 (100), 69 (84), 55 (62).

Acetylation of compound 528. (5S,8R,9S,10S)-8,9-Epoxyhomodriman-12-yl acetate 523.

Pure epoxyalcohol **528** (28 mg, 0.11 mmol) was dissolved in 0.5 mL of dry pyridine and treated with 0.2mL of acetic anhydride at room temperature. The reaction mixture was left overnight. Then it was poured into ice water (10 mL) and extracted with diethyl ether (3 · 10mL). The ether extracts were washed successively with a 10% aqueous solution of sulfuric acid (5 mL), brine (5mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (34 mg), which was subjected to FC on a short SiO_2 column.

Elution with EtOAc/light petroleum ether mixture (3:97) gave pure (5S,8R,9S,10S)-8,9-epoxydriman-12-yl acetate **523** (32mg, 97%): R_f (10% EtOAc/light petroleum ether) 0.42; $[\alpha]_D^{25}$ +50.3 (c 0.7, CHCl3); IR (liquid film, cm-1) 1743, 1460, 1237; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (t, 2H, H_2-12), 2.08 (m, 1H, H-11a), 2.02 (–OAc), 1.90 (m, 1H, H-7a), 1.89 (m, 1H, H-11b), 1.80 (m, 1H, H-7b), 1.72(m, 1H, H-1a), 1.52(m, 2H, H_2-2), 1.50 (m, 1H, H-5), 1.36 (m, 1H, H-3a), 1.35 (m, 2H, H-1b and H-6a), 1.22 (s, 3H, H_3-13), 1.20 (m, 1H, H-6b), 1.15 (m, 1H, H-3b), 0.98 (s, 3H, H_3-14), 0.82(s, 3H, H_3-15), 0.80 (s, 3H, H_3-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.0 ($COCH_3$), 69.7 (s, C-9), 62.3 (t, C-12), 61.9 (s, C-8), 42.3 (d, C-5), 41.4 (t, C-3), 38.2 (s, C-10), 34.4 (t, C-1), 33.5 (q, C-15), 32.9 (s, C-4), 29.0 (t, C-7), 25.4 (t, C-11), 21.7 (q, C-13), 21.4 (q, C-16), 21.0 ($COCH_3$), 18.4 (t, C-2), 17.1 (t, C-6), 16.9 (q, C-14); EIMS (m=z) 294 (M^+, 1.6%), 276 (5), 234 (16), 219 (28), 191 (23), 163 (100), 133 (29), 119 (46), 97 (49); HREIMS: found 294.2191, $C_{18}H_{30}O_3$ requires 294.2195.

Acetylation of compound 643. (5S,8S,9R,10S)-8,9-epoxyhomodriman-12-yl acetate 527

Pure epoxyalcohol **529** (10 mg, 0.04 mmol) was dissolved in 0.5 mL of dry pyridine and treated with 0.2 mL of acetic anhydride at room temperature. The reaction mixture was left overnight. Then it was poured into ice water (10 mL) and extracted with ether (3 · 10 mL). The ether extracts were washed successively with a 10% aqueous solution of sulfuric acid (5mL), brine (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product (14 mg), which was subjected to FC on a short SiO_2 column. Elution with EtOAc/light petroleum ether mixture (3:97) gave pure (5S,8S,9R,10S)-8,9-epoxyhomodriman-12-yl acetate **527** (11 mg, 97%): R_f (10% EtOAc/light petroleum ether) 0.42; $[\alpha]_D^{25}$ +30.6 (c 0.6, $CHCl_3$); IR (liquid film, cm^{-1}) 1743, 1465, 1234; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (m, 2H, H_2-12), 2.05 (m, 1H, H-2a), 2.04 (–OAc), 2.03 (m, 1H, H-11a), 1.89 (m, 1H, H-11b), 1.81 (m, 1H, H-1a), 1.70 (m, 1H, H-2a), 1.65 (m, 1H, H-7b), 1.58 (m, 1H, H-2b), 1.39 (m, 1H, H-3a), 1.36 (m, 1H, H-1b), 1.31 (s, 3H, H_3-13), 1.30 (m, 1H, H-6a), 1.20 (m, 1H, H-6b), 1.14 (m, 1H, H-3b), 1.02(s, 3H, H_3-14), 0.83 (s, 3H, H_3-15), 0.77 (s, 3H, H_3-16), 0.76 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75.5MHz) δ 171.0 ($COCH_3$), 70.6 (s, C-9), 64.5 (s, C-8), 62.3 (t, C-12), 53.7 (d, C-5), 41.3 (t, C-3), 38.4 (s, C-10), 37.4 (t, C-1), 35.6 (t, C-7), 33.8 (s, C-4), 33.1 (q, C-15), 30.1 (t, C-11), 21.9 (q, C-16), 21.0 (q, C-13), 21.0 ($COCH_3$) 19.7 (t, C-2), 16.8 (t, C-6), 16.6 (q, C-14); EIMS (m=z) 294 (M^+, 3%), 276 (6), 234 (28), 219 (34), 191 (24), 163 (100), 133 (31), 119 (54).

Ring contraction reaction of epoxyacetate 523. **(5S,8R,10S)-9-(2-acetoxyethyl)-austrodor-9-one 530.**

The substrate **523** (300 mg, 1.02 mmol) was dissolved in dichloromethane (5 mL) and tris-(p-bromophenyl)-aminium hexachloroantimonate ($RSbCl_6$) (17 mg, 0.02 mmol) was added. The solution was left under stirring for 1 h at room temperature. After this period, the solvent was evaporated off and the crude material was subjected to FC on a silica gel column. Elution with Et_2O/benzene mixture (1:99) gave pure (5S,8R,10S)-9-(2-acetoxy-ethyl)-austrodor-9-one **530** (135 mg, 45%): R_f (5% EtOAc/benzene) 0.43; $[\alpha]_D^{25}$ 2.4 (c 1.6, $CHCl_3$); CD (n-hexane), η_{241} +700, η_{293} -1850; IR (liquid film, cm^{-1}) 1734, 1695; ^1H NMR ($CDCl_3$, 400MHz, numbering is given as shown in formula to make clear the comparison with the precursor) δ 4.33 (dd, J ¼ 6:8, 6.1 Hz, 2H, H_2-12), 2.81 (dt, J ¼ 17:6, 6.8 Hz, 1H, H-11a), 2.70 (dt, J ¼ 17:6, 6.1 Hz, 1H, H-11b), 2.23 (m, 1H, H-7a), 2.01 (–OAc), 1.68 (m, 1H, H-6a), 1.60 (m, 1H, H-1a), 1.56 (m, 1H, H-2a), 1.48 (m, 1H, H-2b), 1.40 (m, 1H, H-6b), 1.38 (m, 2H, H-3a and H-5), 1.22 (m, 1H, H-7b), 1.18 (s, 3H, H_3-13), 0.93 (m, 1H, H-3b), 0.91 (m, 1H, H-1b), 0.883 (s, 3H, H_3-14), 0.877 (s, 3H, H_3-16), 0.86 (s, 3H, H_3-15); ^{13}C NMR ($CDCl_3$, 75.5MHz) δ 214.1 (s, C-9), 170.9 ($COCH_3$), 61.3 (s, C-8), 60.0 (t, C-12), 52.4 (d, C-5), 47.2(s, C-10), 41.1 (t, C-3), 39.8 (t, C-11), 35.4 (t, C-1), 33.7 (q, C-15), 33.2 (s, C-4), 32.7 (t, C-7), 21.7 (t, C-6), 21.5 (q, C-16), 20.9 ($COCH_3$), 20.1 (q, C-13), 20.0 (t, C-2), 16.0 (q, C-14); EIMS (m=z) 234 (M^+), 219 (20), 191 (20), 177 (47), 163 (80), 138 (57), 123 (100), 97 (70), 81 (47).

(5S,8R,10S)-9-Vinyl-austrodor-9-one 531.

The rearranged acetoxy-ketone **530** (29.3 mg, 0.10 mmol) was dissolved in dry THF (1 mL) and TBDSCl (20 mg, 0.13 mmol) was added. The resulting solution was cooled at -78 ºC, while 9.6 mg (0.40 mmol) of NaH were added. After stirring the reaction mixture at room temperature for 4 h, it was diluted with diethyl ether and passed through a short silica gel pad. The crude product was subjected to FC. Elution with Et_2O/benzene mixture (1:99) gave 12 mg (52%) of α,β-unsaturated ketone **531**: R_f (5% EtOAc/benzene) 0.64; $[\alpha]_D^{25}$ -6.4 (c 0.3, $CHCl_3$); CD (n-hexane), η_{234} -1014; IR (liquid film, cm^{-1}) 1687; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.66 (dd, J ¼ 16:9, 10.2Hz, 1H, H-11), 6.22 (dd, J ¼ 16:9, 2.1 Hz, 1H, H-12a), 5.51 (dd, J ¼ 10:2, 2.1 Hz, 1H, H-12b), 2.35 (ddd, J ¼ 16:1, 9.9, 5.2Hz, 1H, H-7a), 1.70 (m, 1H, H-6a), 1.60 (m, 1H, H-2a), 1.58 (m, 1H, H-1a), 1.46 (m, 1H, H-2b), 1.41 (m, 1H, H-6b), 1.38 (m, 1H, H-3a), 1.33 (m, 1H, H-5), 1.28 (m, 1H, H-7b), 1.18 (s, 3H, H_3-13),

0.98 (m, 1H, H-1b), 0.93 (m, 1H, H-3b), 0.91 (s, 3H, H_3-14), 0.88 (s, 3H, H_3-16), 0.84 (s, 3H, H_3-15); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 204.9 (s, C-9), 134.3 (d, C-11), 125.9 (t, C-12), 60.3 (s, C-8), 53.0 (d, C-5), 46.9 (s, C-10), 41.0 (t, C-3), 35.5 (t, C-1), 33.6 (q, C-15), 33.2(s, C-4), 32.2 (t, C-7), 21.6 (t, C-6), 21.4 (q, C-16), 20.2 (q, C-13), 19.9 (t, C-2), 15.8 (q, C-14); EIMS (m=z) 234 (M^+, 11%), 219 (8), 201 (11), 191 (3), 179 (28), 150 (23), 138 (87), 123 (100), 97 (20); HREIMS: found 234.1980, $C_{16}H_{26}O$ requires 234.1983.

(5S,8R,10S)-Austrodoric acid 521.

Ketone **531** (8 mg, 0.03 mmol) was dissolved in *tert*-butanol (0.5 mL) and water (0.1 mL) and $NaIO_4$ (37 mg, 0.17 mmol), along with a 2.5% solution of OsO_4 in *tert*-butanol (4.4 mL, 0.00035 mmol), was added to the resulting solution. The reaction mixture was stirred at 45 ºC for 12h. Then it was diluted with ether, filtrated and the filtrate was washed with brine. The crude material (11 mg) was subjected to FC. Elution with EtOAc/light petroleum ether mixture (3:97) gave 5 mg (70%) of pure compound **521**: R_f (20% EtOAc/light petroleum ether) 0.25; $[\alpha]_D^{25}$ -2.0 (c 0.15, $CHCl_3$); CD (n-hexane), η_{214} -470; IR (liquid film, cm^{-1}) 1685; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (m, 1H, H-7a), 1.68 (m, 1H, H-6a), 1.62(m, 1H, H-5), 1.60 (m, 1H, H-2a), 1.58 (m, 1H, H-1a), 1.52(m, 1H, H-2b), 1.45 (m, 1H, H-6b), 1.42(m, 2H, H-3a, H-7b), 1.17 (s, 3H, H_3-10), 1.12(ddd, J ¼ 13, 13, 4 Hz, 1H, H-1b), 1.02(ddd, J ¼ 13, 13, 4 Hz, 1H, H-3b), 0.90 (s, 3H, H_3-14), 0.87 (s, 6H, H_3-12 and H_3-13); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 182.2 (s, C-11), 56.4 (s, C-9), 53.3 (d, C-5), 46.7 (s, C-8), 41.2(t, C-3), 35.3 (t, C-1), 33.8 (q, C-13), 33.3 (s, C-4), 33.1 (t, C-7), 21.6 (t, C-6), 21.6 (q, C-14), 20.5 (q, C-10), 20.1 (t, C-2), 15.7 (q, C-12); EIMS (m=z) 2 2 4 (M^+, 3%), 209 (13), 191 (1.6), 163 (11), 138 (11), 123 (100), 95 (16).

(+)-Drim-8,12-en-11-yl methanesulfonate 537.

Mesylchloride (0.7 mL, 9.04 mmol) and 4-dimethylamino pyridine (24.0 mg, 0.20 mmol) were added to a cooled solution (at 0 °C) of albicanol **533** (241.5 mg, 1.09 mmol) in dry pyridine (10 mL). The mixture was stirred for 4 h at this temperature, then warmed to room temperature and stirred for other 12 h. The reaction was quenched with ice, and pyridine was removed *in vacuo*. The residue was dissolved in ether, worked-up as usual and the residue (312 mg) was purified by flash chromatography (2% diethyl ether/ light petroleum ether) to give compound **537** (275 mg, 0.91 mmol, 84%). R_f = 0.17

(20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +16.9 (*c* = 0.40, $CHCl_3$). IR (film): ν(~) 1357 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.76 (s, 3 H, C-13), 0.82 (s, 3 H, C-14), 0.89 (s, 3 H, C-15), 1.14 (dd, $J_{H–H}$ = 13, 3 Hz, 1 H, C-5), 1.20 (m, 1 H, C-3, Ha), 1.30 (m, 1 H, C-1, Ha), 1.34 (dd, $J_{H–H}$ = 13, 4 Hz, 1 H, C-6, Ha), 1.42 (m, 1 H, C-3, Hb), 1.53 (m, 2 H, C-2), 1.72 (m, 1 H, C-1, Hb), 1.77 (m, 1 H, C-6, Hb), 2.03 (ddd, $J_{H–H}$ = 13, 13, 5 Hz, 1 H, C-7, Ha), 2.15 (m, 1 H, C-9), 2.42 [ddd, $J_{H–H}$ = 13, 4, 2 Hz, 1 H, C-7, Hb), 2.98 (s, 3 H, $–OSO_2CH_3$), 4.34 (dd, $J_{H–H}$ = 10, 10 Hz, 1 H, C-11, Ha), 4.49 (dd, $J_{H–H}$ = 10, 4 Hz, 1 H, C-11, Hb), 4.62 [bs, 1H, C-12, Ha), 4.91 (bs, 1 H, C-12, Hb). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.2 (q, C-13), 19.1 (t, C-2), 21.7 (q, C-14), 23.8 (t, C-6), 33.2 (s, C-4), 33.6 (q, C-15), 37.4 (t, C-7), 37.5 (q, $–OSO_2CH_3$), 39.1 (t, C-1), 39.5 (s, C-10), 41.7 (t, C-3), 55.0 (d, C-5 or C-9), 55.1 (d, C-9 or C-5), 66.6 (t, C-11), 107.7 (t, C-12), 145.6 (s, C-8). MS (EI): *m/z* (%) = 300 (3) [M^+], 285 (10), 257 (5), 244 (8), 204 (51), 189 (38), 161 (21), 137 (100), 123 (72), 93 (80), 81 (72), 55 (49). HRMS (ESI): $(M+Na)^+$, found 323.2604. $(C_{16}H_{28}O_3S+Na)^+$ requires 323.2596.

(-)-Drim-8,12-ene 538.

Lithium aluminium hydride (540 mg, 14.21 mmol) was added under argon atmosphere to a solution of mesylate **537** (1.41 g, 4.69 mmol) in anhydrous diethyl ether (35 mL). The reaction mixture was refluxed for 4 h. The mixture was worked-up as usual and the product obtained (0.92 g) was purified by flash chromatography (light petroleum ether) to give drim-8,12-ene **538** (904.5 mg, 4.36 mmol, 93 %). R_f = 0.93 (2 % ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –10.3 (*c* = 0.57, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 0.67 [s, 3 H, C(13)–H], 0.82 [s, 3 H, C(14)–H], 0.88 [s, 3 H, C(15)–H], 0.89 [s, 3 H, C(11)–H], 1.05 [ddd, $J_{H–H}$ = 13, 13, 4 Hz, 1 H, C(1)–Ha], 1.11 [dd, $J_{H–H}$ = 13, 3 Hz, 1 H, C(5)–H], 1.18 [ddd, $J_{H–H}$ = 13, 13, 4 Hz, 1 H, C(3)–Ha], 1.33 [dd, $J_{H–H}$ = 13, 4 Hz, 1 H, C(6)–Ha], 1.40 [m, 1 H, C(3)–Hb], 1.45 [m, 2 H, C(2)–H], 1.66 [m, 1 H, C(1)–Hb], 1.70 [m, 1 H, C(6)–Hb], 1.81 [m, 1 H, C(9)–H], 2.05 [ddd, $J_{H–H}$ = 13, 13, 5 Hz, 1 H, C(7)–Ha], 2.38 [ddd, $J_{H–H}$ = 13, 4, 2 Hz, 1 H, C(7)–Hb], 4.51 [dd, $J_{H–H}$ = 3.4, 1.7 Hz, 1 H, C(12)–Ha], 4.71 [dd, $J_{H–H}$ = 3.4, 1.7 Hz, 1 H, C(12)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.4 (q, C-11), 13.3 (q, C-13), 19.4 (t, C-2), 21.8 (q, C-14), 23.9 (t, C-6), 33.6 (q, C-15), 33.9 (s, C-4), 37.4 (t, C-7), 39.4 (t, C-1), 39.7 (s, C-10), 42.3 (t, C-3), 50.3 (d, C-9), 55.4 (d, C-5), 105.7 (t, C-12), 145.6 (s, C-8). MS (EI): *m/z* (%) = 206 (23)

[M^+], 191 (34), 177 (13), 163 (11), 150 (16), 137 (100), 123 (31), 121 (28), 109 (31), 95 (47), 81 (39), 69 (23), 55 (16).

(-)-12-Nordriman-8-one 539.

Acetic acid (1.4 mL), a 2.5 % solution of osmium tetraoxide (13.7 mg) in *tert*-butanol (0.55 mL), and a solution of sodium periodate (694 mg, 3.24 mmol) in water (2.0 mL) were added to a solution of hydrocarbon **538** (304 mg, 1.48 mmol) in dry dioxane (29 mL). The reaction mixture was stirred at room temperature for 24 h, then additional aliquots of a 2.5% solution of osmium tetraoxide (13.7 mg) in *tert*-butanol (0.55 mL), and a solution of sodium periodate (694 mg, 3.24 mmol) and water (2.0 mL) were added. The reaction mixture was stirred for further 48 h and monitored by TLC. At the end of this period the reaction was complete. The mixture was worked up as usual and the product recovered (308 mg) was purified by silica-gel flash chromatography (2% diethyl ether/light petroleum ether) to give 12-nordriman-8-one **539** (285.5 mg, 1.37 mmol, 93%). R_f = 0.70 (30% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –50.3 (*c* = 0.89, $CHCl_3$). IR (film): ν(~) 1711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.73 [s, 3 H, C(12)–H], 0.87 [s, 3 H, C(14)–H], 0.89 [d, $J_{H–H}$ = 7 Hz, 3 H, C(11)–H], 0.97 [s, 3 H, C(13)–H], 1.15 [m, 1 H, C(1)–Ha], 1.26 [m, 1 H, C(3)–Ha], 1.47 [m, 1 H, C(7)–Hb], 1.49 [m, 1 H, C(5)–H], 1.50 [m, 2 H, C(2)–H], 1.69 [m, 1 H, C(1)–Hb], 1.69 [m, 1 H, C(6)–Ha] 2.02 [m, 1 H, C(6)–Hb], 2.20 [q, $J_{H–H}$ = 7 Hz , 1H, C(9)–H], 2.29 [ddd, $J_{H–H}$ = 14, 14, 7 Hz , 1 H, C(7)–Ha], 2.42 [ddd, $J_{H–H}$ = 14, 5, 2 Hz, 1 H, C(7)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 6.9 (q, C-11), 13.8 (q, C-12), 18.9 (t, C-2), 21.7 (q, C-13), 23.5 (t, C-6), 33.5 (q, C-14), 33.6 (s, C-4), 39.4 (t, C-1), 41.5 (s, C-10), 41.8 (t, C-3 or C-7), 42.0 (t, C-7 or C-3), 54.1 (d, C-5), 58.0 (d, C-9), 213.1 (s, C-8). MS (EI): *m/z* (%) = 208 (67) [M^+], 193 (18), 175 (18), 166 (28), 147 (10), 137 (100), 123 (87), 121 (43), 109 (44), 95 (61), 81 (47), 69 (29), 55 (20).

12-Nordriman-8-ols 540a and **540b.**

Cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, 250 mg, 0.67 mmol) was added to a solution of ketone **539** (193 mg, 0.93 mmol) in MeOH (8.9 mL). The suspension was stirred at room temperature for 10 min and cooled to –50 °C. Sodium borohydride ($NaBH_4$, 105.3 mg, 2.79 mmol)

was added in small portions. The reaction was stirred at –20 °C for 1 h. The reaction was quenched with 10 % sulfuric acid aqueous solution. The mixture was worked up as usual and the product (190 mg) was purified by silica-gel flash chromatography (diethyl ether/light petroleum ether gradient). The main diastereoisomer **540a** (118.0 mg, 0.57 mmol, 61%) was eluted by 2% diethyl ether/light petroleum ether, whereas the minor diastereisomer **540b** (68.1 mg, 0.32 mmol, 35%) was recovered with 3% diethyl ether/light petroleum ether.

(+)-12-Nordriman-8β-ol 540a: R_f = 0.64 (30% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +1.07 (*c* = 0.47, $CHCl_3$). IR (film): ν(~) 3649 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.86 [s, 3 H, C(13)–H], 0.87 [m, 1H, C(1)–Ha], 0.88 [s, 3 H, C(14)–H], 0.89 [m, 1 H, C(5)–H], 0.94 [d, $J_{H–H}$ = 7 Hz, 3 H, C(11)–H], 0.99 [s, 3 H, C(12)–H], 1.15 [ddd, $J_{H–H}$ = 13, 13, 4 Hz, 1 H, C(3)–Ha], 1.25 [m, 1 H, C(9)–H], 1.40 [m, 1 H, C(2)–Ha], 1.41 [m, 1 H, C(3)–Hb], 1.58 [m, 3 H, C(6)–H and C(7)–Ha], 1.60 [m, 1 H, C(2)–Hb], 1.65 [m, 1 H, C(1)–Hb], 1.91 [m, 1 H, C(7)–Hb], 3.76 [bs, w ½ = 7 Hz, 1 H, C(8)–H]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.7 (q, C-11), 15.2 (q, C-12), 17.1 (q, C-3), 18.3 (t, C-2), 21.7 (q, C-13), 33.2 (s, C-4), 33.6 (q, C-14), 35.3 (t, C-8), 39.4 (t, C-1 and s, C-10), 42.2 (t, C-3), 48.7 (d, C-9), 56.0 (d, C-5), 72.9 (d, C-8). MS (EI): *m/z* (%) = 210 (11) [M^+], 192 (33), 177 (91), 163 (13), 149 (20), 137 (67), 124 (100), 109 (87), 95 (79), 81 (77), 69 (66), 55 (49).

(-)-12-Nordriman-8α-ol 540b: R_f = 0.54 (30% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –15.0 (*c* = 0.33, $CHCl_3$). IR (film): ν(~) 3650 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.77 [s, 3 H, C(12)–H], 0.82 [s, 3H, C(13)–H], 0.87 [s, 3 H, C(14)–H], 0.90 [d, $J_{H–H}$ = 7 Hz, 3 H, C(11)–H], 0.92 [m, 2 H, C(1)–Ha and C(5) –H], 1.03 [m, 1 H, C(9)–H], 1.13 [ddd, $J_{H–H}$ = 13, 13, 4 Hz, 1 H, C(3)–Ha], 1.25 [m, 1 H, C(7)–Ha], 1.42 [m, 1 H, C(3)–Hb], 1.45 [m, 2 H, C(2)–H], 1.63 [m, 2 H, C(6)–H], 1.69 [m, 1 H, C(1)–Hb], 2.09 [m, 1 H, C(7)–Hb], 3.37 [ddd, $J_{H–H}$ = 10, 10, 5 Hz, 1 H, C(8)–H]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.95 (q, C-11), 13.6 (q, C-12), 18.6 (t, C-2), 20.9 (t, C-6), 21.8 (q, C-13), 33.5 (s, C-4), 33.5 (q, C-14), 36.8 (t, C-7), 37.3 (s, C-7), 39.3 (t, C-1), 42.0 (t, C-3), 52.8 (d, C-9), 54.7 (d, C-5), 72.2 (d, C-8). MS (EI): *m/z* (%) = 210 (8) [M^+], 192 (23), 177 (75), 163 (10), 149 (13), 137 (44), 124 (100), 109 (82), 95 (47), 81 (41), 69 (38), 55 (18).

(+)-12-Nordrim-8-ene 541.

Triphenylphosphine (Ph_3P, 871.2 mg, 3.33 mmol) and diethylazodicarboxylate (DEAD, 586 mg, 3.37 mmol) were added to a solution of alcohols **540a** and **540b** (120 mg, 0.57 mmol) in anhydrous tetrahydrofuran (17.5 mL). The reaction mixture was refluxed for 4 h and then worked up as usual. The product obtained (105 mg) was purified by silica-gel flash chromatography (light petroleum ether) to give compound **541** [184] (96.7 mg, 0.50 mmol, 88%). R_f = 0.95 (2% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +64.0 (*c* = 0.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 [s, 3 H, C(13)–H], 0.89 [s, 3 H, C(14)–H], 1.01 [s, 3 H, C(12)–H], 1.12 [m, 1 H, C(1)–Ha], 1.18 [m, 1 H, C(3)–Ha], 1.19 [m, 1 H, C(5)–H], 1.42 [m, 1 H, C(3)–Hb], 1.45 [m, 2 H, C(2)–Ha and C(6)–Ha], 1.58 [bs, 3 H, C(11)–H], 1.60 [m, 1 H, C(6)–Hb], 1.65 [m, 1 H, C(2)–Hb], 1.72 [m, 1 H, C(1)–Hb], 2.03 [m, 2 H, C(7)–H], 5.17 [sharp m, 1 H, C(8)–H]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.1 (q, C-11), 18.6 (t, C-2), 18.9 (t, C-6), 19.6 (q, C-12), 21.6 (q, C-13), 26.8 (t, C-7), 33.3 (s, C-4), 33.3 (q, C-14), 36.8 (t, C-1), 37.9 (s, C-9), 41.9 (t, C-3), 51.6 (d, C-5), 120.4 (d, C-8), 144.3 (s, C-9). MS (EI): *m/z* (%) = 192 (15) [M^+], 177 (13), 149 (100), 123 (44), 107 (39), 95 (34), 81 (38).

Mixture of 8-epoxy-12-nordrimanes 534a and **534b.**

Disodium hydrogenphosphate (Na_2HPO_4, 187 mg, 1.32 mmol) was added to a solution of 3-chloroperoxybenzoic acid (*m*-CPBA, 137 mg, 0.79 mmol) in reagent grade chloroform (3 mL) [177]. The mixture was cooled to 0 °C (ice bath) and alkene **541** (96 mg, 0.50 mmol) in chloroform (1 mL) was added dropwise. After stirring for 2 h, disodium hydrogenphosphate was filtered and washed with chloroform. The combined chloroform layers were washed with a 5% solution of sodium hydroxide (5 mL), water (3 × 5 mL), brine (5 mL), dried over sodium sulfate, filtered and evaporated *in vacuo* to give 97 mg of crude epoxides **534a** and **534b** [177]. This residue was purified by flash chromatography (2% diethyl ether /light petroleum ether) to give the mixture of epoxides **534a** and **534b** (91.2 mg, 0.43 mmol, 87%; ratio **534a**/**534b**, 4:1). Selected ^{1}H NMR main diastereoisomer **534a** (300 MHz, $CDCl_3$) δ = 0.81 [s, 3 H, C(14)–H], 0.84 [s, 3 H, C(13)–H], 1.06 [s, 3 H, C(12)–H], 1.19 [s, 3 H, C(11)–H], 2.85 [sharp m, 1 H, C(8)–H].

(+)-14(10→9)-abeo-12-nordrim-4(10)-en-8α-ol 542. Procedure A [178].

Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$, 12.3 mg, 0.09 mmol) was added to a stirred solution of epoxides **534a** and **534b** (18.0 mg, 0.09 mmol) in benzene (1.0 mL) at room temperature. The mixture was stirred at room temperature for 40 min and poured into water (2 mL). Usual work-up gave a residue (17.4 mg), which was submitted to flash chromatography. Elution with 2% diethyl ether/light petroleum ether gave compound **542** (9.0 mg) as major reaction product.

Procedure B [89].

Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$, 6.5 mg, 0.046 mmol) was added to a stirred solution of epoxides **534a** and **534b** (9.0 mg, 0.043 mmol) in nitromethane (0.7 mL) at –23 ºC. The mixture was stirred for 1 h and subsequently poured into water (1 mL). After usual work-up, the crude reaction product (8.7 mg), containing the alcohol **542** as main compound, was recovered.

Procedure C [179].

A solution of fluorosulfonic acid (FSO_3H, 24.8 mg, 0.25 mmol) in 2-nitropropane (0.23 mL) was added to a solution of epoxides **534a** and **534b** (10.3 mg, 0.049 mmol) in 2-nitropropane (0.7 mL) cooled at –78 ºC, by stirring vigorously. After 15 min of stirring at the same temperature, the mixture was quenched by adding an excess of triethylamine (Et_3N) in *n*-hexane (1:1, 0.35 mL). The cooling bath was removed and water (1 mL) was added carefully to the reaction mixture. Usual work-up gave the crude product (9.8 mg), the main component of which was compound **542**.

(+)-14(10→9)-abeo-12-nordrim-4(10)-en-8α-ol 542: R_f = 0.47 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +2.56 (*c* = 0.9, $CHCl_3$). CD (*n*-hexane) θ_{211} +223, θ_{217} –175, θ_{225} +138. IR (film): ν(~) 3655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.96 [s, 3 H, C(14)–H], 0.97 [s, 6 H, C(12)–H and C(13)–H], 1.02 [s, 3 H, C(11)–H], 1.42 [m, 2 H, C(3)–H], 1.58 [m, 2 H, C(2)–H], 1.66 [m, 1 H, C(7)–Ha], 1.78 [m, 1 H, C(7)–Hb], 1.93 [m, 2 H, C(1)–H], 2.04 [m, 1 H, C(6)–Ha], 2.12 [m, 1 H, C(6)–Hb], 3.46 [dd, J_{H-H} = 9, 3 Hz, 1 H, C(8)–H]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.8 (t, C-2), 21.2 (q, C-12), 22.6 (t, C-6), 25.7 (q, C-11), 25.9 (t, C-1), 26.8 (t, C-7), 28.0 (q, C-13 or C-14), 28.5 (q, C-14 or C-13), 34.1 (s, C-4), 39.3 (s, C-9), 39.6 (t, C-3), 76.0 (d, C-8), 132.7 (s, C-10), 133.5 (s,

C-5). MS (EI): *m/z* (%) = 208 (20) [M^+], 190 (28), 175 (100), 149 (29), 133 (10), 119 (21), 105 (26), 79 (7).

Absolute stereochemistry of compound 542.

(*S*)- and (*R*)-α-methoxy-α-trifluoromethyl-phenylacetic esters of alcohol **542** were prepared by treatment of **542** (2 mg for each ester) with *R*(–)- and *S*(+)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride (0.05 mL), respectively, in dry pyridine (0.5 mL) at room temperature for 16 h. Assignment of the ^{1}H NMR signals of the esters was achieved by analyzing ^{1}H-^{1}H COSY NMR experiments. Selected ^{1}H NMR chemical shifts for *S*(+)-α-methoxy-α-trifluoromethyl-phenylacetic ester (400 MHz, $CDCl_3$): δ = 0.92 [s, 3H, C(12)–H], 0.94 [s, 3H, C(11)–H], 0.95 [s, 3H, C(14)–H], 0.97 [s, 3H, C(13)–H], 1.80 [m, 1H, C(7)–Ha], 1.92 [m, 1H, C(7)–Hb], 1.97 [m, 2H, C(6)–H]. Selected ^{1}H NMR chemical shifts for *R*(–)-α-methoxy-α-trifluoromethyl-phenylacetic ester (400 MHz, $CDCl_3$): δ = 0.89 [s, 3H, C(14)–H], 0.96 [s, 6H, C(12)–H and C(13)–H], 1.01 [s, 3H, C(11)–H], 1.76 [m, 1H, C(7)–Ha], 1.83 [m, 1H, C(7)–Hb], 1.92 [m, 2H, C(1)–H], 2.05 [m, 2H, C(6)–H].

(+)-8,11-Drimane-diol 544.

A solution of sodium hydroxide (441 mg, 11.01 mmol) in water (several drops) and ethanol (2 mL) was added to a solution of 11-acetoxy-8α-drimanol **532** (619 mg, 2.20 mmol) in ethanol (3 mL). The resulting reaction mixture was stirred at gentle reflux (heating bath temperature 87 ºC) for 2 h. Then, the dilution with water (20 mL) and usual work-up gave crude compound **544** [172] (520 mg, 2.18 mmol), which was used in the next step without purification. R_f = 0.13 (30% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +1.22 (*c* = 0.3, $CHCl_3$). Selected ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 [s, 6 H, C(13)–H and C(14)–H], 0.88 [s, 3 H, C(15)–H], 1.35 [s, 3 H, C(12)–H], 3.93 [d, 2 H, $J_{H–H}$ = 6.5 Hz, C(11)–H].

8-Hydroxy-driman-11-al 543.

A solution of dimethyl sulfoxide (0.68 ml, 9.57 mmol) in dichloromethane (15 mL) was added dropwise to a stirred solution of oxalyl chloride (0.42 mL, 4.79 mmol) in dichloromethane (17.5 mL)

cooled at –60 ºC. After 3 min of stirring at this temperature, a solution of compound **544** (520 mg, 2.18 mmol) in dichloromethane (15 mL) was added dropwise. After 20 min of stirring (–60 ºC) triethylamine (3.36 mL, 23.94 mmol) was added to the reaction mixture, after other 15 min the cooling bath was removed and water (25 mL) was added at room temperature. After separation of the phases, the aqueous phase was extracted with dichloromethane (3 × 25 mL) and the combined organic phase was subsequently washed with a 20% sulfuric acid solution, a saturated sodium hydrogencarbonate solution, brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave crude oxyaldehyde **543** [182] (550 mg), which was used in the next step without purification. R_f = 0.41 (30% ethyl acetate/light petroleum ether). Selected ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.83 [s, 3 H, C(14)–H], 0.89 [s, 3 H, C(15)–H], 1.12 [s, 3 H, C(13)–H], 1.38 [s, 3 H, C(12)–H], 10.02 [d, 1 H, $J_{H–H}$ = 1.1 Hz, C(11)–H].

(+)-Drim-8(9)-en-11-al 545.

Crude oxyaldehyde **543** (515 mg, 2.l6 mmol) was dissolved in dry benzene (110 mL) and sublimed iodine (442 mg, 1.741 mmol) was added to the resulting solution on stirring under argon atmosphere. The reaction mixture was refluxed for 2 h on heating using an oil bath (95 ºC). After that, the reaction mixture was quenched with a 5% sodium thiosulfate solution ($Na_2S_2O_3$, 50 mL). The separation of the phases and the extraction of the aqueous phase with diethyl ether (3 × 25 mL) gave the combined organic phase which was dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave crude α,β-unsaturated aldehyde **545** (467 mg), which was used in the next step without purification. A small portion of crude aldehyde **545** was subjected to flash chromatography and the spectral data of pure compound were in agreement with literature data [183]. R_f = 0.73 (30% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +19.2 (*c* = 0.7, $CHCl_3$). Selected ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 [s, 3 H, C(14)–H], 0.90 [s, 3 H, C(15)–H], 1.18 [s, 3 H, C(13)–H], 2.03 [s, 3 H, C(12)–H], 2.26 [m, 1 H, C(7)–Ha], 2.55 [m, 1 H, C(7)–Hb], 10.04 [s, 1 H, C(11)–H].

(+)-Drim-8(9)-en-11-ol 546.

Crude aldehyde **545** (467 mg, 2.l2 mmol) was dissolved in ethanol (15 mL) and sodium borohydride (165 mg, 4.4 mmol) was added to this solution on stirring at 0 ºC. After 2 h of stirring

at this temperature, the reaction mixture was carefully quenched by addition of 20% sulfuric acid solution to an acidic pH. Usual work-up gave a crude product (399 mg), which was submitted to flash chromatography (5% ethyl acetate/light petroleum ether) to give pure compound **546** [185] (401 mg, 1.80 mmol, 83% after 3 steps). R_f = 0.43 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +92.2 (*c* = 0.1, $CHCl_3$). IR (film): ν(~) 3323 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.84 [s, 3 H, C(14)–H], 0.89 [s, 3 H, C(15)–H], 0.96 [s, 3 H, C(13)–H], 1.13 [bd, 1 H, C(5)–H], 1.16 [ddd, J_{H-H} = 13, 13, 4 Hz, 1 H, C(3)–Ha], 1.25 [ddd, J_{H-H} = 13, 13, 4 Hz, 1 H, C(1)–Ha], 1.41 [m, 2 H, C(2)–Ha and C(3)–Hb], 1.51 [m, 1 H, C(6)–Ha], 1.62 [m, 1 H, C(6)–Hb], 1.66 [m, 1 H, C(2)–Hb], 1.72 [s, 3 H, C(12)–H], 1.87 [m, 1 H, C(1)–Hb], 2.06 [m, 2 H, C(7)–H], 4.04 [d, J_{H-H} = 11.5 Hz, 1 H, C(11)–Ha], 4.20 [d, J_{H-H} = 11.5 Hz, 1 H, C(11)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 18.9 (t, C-2), 18.9 (t, C-6), 18.9 (q, C-12), 20.7 (q, C-13), 21.6 (q, C-14), 33.2 (s, C-4), 33.2 (q, C-15), 33.7 (t, C-7), 36.8 (t, C-1), 38.0 (s, C-10), 41.6 (t, C-3), 51.7 (d, C-5), 132.4 (s, C-8), 141.0 (s, C-9). MS (EI): *m/z* (%) = 222 (13) $[M^+]$, 204 (7), 191 (26), 177 (5), 161 (8), 147 (7), 135 (11), 124 (43), 121 (21), 109 (100), 95 (28), 81 (18), 69 (18), 55 (16). HRMS (ESI): $(M+Na)^+$, found 245.1877. $(C_{15}H_{26}O+Na)^+$ requires 245.1882.

8,9-Epoxydriman-11-ols 547a and 547b.

Compound **546** (275 mg, 1.24 mmol) was dissolved in diethyl ether (10 mL) and treated with an etherial solution of monoperphthalic acid (6.52 mL, 2.48 mmol) at 0 ºC. The reaction mixture was left overnight at this temperature on stirring. After this time TLC showed complete conversion of the initial substratum. The reaction mixture was washed with a 5% solution of sodium hydroxide, then with brine to neutral pH. The drying over sodium sulfate and the subsequent evaporation of the solvent gave the crude reaction product, which was submitted to flash chromatography (7.5% ethyl acetate/light petroleum ether) to give epoxide **547a** (221 mg, 0.93 mmol, 75%) and epoxide **547b** (75 mg, 0.32 mmol, 26%).

(+)-8,9-α-Epoxydriman-11-ol 547a: R_f = 0.23 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +60.5 (*c* = 0.21, $CHCl_3$). IR (film): ν(~) 3481, 1459, 1382, 1032 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.80 [s, 3 H, C(14)–H], 0.84 [s, 3 H, C(15)–H], 0.96 [s, 3 H, C(13)–H], 1.16 [ddd, J_{H-H} = 13, 13,

5 Hz, 1 H, C(3)–Ha], 1.29 [s, 3 H, C(12)–H], 1.37 [m, 1 H, C(1)–Ha], 1.38 [m, 1 H, C(3)–Hb], 1.40 [m, 2 H, C(6)–H], 1.42 [m, 1 H, C(5)–H], 1.54 [m, 2 H, C(2)–H], 1.79 [m, 1 H, C(1)–Hb], 1.85 [m, 1 H, C(7)–Ha], 1.98 [m, 1 H, C(7)–Hb], 3.54 [d, J_{H-H} = 11 Hz, 1 H, C(11)–Ha], 3.86 [dd, J_{H-H} = 12 Hz, 1 H, C(11)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.1 (q, C-13), 17.3 (t, C-6), 18.3 (t, C-2), 21.4 (q, C-14), 21.5 (q, C-12), 29.3 (t, C-7), 32.9 (s, C-4), 33.3 (q, C-15), 33.9 (t, C-1), 37.1 (s, C-10), 41.3 (t, C-3), 43.1 (d, C-5), 56.8 (t, C-11), 64.5 (s, C-8), 71.2 (s, C-9). MS (EI): *m/z* (%) = 238 (25) [M^+], 220 (3), 207 (8), 180 (20), 177 (13), 163 (7), 137 (13), 123 (13), 109 (15), 95 (15), 85 (100), 69 (16), 55 (18). HRMS (ESI): $(M+Na)^+$, found 245.1839. $(C_{15}H_{26}O_2+Na)^+$ requires 261.1831.

(+)-8,9-β-Epoxydriman-11-ol 547b: R_f = 0.16 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +32.3 (*c* = 1.15, $CHCl_3$). IR (film): ν(~) 3468, 1461, 1382, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.79 [s, 3 H, C(14)–H], 0.84 [s, 3 H, C(15)–H], 0.85 [m, 1 H, C(5)–H], 1.08 [s, 3 H, C(13)–H], 1.21 [m, 1 H, C(6)–Ha], 1.33 [m, 1 H, C(6)–Hb], 1.37 [s, 3 H, C(12)–H], 1.42 [m, 1 H, C(3)–Ha], 1.48 [m, 1 H, C(1)–Ha], 1.57 [m, 1 H, C(2)–Ha], 1.65 [m, 1 H, C(7)–Ha], 1.70 [m, 1 H, C(3)–Hb], 1.71 [m, 1 H, C(2)–Hb], 1.86 [m, 1 H, C(1)–Hb], 2.00 [m, 1 H, C(7)–Hb], 3.74 [d, J_{H-H} = 12 Hz, 1 H, C(11)–Ha], 3.82 [d, J_{H-H} = 12 Hz, 1 H, C(11)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.7 (t, C-6), 19.4 (t, C-2), 20.0 (q, C-12), 21.8 (q, C-14), 33.1 (q, C-15), 33.7 (s, C-4), 35.4 (t, C-1), 35.8 (t, C-8), 37.7 (s, C-10), 41.2 (t, C-3), 53.6 (d, C-5), 61.1 (d, C-11), 64.8 (s, C-8), 71.7 (s, C-9). MS (EI): *m/z* (%) = 238 (15) [M^+], 220 (3), 205 (8), 192 (21), 179 (13), 177 (48), 163 (15), 149 (18), 137 (34), 123 (56), 109 (100), 95 (79), 81 (62), 69 (69), 55 (59).

(+)-8,9-α-Epoxydriman-11-yl acetate 535.

Pure epoxyalcohol **547a** (203 mg, 0.85 mmol) was dissolved in pyridine (2 mL) and treated with acetic anhydride (0.5 mL). The reaction mixture was left overnight and than quenched with ice. The dilution with water and usual work-up gave a crude product (227 mg), which was submitted to flash chromatography (3% ethyl acetate/light petroleum ether) to afford pure epoxyacetate **535** (207 mg, 0.74 mmol, 87%). R_f = 0.54 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = +27.8 (*c* = 0.27, $CHCl_3$). IR (film): nu(tilde) 1744, 1240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.80 [s, 3 H,

C(14)–H], 0.82 [s, 3 H, C(15)–H], 1.05 [s, 3 H, C(13)–H], 1.15 [ddd, J_{H-H} = 13, 13, 5 Hz, 1 H, C(3)–Ha], 1.29 [s, 3 H, C(12)–Ha], 1.35 [m, 4 H, C(1)–Ha, C(3)–Hb and C(6)–H], 1.45 [dd, J_{H-H} = 13, 2.5 Hz,1 H, C(5)–H], 1.52 [m, 2 H, C(2)–Hb], 1.69 [m, 1 H, C(1)–Hb], 1.82 [dd, J_{H-H} = 15, 8 Hz, 1 H, C(7)–Ha], 1.93 [m, 1 H, C(7)–Hb], 2.05 [s, 3 H, –$OCOCH_3$], 4.03 [d, J_{H-H} = 12 Hz, 1 H, C(11)–Ha], 4.47 [d, J_{H-H} = 12 Hz, 1 H, C(11)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.9 (q, C-13), 17.1 (t, C-6), 18.3 (t, C-2), 21.0 (q, –OCO<u>CH_3</u>), 21.4 (q, C-14), 22.0 (q, C-12), 29.3 (t, C-7), 32.9 (s, C-4), 33.6 (q, C-15), 34.6 (t, C-1), 37.4 (s, C-10), 41.2 (t, C-3), 42.7 (d, C-5), 63.2 (s, C-8), 63.2 (t, C-11), 68.9 (s, C-9), 170.5 (s, –O<u>CO</u>CH_3). MS (EI): *m/z* (%) = 238 (92) [M – $COCH_3$] $^+$, 220 (67), 205 (25), 177 (93), 166 (53), 149 (38), 143 (49), 123 (94), 101 (100), 81 (50), 69 (54), 55 (38). HRMS (ESI): $(M+Na)^+$, found 303.1946. $(C_{17}H_{28}O_3+Na)^+$ requires 303.1936.

9-Acetoxymethylaustrodor-9-one 548. Procedure A.

Pure epoxyacetate **535** (78 mg, 0.28 mmol) was dissolved in dichloromethane (3 mL) and treated with *tris*-(*p*-bromo-phenyl)-aminium-hexachloro-antimonate (4.6 mg, 0.0056 mmol). The reaction mixture was stirred at room temperature for 2 h. Then the solvent was evaporated at reduced pressure and the crude product was submitted to flash chromatography (4% ethyl acetate/light petroleum ether) to give pure acetoxyketone **548** (68 mg, 0,24 mmol, 87%).

Procedure B.

Pure epoxyacetate **535** (39.7 mg, 0.14 mmol) was dissolved in 2-nitropropane (0.7 mL) and to the resulting solution, cooled at –78 ºC, a solution of fluorosulfonic acid (FSO_3H, 0.82 μL, 0.014 mmol, 0.1 mol equiv.) in 2-nitropropane (0.3 mL) was added under argon. After 30 min of stirring, the reaction mixture was quenched with a solution of triethylamine (0.1 mL) in light petroleum ether (0.1 mL). Removal of cooling bath, dilution with brine (10 mL) and usual work-up gave crude acetoxyketone **548** (39 mg).

(-)-9-Acetoxymethylaustrodor-9-one 548: R_f = 0.55 (20% ethyl acetate/light petroleum ether). $[\alpha]_D^{25}$ = –30.9 (*c* = 0.23, $CHCl_3$). CD (*n*-hexane) θ_{211} +416, θ_{291} –2458. IR (film): ν(~) 1717, 1653, 1541 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 [s, 3 H, C(15)–H], 0.87 [s, 3 H, C(13)–H or C(14)–H], 0.88 [s, 3 H, C(14)–H or C(13)–H], 0.99 [m, 1 H, C(3)–Ha], 1.04 [m, 1 H, C(1)–Ha], 1.20

[s, 3 H, C(12)–H], 1.28 [m ,1 H, C(7)–Ha], 1.35–1.60 [m, 2 H, C(2)–H], 1.38 [m, 1 H, C(3)–Hb], 1.40 [m, 1 H, C(6)–Ha], 1.58 [m, 1 H, C(1)–Hb], 1.67 [m, 1 H, C(6)–Hb], 2.16 [s, 3 H, –OCOCH$_3$], 2.19 [m, 1 H, C(7)–Hb] 4.66 [d, $J_{H–H}$ = 17 Hz, 1 H, C(11)–Ha], 4.96 [d, $J_{H–H}$ = 17 Hz, 1 H, C(11)–Hb]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.1 (q, C-13), 19.1 (q, C-12), 20.0 (t, C-2), 20.6 (q, –OCO<u>CH$_3$</u>), 21.5 (q, C-14), 21.8 (t, C-6), 33.2 (s, C-4), 33.2 (t, C-7), 33.7 (q, C-15), 35.2 (t, C-1), 40.7 (t, C-3), 47.4 (s, C-10), 52.2 (d, C-5), 59.9 (s, C-8), 67.8 (7, C-11), 170.4 (s, –O<u>CO</u>CH$_3$), 208.9 (s, C-9). MS (EI): *m/z* (%) = 280 (3) [M^+], 220 (15), 205 (5), 179 (49), 143 (100), 123 (90), 109 (38), 101 (84), 81 (21), 69 (28), 55 (13). HRMS (ESI): $(M+Na)^+$, found 303.1940. $(C_{17}H_{28}O_3+Na)^+$ requires 303.1936.

Mixture of 9-hydroxymethylaustrodor-9-diols 549.

Acetoxyketone **548** (38 mg, 0.14 mmol) was dissolved in dry diethyl ether (3 mL) and the resulting solution was treated with lithium aluminum hydride (21 mg, 0.54 mmol) at 0 ºC. After stirring for 3 h at room temperature, the reaction mixture was quenched with water and usual work-up gave the crude reaction product, which was submitted to flash chromatography (20% ethyl acetate/light petroleum ether) to give a mixture of diols **549** (32 mg, 0.13 mmol, 98 %). Selected ^{1}H NMR chemical shifts (400 MHz, $CDCl_3$): δ 3.40–4.00 [C(9)–H, C(11)–H].

Austrodoral 522.

A sample of diols **549** (12 mg, 0.05 mmol) was dissolved in a mixture of tetrahydrofuran (0.5 mL) and water (0.3 mL) and the resulting solution was treated on stirring with sodium periodate (32 mg, 0.15 mmol). After stirring for 3 h at room temperature, the reaction mixture was worked-up as usual to afford pure austrodoral **522** [163] (10.5 mg, 0.05 mmol). R_f = 0.70 (20% ethyl acetate /light petroleum ether). $[\alpha]_D^{25}$ = +18.3 (*c* = 0.45, $CHCl_3$). CD (*n*-hexane) θ_{303} +997. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.86 [s, 3 H, C(13)–H], 0.88 [s, 3 H, C(12)–H], 0.89 [s, 3 H, C(14)–H], 0.97 [ddd, $J_{H–H}$ = 13, 13, 4 Hz, 1 H, C(3)–Ha], 1.04 [s, 3 H, C(10)–H], 1.20 [m, 1 H, C(1)–Ha], 1.25 [m, 1 H, C(5)–H], 1.30 [m, 1 H, C(7)–Ha], 1.41 [m, 1 H, C(6)–Ha], 1.42 [m, 1 H, C(3)–Hb], 1.51 [m, 1 H, C(2)–Ha], 1.60 [m, 1 H, C(2)–Hb], 1.65 [m, 1 H, C(1)–Hb], 1.68 [m, 1 H, C(6)–Hb], 2.16 [ddd, $J_{H–H}$ = 13, 10, 6

Hz, 1 H, C(7)–Hb], 9.68 [s, 1 H, C(11)–Ha]. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.9 (q, C-12), 16.4 (q, C-10), 19.6 (t, C-2), 21.4 (q, C-14), 21.4 (t, C-6), 28.6 (t, C-7), 33.1 (t, C-1), 33.2 (s, C-4), 33.6 (q, C-13), 41.2(t, C-3), 46.6 (s, C-8), 54.7 (d, C-5), 58.3 (s, C-9), 207.9 (s, C-11). MS (EI): *m/z* (%) = 208 (10) [M^+], 191 (13), 177 (11), 150 (5), 137 (75), 123 (100), 95 (66), 81 (47), 67 (34).

General procedure for acid-induced rearrangement of (5S,8R,9S,10S)-8,9-epoxyhomodriman-12-yl acetate 523.

Epoxyacetate **523** (30 mg, 0.11 mmol) was dissolved in 1 mL of reaction solvent (see Table 4.1) and treated with the solution of the corresponding acid (0.11 mmol in 0.1 mL of reaction solvent) at reaction temperature and for duration as shown in Table 1. The reaction mixture was quenched then with 1 mL of Et_3N-hexane mixture (1:1). Work-up included dilution with 10 mL water, extraction with diethyl ether (3×15 mL), washing ethereal extract with brine to neutral and drying over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude material which was subjected to column chromatography. Gradient elution with EtOAc in hexanes provided pure acetates **558** and **560**, and a mixture of acetates **530** and **559**, which was subjected to hydrolysis.

(+)-14(10→9)-abeohomodrim-4(10),8(12)-dien-12-yl acetate 558: Colorless viscous liquid, R_f = 0.59 (ethyl acetate/petr. ether 3:17). $[\alpha]_D^{25}$ +54.3 (c 0.35, $CHCl_3$). IR (liquid film, cm^{-1}): 2925, 1742, 1460, 1364, 1234, 1034, 880. NMR spectra – 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). Anal. calcd for $C_{18}H_{28}O_2$: C 78.21, H 10.21, O 11.58. Found: C 78.23, H 10.20.

(+)-8α-hydroxy-14(10→9)-abeohomodrim-4(10)-en-12-yl acetate 560.

Colorless viscous liquid. R_f = 0.11 (ethyl acetate/petr. ether 3:17). $[\alpha]_D^{25}$ +34.4 (c 0.25, $CHCl_3$). IR (liquid film, cm^{-1}): 3460, 2927, 1737, 1461, 1364, 1239, 1142, 1082, 1031, 964, 913. NMR spectra – see Table 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). Anal. calcd for $C_{18}H_{30}O_3$: C 73.43, H 10.27, O 16.30. Found: C 73.35, H 10.15.

Hydrolysis of the mixture of acetates 530 and 559.

The mixture of acetates **530** and **559** (70 mg, 75/25 according to NMR data) was dissolved in anhydrous methanol (3 mL) and the obtained solution was treated with potassium carbonate (70 mg) at room temperature on stirring overnight. Following evaporation of the solvent under reduced pressure gave a solid residue, which was partitioned in water (10 mL) and ether (3×15 mL). Combined etheric fractions have been washed with diluted sulfuric acid, saturated sodium bicarbonate and brine, and then dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude material, which was subjected to column chromatography. Gradient elution with increasing concentration of EtOAc in hexanes provided pure methyl ether **562**, followed by alcohol **561**.

(+)-4(8)α-oxy-14(10→9)-abeohomodriman-12-ol 561: Colorless viscous liquid. R_f = 0.25 (ethyl acetate/petr. ether 3:17). $[\alpha]_D^{25}$ +23.9 (c 0.47, $CHCl_3$). IR (liquid film, cm^{-1}): 3400, 2932, 2870, 1452, 1386, 1073, 1041, 1012, 853. NMR spectra – see Table 2. EIMS: *m/z* (%) = 252 (15) [M^+], 234 (7), 219 (8), 207 (80), 189 (20), 179 (100), 161 (40), 151 (20), 138 (30), 119 (50), 107 (60), 95 (60), 81 (35), 69 (37), 55 (50), 43 (90). Anal. calcd for $C_{16}H_{28}O_2$: C 76.14, H 11.18, O 12.68. Found: C 76.03, H 11.03.

(-)-9-(2-methoxyethyl)-austrodor-9-one 562: Colorless viscous liquid. R_f = 0.32 (ethyl acetate/petr. ether 3:17). $[\alpha]_D^{25}$ -2.4 (c 0.2, $CHCl_3$). IR (liquid film, cm^{-1}): 2926, 1693, 1464, 1383, 1369, 1161, 1118, 995, 967. NMR spectra – see Table 4.2. EIMS: *m/z* (%) = 265 (1) [M^+], 248 (2), 234 (4), 219 (4), 201 (7), 179 (10), 163 (7), 150 (7), 138 (30), 129 (97), 123 (100), 109 (25), 97 (85), 81 (30), 69 (50), 55 (40), 41 (30). Anal. calcd for $C_{17}H_{30}O_2$: C 76.64, H 11.35, O 12.01. Found: C 76.53, H 11.20.

Acetylation of alcohol 561.

Alcohol **561** (15 mg, 0,063 mmol) was dissolved in dry pyridine (1 mL) and treated with acetic anhydride (0.25 mL) at r.t. overnight. Workup included distillation of the solvent under reduced pressure and partitioning of the residue in water (10 mL) and ether (3×15 mL). Combined etheric fractions have been washed with diluted sulfuric acid, saturated sodium bicarbonate and brine, and then dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave 18 mg (0.063 mmol) of pure acetate **559**.

(+)-4(8)α-oxy-14(10→9)-abeohomodriman-12-yl acetate 559: Colorless viscous liquid. R_f = 0.33 (ethyl acetate/petr. ether 3:17). $[\alpha]_D^{25}$ +23.03 (c 0.33, $CHCl_3$). IR (liquid film, cm^{-1}): 2967, 2930, 2870, 1742, 1365, 1238, 1074, 1034, 854. NMR spectra – see Table 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). Anal. calcd for $C_{18}H_{30}O_3$: C 73.43, H 10.27, O 16.30. Found: C 73.35, H 10.08.

(8S,9R)-30(10→9)-abeodrim-4(10)-enyl-(13*E*,17*E*,21*E*-15-phenylsulfonyl-16-oxo)-farnesyl benzyl ether 564.

Drim-8(27)-enyl-(13*E*,17*E*,21*E*-15-phenylsulfonyl-16-oxo)-farnesyl benzyl ether **467** (40 mg, 0.06 mmol) was dissolved in 2-nitropropane (0.7 mL) and a solution of FSO_3H (0.017 mL, 0.3 mmol, 5 equiv.) in 2-nitropropane (0.2 mL) was added under argon to the resulting solution at –78 °C. After 20 min of stirring, the reaction mixture was quenched with a solution of triethylamine (0.5 mL) in light petroleum ether (0.5 mL). Removal of the cooling bath, dilution with brine (10 mL), and usual work-up gave crude product (42 mg), which was submitted to flash chromatography (1% ethyl acetate/benzene) to give compound **564** (25 mg, 62%). IR (liquid film) ν_{max}: 740, 1145, 1312, 1385, 1451, 1668, 1793, 2286, 2993, 3362 cm^{-1}. ^1H NMR (see: Table 4.3). ^{13}C NMR (see: Table 4.3). Found (%): C, 77.12; H, 8.91. $C_{43}H_{58}SO_4$. Calculated (%): C, 76.97; H, 8.71.

4.6. Conclusions to chapter 4

A stereospecific synthesis of austrodoric acid **521**, a marine nor-sesquiterpene exhibiting an unprecedented carbon backbone, has been accomplished in seven steps from commercial homodrimane (+)-sclareolide **524** [164],[165].

An alternative synthetic method towards austrodorane skeleton has been elaborated. It comprises a new highly selective synthesis of isodrimenol **546**, followed by epoxidation and ring contraction. Natural austrodoral **522** was synthesized starting from 8,11-drimane diol **544** readily available from commercial (+)-sclareolide **524**, in an overall yield of 44% after 8 synthetic steps. *nor*-Sesquiterpene hydrocarbon **541**, a key intermediate in the synthesis of natural hydroquinones, has been also prepared in optically active form [173].

Rearrangement of homodrimanic epoxides has been investigated using different acid inducers and reaction conditions. As a result, it was possible to control the selectivity of the rearrangement process. Besides ring contraction, the rearrangement can include a cascade of epoxide opening, followed by methyl and proton shifts. The second reaction pathway provided a biomimetic protocol for the efficient synthesis of the halimanic bicyclic fragment in optically active form. The lateral chain length has proved to be the crucial factor influencing methyl migration to compete with ring contraction [188].

The rearrangement process can dominate in terpenic substrates with both open chains and double functionalization. A remarkable interference of heteroatomic functional groups was shown on the example of the triterpenic sulfone **579**, which resulted in total inhibition of the polyenic system under superacidic treatment. This substrate-controlled event promotes efficiently only the reactivity of the bicyclic fragment, forcing a less expected reaction pathway which includes a very selective deep skeletal rearrangement. Such a reactivity can be very useful for planning biomimetic schemes to cyclic terpenoids with complex rearranged skeletal and pendant head terpenic units [123].

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

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

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

5.1 Synthesis of the perhydroindanic fragment of norrisolide

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

Sponges are among the marine sources that constantly provide new opportunities and challenges to synthetic organic chemists. A large group of diterpenic compounds originate from marine sponges

and are named spongianes. The characteristic feature of this group is the tetracyclic skeleton **565** (Figure 5.1). The first reported member of this family was isoagatholactone **566** isolated by Cimino et al. from a Mediterranean specimen of *Spongia officinalis* [214] in 1974. Following reports in the literature showed numerous examples of isolated compounds of this family [215.] To date, there are around seventy known spongianes, which mainly differ in the extent of oxidation at C(17) and C(19) and the oxidation pattern on rings A-D. They are also considered biosynthetic precursors of rearranged spongianes like gracilane **567** or norrisolide **568**. And the diversity of rearranged spongianes is even more impressive. The basic interest for the spongianes is due to their spectrum of biological activities, including cytostatic, cytotoxic, antimicrobial and antiinflamatory action [215].

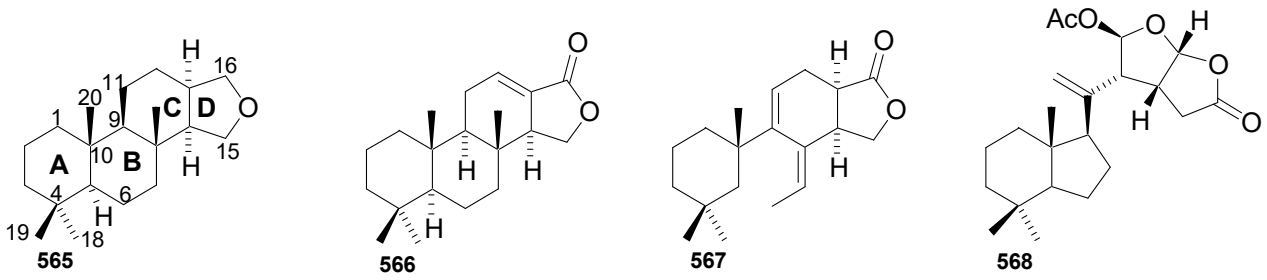


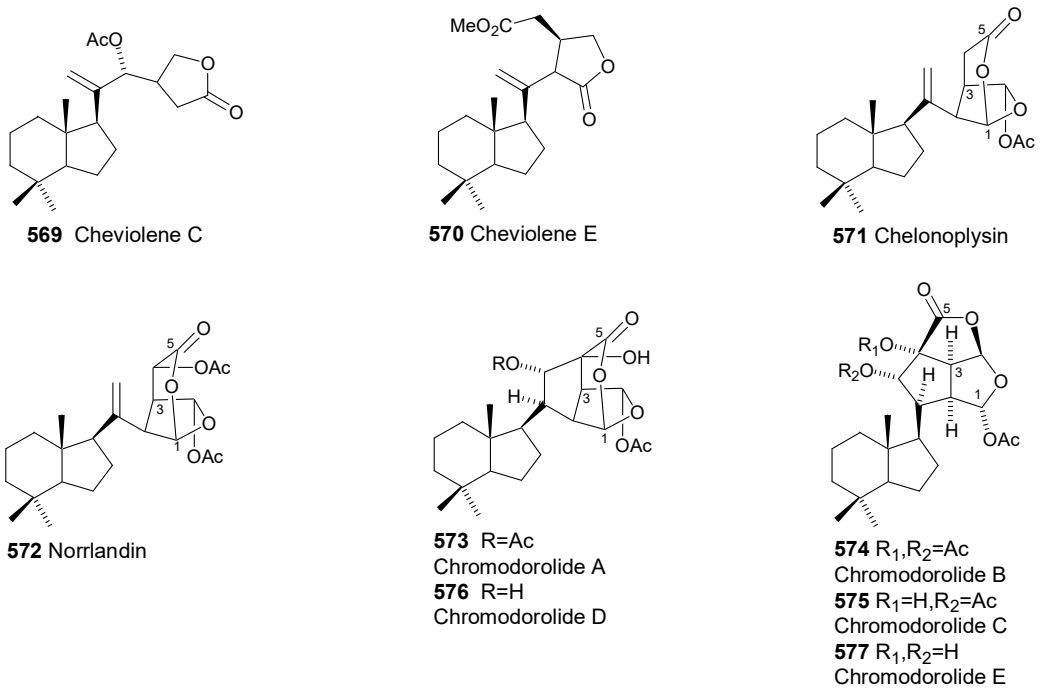
Figure 5.1. Representatives of spongiane diterpenoids.

During the past two decades, several syntheses of compounds with the spongiane carbon framework have been reported starting basically from different diterpenic compounds like manool [216] methyl isocopalate [217] labda-8(20),13,dien-15-oic acid [218] or monoterpenic optically active carvone [219]. Elegant biomimetic procedures have been also reported and consisted of radical cyclization of suitable constructed open chain substrates [220],[221],[222]. It is also noteworthy mentioning a recent published synthesis of C(17)-functionalized spongianes starting from (+)-podocarp-8(14)-en-13-one [223]. Most of the reports devoted to this subject relate to the synthesis of cycle A- and D-functionalized compounds, along with C(17)-oxidized derivatives.

On the other hand, reports on the synthesis of rearranged spongianes are limited to publications related to gracilanes [224],[225] and norrisolide **568** chemistry [226],[227],[228]. In particular, norrisolide is very interesting from the biological activity point of view, and this is due to its effect of inducing an irreversible vesiculation of Golgi membranes, without affecting the microtubules structure [228]. It was shown that perhydroindane core of **568** is critical for binding to the target

protein. This property is connected to potential therapeutic applications of **568**, since this mechanism of action is similar to that observed for the well explored ilimaquinone, a compound with antimicrobial, anti-HIV, anti-inflammatory and antimitotic activities [229].

The perhydroindane fragment of **568** is relatively rare in natural products [215], and the known compounds have a specific structure, including also a highly oxygenated fragment, which is important for the bioactivity profile too. Examples are cheviolenes C **569** and E **570**, chelonoplysin **571** and norrlandin **572**, chromodorolides A-E **573-577** (Figure 5.2). In particular, chromodorolides have shown significant cytotoxicity against the P388 mouse leukemia cell line and chromodorolide A **573** possesses antimicrobial and nematocidal activity.



569 Cheviolene C

570 Cheviolene E

571 Chelonoplysin

572 Norrlandin

573 R=Ac
Chromodorolide A
576 R=H
Chromodorolide D

574 R_1,R_2=Ac
Chromodorolide B
575 R_1=H,R_2=Ac
Chromodorolide C
577 R_1,R_2=H
Chromodorolide E

Figure 5.2. Rearranged spongianes having perhydrindane bicyclic fragment.

The total synthesis of norrisolide **568** has been published by Theodorakis and co-workers [226]. The synthetic sequence comprises more than 20 steps and the key reaction is assembling of the norrisolide skeleton by coupling of bicyclic fragments **578** and **579** obtained respectively from optically active diketone **580** and butenolide **581** (Figure 5.3).

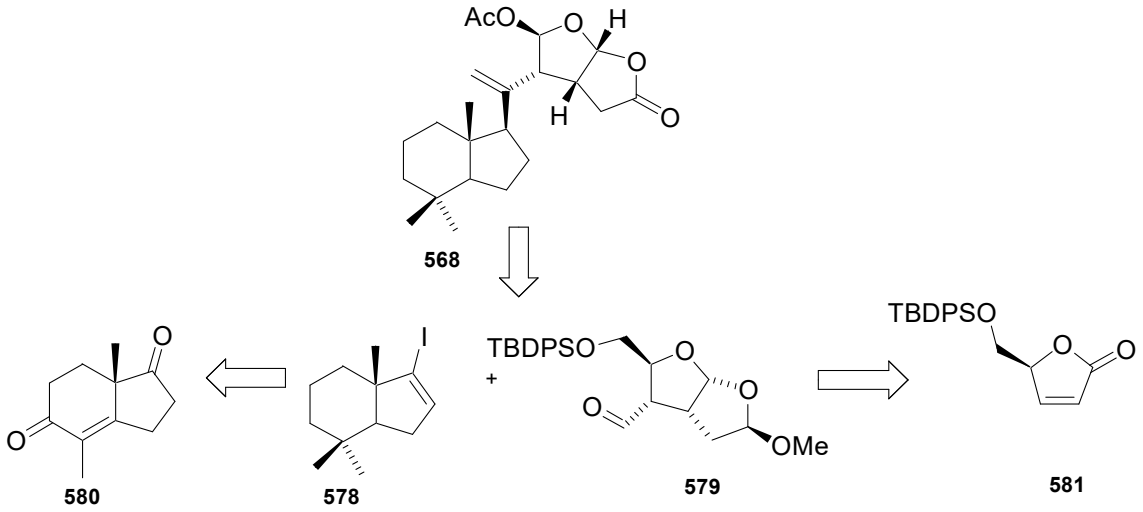


Figure 5.3. Theodorakis' strategy for the synthesis of norrisolide **568**.

A similar synthetic strategy was developed by the group of Snaper [227] in a recently reported synthesis of **568** (Figure 5.4). It was based on a convergent strategy and the key step was a Shapiro reaction between the sulfonylhydrazone derived from ketone **582** and Weinreb amide **583**. Perhydrindanic ketone **582** was obtained from diene **584** via a ring closing metathesis reaction and heterocyclic fragment from butenolide **585**. The synthesis comprised 14 steps in the longest linear sequence.

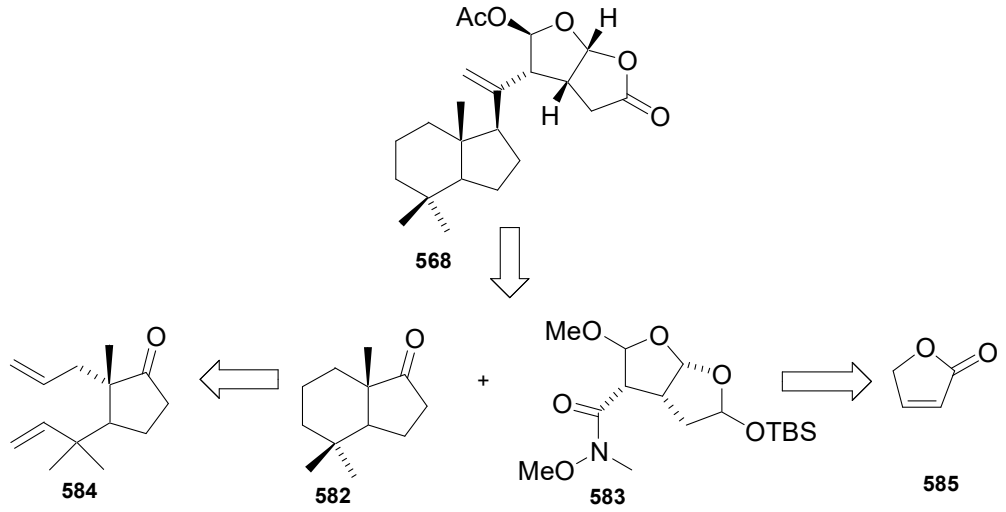


Figure 5.4. Snapper's strategy for the synthesis of norrisolide **568**.

Both these works report ketone **582** as the key perhydrindanic unit on their path towards natural **568** and in spite of the apparent structural simplicity, the synthesis of **568** required substantial efforts. In fact, other authors have also targeted this versatile building block with more or less success [228],[229],[230]. We have decided to change the coupling strategy towards compounds of norrisolide family and considered another perhydrindanic precursor for this extraordinary rearranged spongianes. The impetus for this strategy was a work of Reiser and co-workers who reported a very efficient synthesis of a suitable *cis*-fused 5-oxofuro[2,3-b]furan synthon **586**, starting from the readily available methylfuroate **587** [231]. It could be a coupling partner for an aldehyde of hydrindane structure **588** to provide the norrisolide skeleton (Figure 5.5).

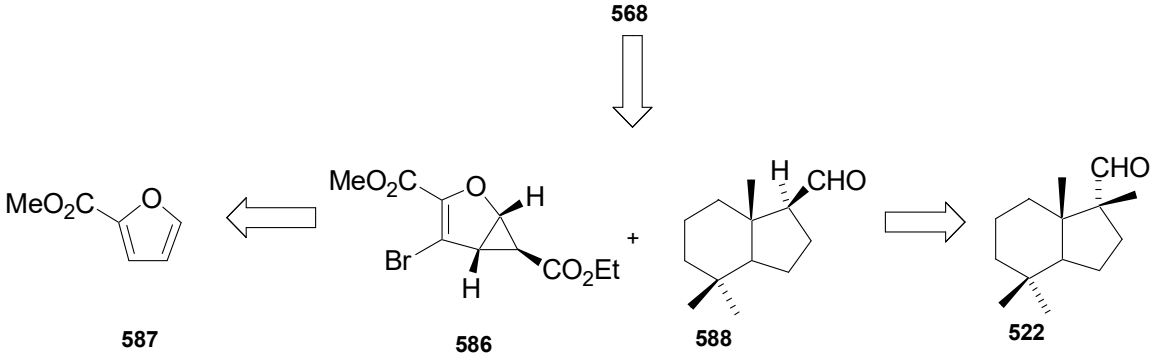


Figure 5.5. Reiser's strategy for the synthesis of norrisolide **568**.

The aldehyde **588** could be obtained in a relatively short synthetic sequence, starting from compounds of hydrindane structure like austrodoral **522**. The synthetic problem on this route comprises removal of one mehyl group from **522** and reversing the stereochemistry of the formyl functional group, which is β-oriented in **588**. We applied a degradation approach in order to successfully face this challenge. The transformation of aldehyde **522** to the shorter analogue **588** included only 5 synthetic steps and is represented in Figure 5.6 [232],[233].

The first transformation of the aldehyde **522** was a Baeyer-Williger oxidation promoted by *m*-CPBA under buffered conditions. Although in a previous work [229] this reaction provided only a modest yield of formate **589**, we have found that purification of peracid by removal of 3-chloro-benzoic acid and carefully drying provided a much better yield of the desired ester. This transformation was amendable on a multigram scale. Hydrolysis of the formate **589** provided the tertiary alcohol **590**, which was investigated under different dehydration conditions. Unfortunately,

as it was observed previously [229], the dehydration of this substrate showed a clear tendency to provide the rearranged hydrocarbon **591**. A careful selection of dehydration agents showed better results with Martin's sulfurane and finally the Swern oxidation protocol, using DIPEA as amine quenching reagent allowed a good dehydration yield with a satisfactory selectivity of exocyclic olefin **592**.

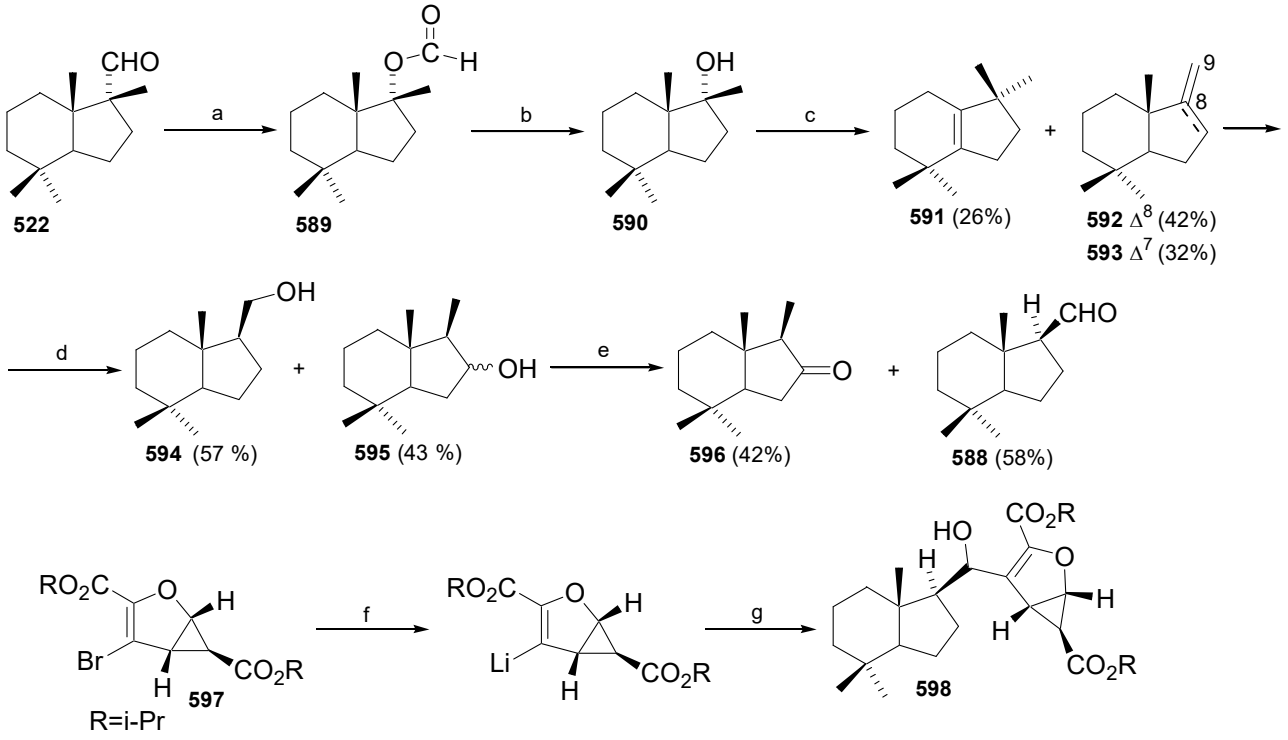


Figure 5.6. Synthesis of an advanced precursor **598** of norrisolide. Reagents and conditions: (a) *m*-CPBA (pure), $NaHCO_3$, DCM, 90%; (b) KOH, 90%; (c) Swern oxidation, DIPEA, 73%; (d) BH_3-DMS, then NaOH-H_2O_2, 74%; (e) PCC, 89%; (f) *t*-BuLi, Trapp mix., -115 ^oC; (g) + **588**, then H_2O, 60%.

The mixture of hydrocarbons **591**-**593** was not separated, but submitted to the next hydroboration-oxidation sequence. The rearranged compound **591** remained intact under reaction conditions and the mixture of alcohols **594** and **595** was oxidized with PCC to provide the mixture of aldehyde **588** and ketone **596**, which was readily separated by flash chromatography.

As a proof of concept, the aldehyde **588** was coupled with the lithiated bromide **597** and the coupled product **598** was successfully isolated. It represents an advanced precursor of norrisolide **568**,

basing on the transformations involving the highly oxygenated fragment reported previously [231]. The obtained perhydrindanic aldehyde **588** can be also used for the synthesis of other compounds of these series.

5.2 Biomimetic degradation processes based on ozonolysis.

Oxygen-containing heterocycles are structural motifs widely found in natural products of different origins. A range of biologically active compounds such as *C*-nucleosides, ionophore antibiotics, acetogenins, and brevetoxins incorporate cyclic polyether moieties in their structural backbone. Consequently, considerable effort has been undertaken to elaborate new efficient synthetic methods to access cyclic ethers of different ring sizes [234]. Functionalized polyethers are of special interest in synthetic organic methodology, because their synthesis often requires considerable effort. Historically, different strategies have been undertaken in order to access functionalized *O*-heterocycles. The most common strategy is based on a biomimetic approach and consists of assembling the specifically functionalized aliphatic chain, followed by a C-O cyclization reaction, promoted by different electrophilic or radical initiators.

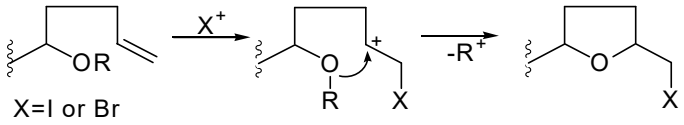


Figure 5.7. Formation of tetrahydrofurans through carbocation generation.

Normally, formation of cyclic ethers is a two-step process involving the formation of a carbocation through electrophilic addition of an olefin, followed by intramolecular nucleophilic attack of an oxygen substituent on the carbocation (Figure 5.7). This strategy works well for the synthesis of tetrahydrofuran ring systems. On the other hand, the utility of a conjugated diene system in such a transformation is underexplored. In our opinion, the conjugated system can contribute to an alternative reaction course and may result in greater flexibility for building functionalized oxygen heterocycles [235],[236].

Research on isolation of polyethers from the marine dionoflagellate *Karenia brevis* has delivered various families of ladder frame polyethers containing conjugated dienes. One of the

examples is brevenal **599** (Figure 5.8), a polyetheric compound which does not possess the toxicity of other brevetoxins, but acts on the contrary, as a brevetoxins antagonist [237].

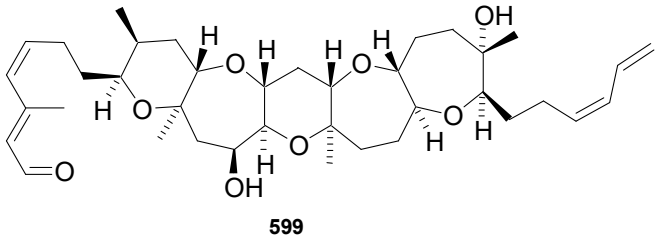


Figure 5.8. The structure of brevenal.

We envisioned, that conjugated diene functionality in **599** could be used for further functionalization of this and other natural ladder frame polyethers of similar structure. In order to check the feasibility of this approach, we have designed a model compound **599** to mimic the lateral chain with conjugated double bonds that incorporates a free hydroxy- group at the γ-position with respect to the olefinic bond. Based on the general mechanism of tetrahydrofuran formation (Figure 5.7), one can assume that the generation of a carbonium ion in the lateral chain, would inevitably lead to a cyclization event involving the free hydroxy- group to provide a functionalized furan ring. The synthesis of the model substrate **600** is presented in Figure 5.9.

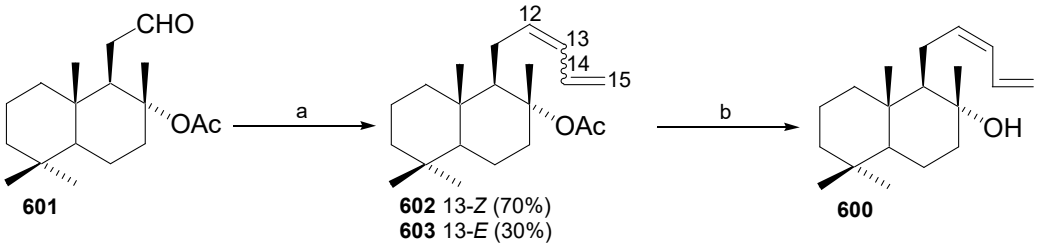


Figure 5.9. Synthesis of model substrate **600**. Reagents and conditions: (a) $[Ph_3PCH_2\text{-}CH{=}CH_2]^+Br^-$, BuLi, THF, 76%; (b) KOH/EtOH, then HPLC.

The bicyclic system of **600** possesses a conjugated double bond in an equatorial position and a tertiary hydroxy- group *trans*-configured relative to the lateral chain. It is noteworthy to mention that an isoprenoid polycycle has recently been used as a model to support an alternative mechanism for the synthesis of marine polyether toxins [238].

Functionalization of conjugated double bonds can be performed by selective ozonolysis, and this type of transformation is well documented for similar substrates [239],[240]. In particular, it was demonstrated that the ozonolysis of conjugated double bonds proceeds sequentially [239], and we also planned to selectively transform the lateral chain of **600** under different ozonolysis conditions.

Following these hypotheses, alcohol **600** was submitted to ozonolysis (Figure 5.10). Ozone was added in slight excess and the reaction was performed at different temperatures. At –70 ºC, the major product after borohydride reduction was the known diol **604** – a product of C(12)-C(13) double bond cleavage. Performing the ozonolysis at 0 ºC provided a compound containing two carbon atoms less than the initial diene side chain suggesting cleavage of the C(13)-C(14) bond. The structure of this compound was determined as **605** using 1D and 2D NMR experiments.

The formation of alcohol **605** was quite unexpected, but the reaction course can be explained on the basis of the Criegee mechanism [241]. It is well known, that this mechanism was the subject of controversial discussions and the most relevant alternative is the so-called unified concept [242].

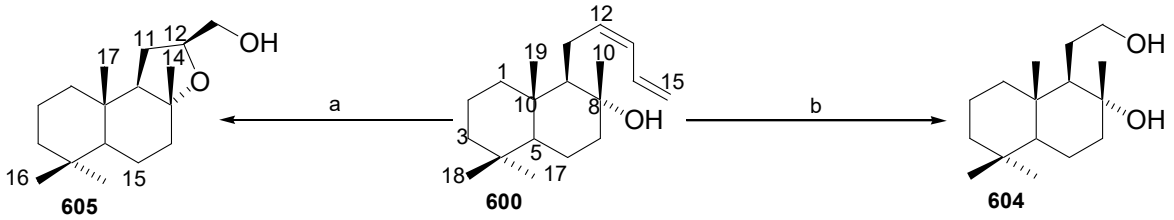


Figure 5.10. Ozonolysis reactions of **600**. Reagents and conditions: (a) O_3/CH_2Cl_2; 0 ºC, then $NaBH_4$; 60%; (b) O_3/CH_2Cl_2; -70 ºC, then $NaBH_4$, 70%.

Recent work on this subject, employing labeled atoms [243], has shown the viability of the Criegee scheme. Our current work brings further experimental evidence for this conclusion. In fact, the formation of alcohol **605** is only possible via Criegee's carbonyl oxide **607** (Figure 5.11). Its stabilization by conjugation with the adjacent double bond leads to a partial positive charge at C(12), intramolecular attack by the hydroxy- group then forms the corresponding heterocycle **609**. Since the stability of the formed vinylic hydroperoxide is extremely low [244], it decomposes to the aldehyde **610**, which is reduced with sodium borohydride to form the alcohol **605**. Similar "abnormal" ozonolysis has been reported and explained on the basis of the intramolecular involvement of the free hydroxy- group in the reaction course [245].

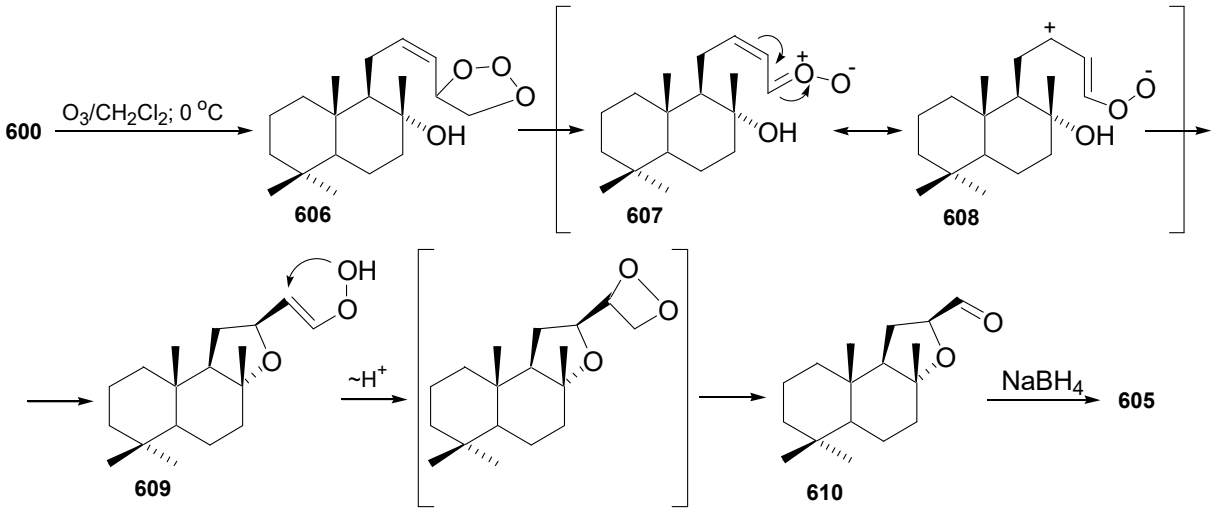


Figure 5.11. Proposed mechanism for the synthesis of tetrahydrofuran **605**.

Tetrahydrofurans similar in structure to alcohol **605** are well known but their formation was based on a different mechanism, suggested on the basis of involvement of iodine in the reaction sequences [246]. From a synthetic point of view, the presence of the hydroxymethylene group at C(12) in alcohol **605** represents an alternative opportunity for further functionalizations.

One of the current challenges of modern chemistry is connected to identification of new sources for bulk and fine chemical production. Extensive use of oil both for energy and chemical industry purposes has led to oil price jumps and made this strategy unacceptable for sustainable development. Therefore, renewable raw materials represent the only viable solution for long term development strategies. Due to the polymeric nature of the most relevant representatives, elaboration of degradation processes is the logic feasible strategy for renewable raw material utilization. Therefore, chemical and microbiological methods of degradation are extensively investigated as potential solutions. Ozonolytic cleavage of organic substrates represents one of the promising pathways in this context. Ozone is a powerful oxidant, can be generated easily "onsite" and unlike other similar oxidants represents no environmental hazards. In order to diminish the limitations of ozonolytic processes, connected primarily to the use of reducing agents, we have initiated a research program for elaboration of sustainable ozonolytic procedures.

The main aspect of the performed investigations deals with the use of water as ozonolysis co-solvent, which allows building of red-ox catalytic cycles based on different inorganic salts, as well as application of environmentally friendly co-oxidants, hydrogen peroxide being the most relevant. Use

of the water-organic solvent mixtures makes work-up procedure very simple and facilitates catalyst recycling. In a representative example, conversion of natural labdanic diterpenoid sclareol **247** to the industrially relevant sclareoloxide **611** (Figure 5.12) was achieved in an excellent 97% yield.

The latter substance represents an organic compound of terpenic structure belonging to the bis-norlabdane family. The interest shown for **611** stems on it olfactive properties, which are expressed as a fine ambergris note. Consequently, sclareoloxide (or norlabdane oxide) is extensively used in aromatization compositions [10],[11], as well as an intermediate in the synthesis of other odorants of terpenic structure [172].

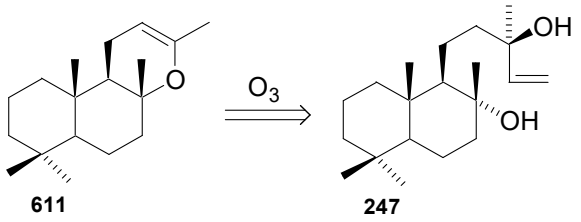


Figure 5.12. Sclareoloxide retrosynthetic scheme.

Industrial production of this compound is based on an oxidative degradation strategy applied to the lateral chain of sclareol **247**. Different reagents have been used as oxidants, including potassium permanganate [247], hypochlorous acid salts in the presence of ruthenium compounds [248], as well as ozone [249]. Off these, potassium permanganate and ruthenium represent expensive reagents, which application assumes large excess, increasing finally the product price. On the other hand the corresponding experimental procedures result in substantial waste materials, which should be also considered, especially in the industrial context. This means additional processing steps, which also contribute to overall process efficiency. Utilization of ozone as oxidant is more advantageous, since the oxidation process is simpler and does not generate relevant wastes. In particular, this process is described in a recent patent [250]. According to this work, ozonization of sclareol is started in an organic solvent and after process initiation an aqueous solution of an inorganic base is added to the reaction mixture in order to keep the reaction pH at basic values (pH 8-13). The following process takes place in a biphasic mixture and for the dissolution of the inorganic base, mixtures of water with other co-solvents, in particular with THF are applied. This procedure is relatively simple, but still suffers from some draw backs. First of all, base addition has to be performed in a controlled manner, in order not to allow the pH values jumps. This add complexity to the process itself. Besides, the use

of different solvent mixtures (DCM, MeOH, H_2O) makes their recycling problematic. Above all, the fact that reaction takes pace in heterogeneous conditions (organic and aqueous phase) limits water access into the organic phase, making reduction of the intermediary ozonides more sluggish. This aspect is very important from the point of view of process safety, since it is known the explosive nature of organic ozonides and peroxides, which is highly relevant especially in industrial context.

We have elaborated an alternative procedure for larger scale sclareoloxide production by sclareol ozonolysis in the presence of water and a co-oxidant under homogeneous conditions [9],[251],[252]. The novelty of the method resides in the use of a co-oxidant, which contribute to a higher rate of lateral chain cleavage in the starting material. Such ozonization strategies are known in the literature, a recent example being the use of lead tetraacetate (LTA) in suprastoicheometric quantities [253]. The effect of this additive is expressed in the scission of the C-C bond according to the classic mechanism of α,β-dioxygenated compounds cleavage (Figure 5.13). This step represents the rate-limiting one and critically contributes to the efficiency of the whole process.

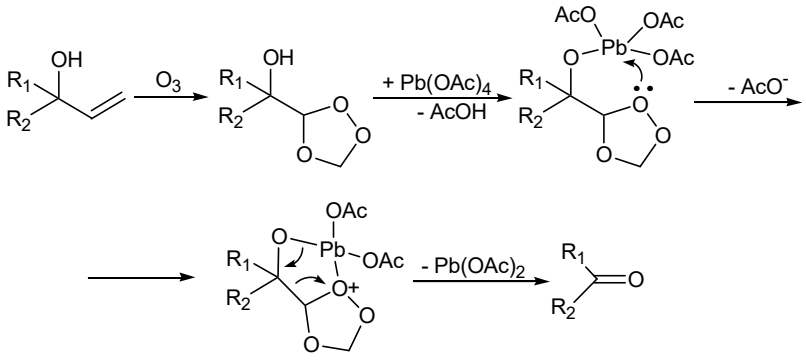


Figure 5.13. Mechanism of LTA mediated C-C cleavage in an ozonolysis process.

But the use of LTA in supra-stoichiometric amounts for the sake of accelerating lateral chain cleavage in sclareol **247** is not advantageous, first of all due to the properties of lead (IV) compounds. LTA is an unstable compound, easily hydrolysable, very toxic and its use in industrial context is strongly discouraged, first of all due to its extremely negative environmental impact.

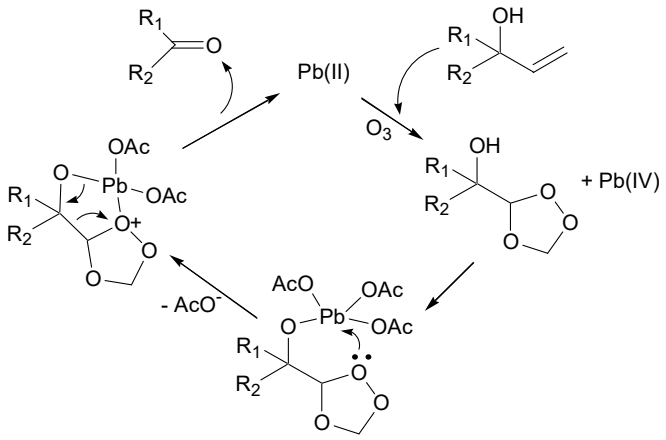


Figure 5.14. Catalytic cycle of allylic alcohols ozonolysis involving Pb(II) catalyst.

Therefore, we considered substitution of LTA with lead diacetate in catalytic amounts, which is well sufficient for acceleration of lateral chain cleavage in **247** under ozonolytic treatment bringing about excellent yields of target sclareoloxide **611**.

Although lead (II) acetate does not have itself the ability to cleave α,β-dioxygenated compounds, under the ozonolysis of the reaction mixture a slow oxidation process takes place under the action of ozone to convert the bivalent salt into LTA. This is sufficient for building a catalytic cycle, contributing dramatically to the rate of the lateral chain cleavage (Figure 5.14).

Due the low solubility of lead (II) acetate in organic solvents, the aqueous acetone is used as a suitable solvent for this transformation. This combination is convenient from different points of view. First of all, it is well known that water represents an efficient quenching reagents for intermediate ozonides and peroxidic species [254]. Acetone is water miscible and allows the reaction to be performed under homogeneous conditions in the presence of inorganic additives. The possibility of facile distillation of acetone after the reaction under reduced pressure makes its recycling a routine operation as well as product isolation and catalyst recovery.

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

Scalarane compounds, discussed in detail in the chapter 1 of the current work, show diverse pharmacological properties and this is directly connected to their structural diversity. It mainly arises

from the different arrangement of the oxidized carbons C(19) and C(20) which can be involved in a cyclization process to form a 5-membered ring more or less oxidized (i.e. scalarin **336** [96]), as well as at C(12), such as in scalaradial **337** and related compounds (Figure 5.15). However, a number of natural scalaranes display additional oxygenated groups at different positions of the tetracyclic framework (i.e. heteronemin **612** [255], 3-keto-deoxoscalarin **613** [256], 6-keto-deoxoscalarin **614** [257]). The B-ring functionalization has been reported also for a series of scalaranes (i.e. **615**) isolated from ferns, the unique report of scalarane occurrence in plants [258].

Although different synthetic pathways towards this class of compounds have been elaborated [102],[103] previous works on synthesis of scalarane derivatives were focused mainly on compounds displaying functional groups in the D-ring. We report here our study towards the functionalization at ring B by using a radical relay halogenation (RRH) method. This investigation resulted in the synthesis of scalarane compounds functionalized at C(6) and C(7) positions [155],[259].

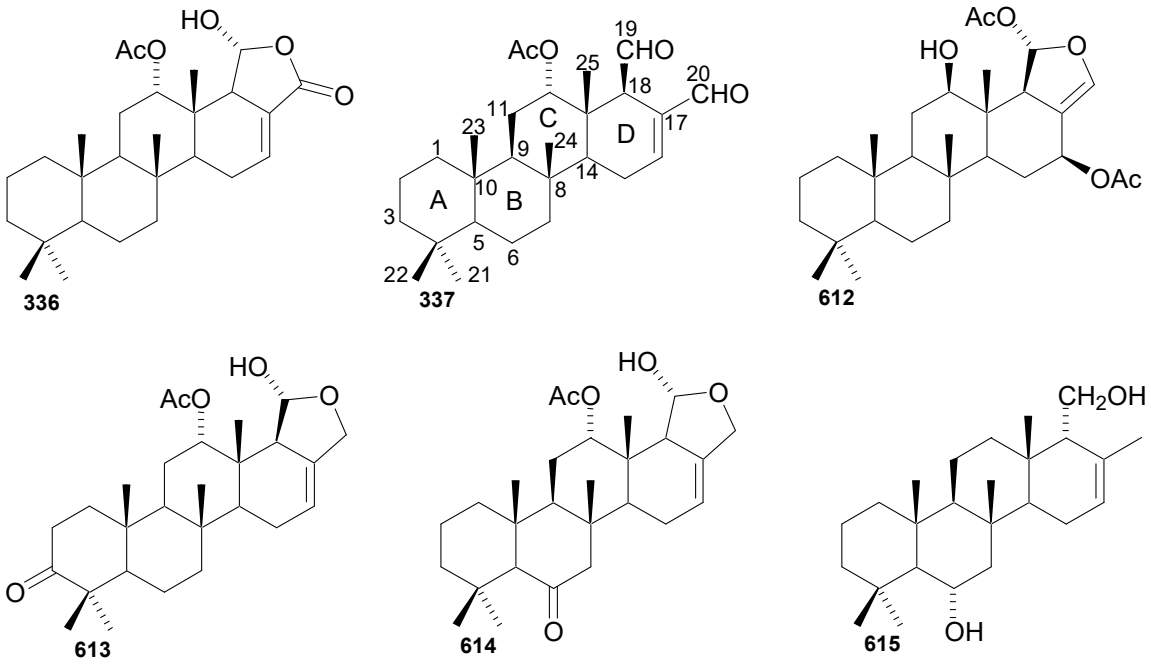


Figure 5.15. Representative members of scalarane family.

The synthetic strategy was based on the assembling of the scalarane skeleton, followed by a remote functionalization procedure. The synthesis of the scalaranic framework was conveniently achieved by a C_5 homologation of the readily available sclareol **247**, followed by a superacid induced

cyclization of the bicyclic ester **508** to the scalarane **343** (Figure 5.16). This transformation sequence was addressed in chapter 2 above.

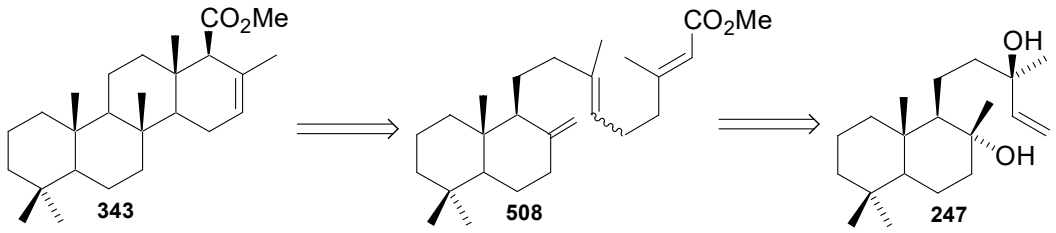


Figure 5.16. Scalarane retrosynthetic scheme.

The subsequent transformation of the ester **343** into a B-ring oxidized scalarane was planned to be performed by the remote functionalization strategy, which has been broadly used in the field of isoprenoids [260].

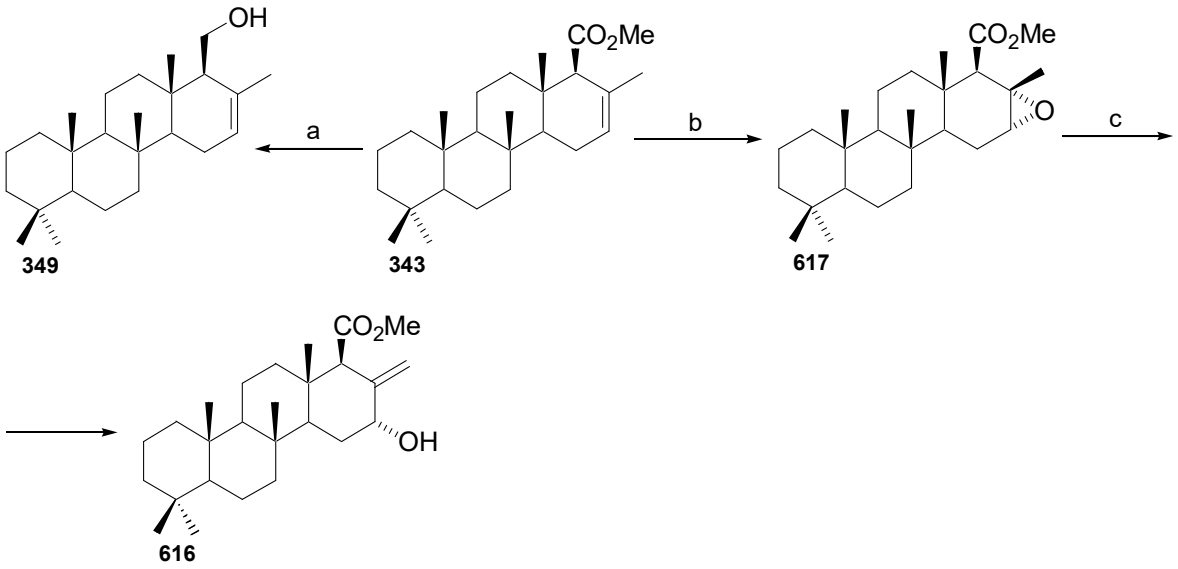


Figure 5.17. Synthesis of scalaranic substrates for remote functionalizations. Reagents and conditions: (a) $LiAlH_4$; (b) *m*-CPBA, DCM; (c) $Al(O\textit{i}\text{-}Pr)_3$; Ph-Me, reflux, quant.

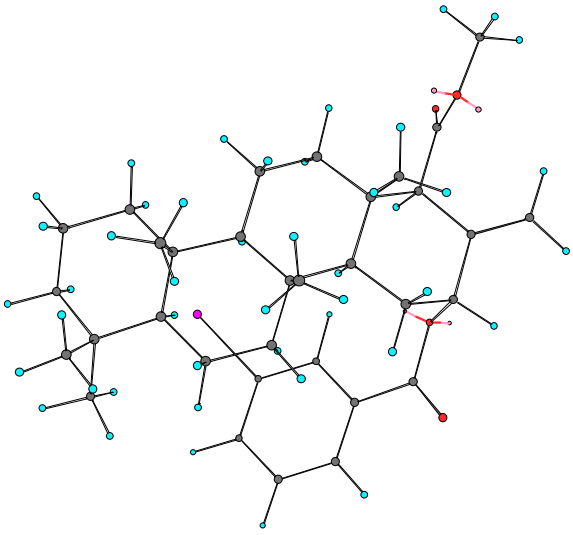
The characteristic feature of these reactions is the generation of a free radical in the molecule of the substrate, that has to contain a suitable functional group playing the role of a "relay" for the free radical formation, followed by the functionalization of nearby disposed C-H bond by this radical. The position of functionalization is governed mostly by steric factors. The ester group of **343** can be

reduced to the alcohol functionality (Figure 5.17) as a radical relay handle but, for the B-cycle functionalization of scalaranic skeleton, the hydroxyl group in the corresponding alcohol **349** is disposed too far and cannot interact specifically with the corresponding C-H bonds due to the steric hindrance of the angular methyl groups.

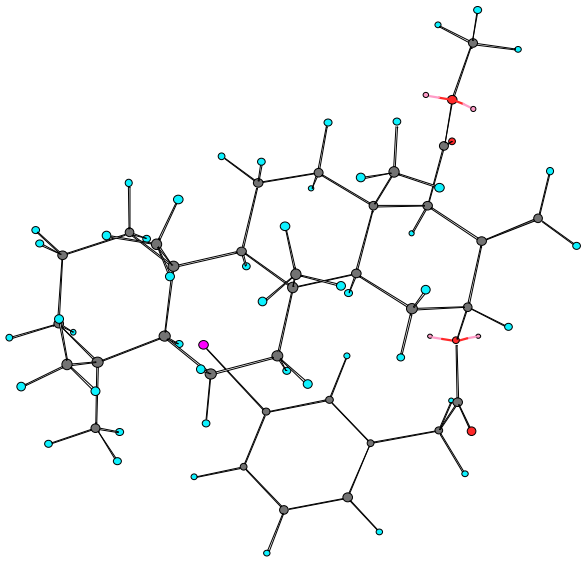
Basing on these judgments, we decided to start from another substrate, the alcohol **616**, obtained in two steps from ester **343** via the epoxide **617** [261], and to apply a well-known remote functionalization procedure, the Radical Relay Halogenation (RRH), which was introduced by Breslow and coworkers [262] and used in the field of steroids. This procedure is based on the interaction of the hydroxyl in the substratum with an aromatic acid, containing the iodine atom in the ring, followed by a photolytic halogenation of the resulting ester under the action of a chlorinating agent. As the result, the iodo-aromatic fragment forms a radical that abstracts the hydrogen atom from a tertiary carbon suitable disposed in the spatial surrounding of the molecule to provide a chloro-derivative. The abstraction position is dependent on geometrical factors. The hydroxyl group at C-16 in compound **616** was recognized as an excellent link for a RRH reaction. In fact, it possesses the α-configuration, which exactly matches the configuration of the tertiary hydrogen atoms H-5 and H-9 in the cycle B. The abstraction of H-5 should lead to a functionalization in the ring B, whereas the abstraction of H-9 should result in the obtaining a functional group at ring C. Besides, after introduction of the additional functionality by RRH, the hydroxyl and the ester groups in cycle D could be manipulated easily to provide the dialdehyde fragment of scalaradial **337** [261] or other naturally occurring scalaranes.

According to the conclusions made by Breslow [262],[263], the substitution of a tertiary hydrogen for a chlorine atom depends mainly on geometrical factors. First of all, in order to achieve the transition state, there should be a match between the distance from the hydroxyl oxygen of the substrate to the tertiary hydrogen to be abstracted and the distance from the same hydroxyl oxygen to the chlorine linked to the aromatic fragment.

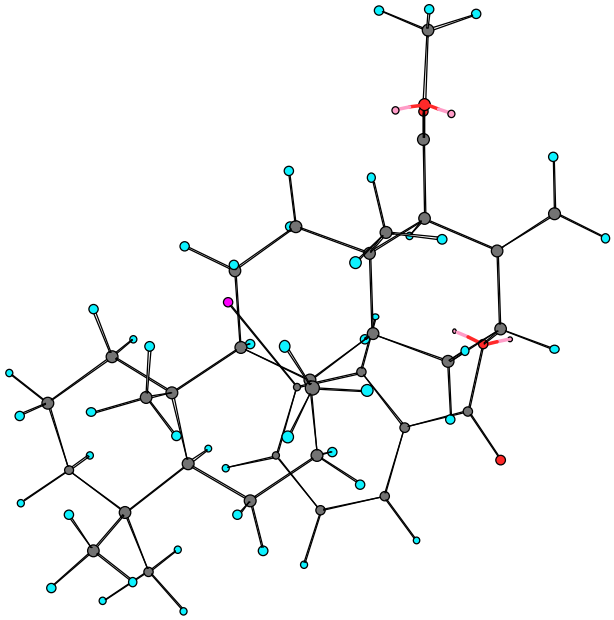
Molecular modelling simulations showed that, from this point of view, both 3-iodobenzoic and 3-phenylacetic acids meet these requirements for the abstraction of the hydrogen at either C-9 or C-5 position of scalaranic skeleton. The calculated distances in compound **616** from the oxygen atom at C-16 to the hydrogen atom at both C-5 and C-9 are 5.93 Å and 4.89 Å, respectively.



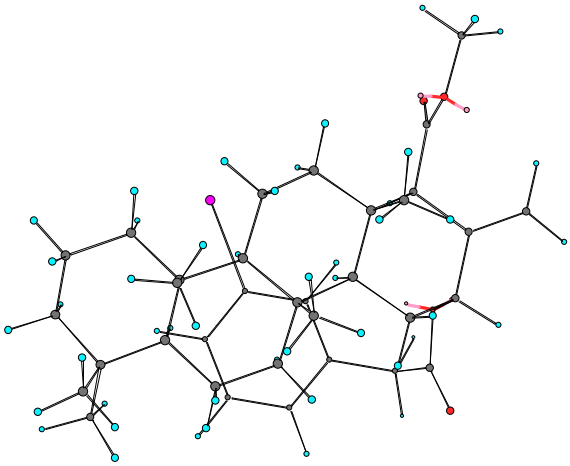
Ester **618**. C-5 abstraction of proton.
Total steric energy E=70Kcal/mol
C-5 - I distance = 4.58 Å.



Ester **619**. C-5 abstraction of proton.
Total steric energy E=62Kcal/mol
C-5 - I distance = 4.28 Å.



Ester **618**. C-9 abstraction of proton.
Total steric energy E=71 Kcal/mol
C-9 - I distance = 4.93 Å.



Ester **619**. C-9 abstraction of proton.
Total steric energy E=60 Kcal/mol
C-9 - I distance = 4.44 Å.

Figure 5.18. Optimized conformations of esters **618** and **619**.

Consequently, 3-iodobenzoic acid (the distance O-Cl in the transition state [262] is 4.3 Å) is a template matching better selection criteria for C-9 abstraction, while 3-iodophenylacetic acid (the distance O-Cl in the transition state [262] is 6.8 Å) is more prone to abstract the hydrogen from C-5

position of the scalarane substrate. The optimized conformations for the aromatic ester derivatives **618** and **619** are drawn in Figure 5.18. The minimal total repulsion energy for all conformations does not differ significantly, so the probability factor to achieve C-5 or C-9 abstraction of hydrogen atoms is almost equal. But according to Breslow [263], another requirement for the RRH process is the possibility of obtaining a linear transition state C--H--Cl--I with a total iodine-carbon separation ≤ 5.37 Å. Analysis of molecular modelling calculation data showed that for both esters **618** and **619** is not possible to adopt a linear arrangement of the C-9--H--Cl--I atoms thus preventing the abstraction of H-9.

So, by these considerations, the RRH reaction on both substrates **618** and **619** should only result in the abstraction of the hydrogen atom at C-5. These theoretical observations were proven by RRH experiments performed with both compounds **618** and **619**, which only gave product **620**. The synthetic sequence leading to B-cycle functionalized scalaranes **620-622** is shown in Figure 5.19. Esterification of the secondary hydroxyl group in compound **616** proceeded smoothly with acyl chlorides of both 3-iodobenzoic acid and 3-iodophenylacetic acid. The acyl chlorides were obtained from the corresponding acids on treatment with an excess of thionylchloride at reflux [264]. The esterification proceeded in benzene at reflux in the presence of pyridine. A catalytic amount of DMF added to the reaction mixture accelerated the reaction rate. In the case of less reactive 3-iodobenzoylchloride a 3-fold excess of chloranhydride assured almost a quantitative yield of the ester **618**.

RRH reactions were performed using different chlorine radical donors and solvent mixtures. In the case of 3-iodobenzyl ester **734** the better yields were obtained using iodophenyldichloride [265] in a mixture of dichloromethane/*tert*-butanol, 2:1, under irradiation with two incandescent lamps (100W+200W) for 2 h at room temperature. The subsequent dehydrohalogenation – hydrolysis with KOH in a dioxane-methanol mixture provided ester **620**. 3-iodophenylacetic ester **619** was transformed into the same product **620** under the action of sulfuryl chloride and dibenzoyl peroxide in carbon tetrachloride at reflux for 5 h, followed by the same dehydrohalogenation – hydrolysis procedure. The structure of compound **620** was determined by high resolution mass spectrometry and a detailed 2D-NMR analysis.

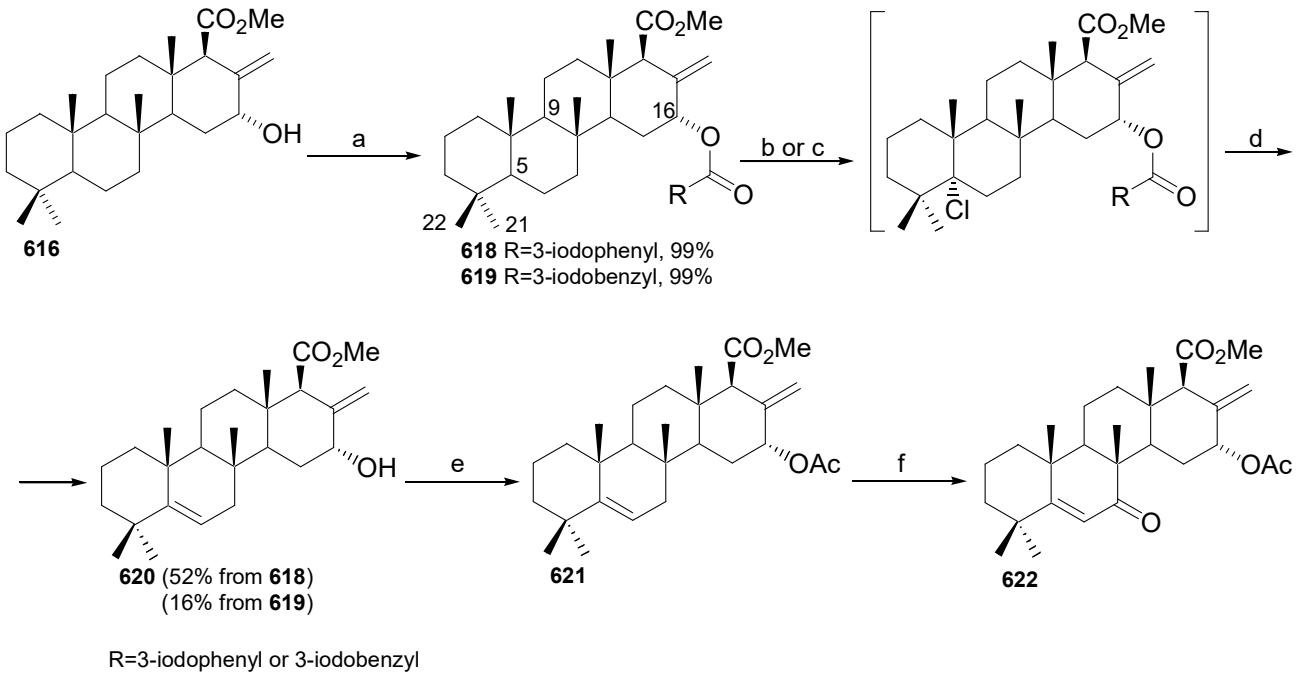


Figure 5.19. Ring B functionalization of methyl 18αH-scalar-16α-ol-17(20)-en-19-oate **616** by Radical Relay Halogenation. Reagents and conditions: (a) R-COCl, Py; (b) $PhICl_2$, DCM, reflux; (c) SO_2Cl_2, DCM, reflux; (d) KOH, dioxane, 70 ºC; (e) Ac_2O/Py, quant.; (f) t-BuOOH, CuI, 55%.

First of all, the molecular formula $C_{26}H_{40}O_3$, deduced by the sodiated ion peak at *m/z* 423 (M+Na) in the HRESIMS spectrum, exhibited the expected additional unsaturation degree with respect to the starting product **616**. Analysis of ^{1}H- and ^{13}C-NMR spectra of **620** in comparison with those of **616** [261], (considering that ^{13}C-NMR values of the pairs C-9/C-18, and C-24/C-25 of ester **616** reported in ref. 261 should be inverted and reassigned as: C-9 (δ 61.3), C-18 (δ 57.5), C-24 (δ 17.3), and C-25 (δ 14.0)) showed that the difference was in the presence of a trisubstituted double bond [δ_C 148.1 (s) and 116.4 (d); δ_H 5.39 (m)] in the scalarane skeleton of **620**. The ^{1}H-^{1}H COSY spectrum indicated that the olefinic proton at δ 5.39 (H-6) was correlated to a methylene (H_2-7) resonating at δ 1.77 (m) and 1.99 (dd, *J*=17,5) linked to a quaternary carbon, according to the position of the double bond either at C-5/C-6 or at C-9/C-11. The expected location in the ring B was supported by the down-field shifted ^{13}C values of both β-methyl groups C-21 (δ 29.4 in **620**, δ 21.3 in **616**) and C-23 (δ 20.3 in **620**, δ 16.2 in **616**) of the scalarane framework, due to the different steric arrangement of ring B and absence of the γ-gauche effect of C-6. All proton and carbon resonances, assigned by

2D-NMR (^{1}H-^{1}H COSY, HMQC and HMBC) experiments as reported in Experimental, were in agreement with the proposed structure **620**.

Once its structure was proved, ester **620** was subsequently used to functionalize the ring B of the scalaranic framework. Accordingly, acetylation of **620** under standard conditions (Ac_2O-Py) provided the acetate **621** in quantitative yield. The subsequent allylic oxidation of **621** was achieved in an acceptable 55% yield using *t*-butyl hydroperoxide-copper iodide procedure [266] to provide the α,β-unsaturated ketone **622** - a versatile substrate for further transformations.

5.4. Application of the oxidative - degradation biomimetic processes for the synthesis of specifically functionalized terpenes. remote C-H functionalizations. Experimental methods and procedures

11-Noraustrodor-8-yl formate 589.

Austrodoral **522** (356 mg, 1.712 mmol) was dissolved in 20 ml dichloromethane followed by sodium hydrogenocarbonate (359 mg, 4.28 mmol) and *m*-CPBA (pure, 438 mg, 4.28 mmol). The reaction mixture was stirred at r.t. overnight, quenched with a 2N solution of sodium thiosulfate (20 ml) and additionally stirred for 30 min. The phases were separated and the aqueous phase was extracted with dichloromethane (3x15 ml) and the combined organic phase was washed with brine and dried over sodium sulfate. Distillation of the solvent at reduced pressure gave the crude product, which was submitted to flash chromatography. Elution with 15% EtOAc in PE gave 346 mg (1.54 mmol, 90%) of pure formate **589** [229]. ^{1}H NMR ($CDCl_3$, 300 MHz, selected peaks). δ 8.07 (s, 1H), 1.47 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H).

11-Noraustrodor-8-ol 590.

Formate **589** was hydrolyzed according to the procedure described in [229]. The obtained tertiary alcohol **590** showed identical analytical data with that described in the literature. ^{1}H NMR ($CDCl_3$, 300 MHz, selected peaks) δ 1.18 (s, 3H), 0.89 (s, 6H), 0.78 (s, 3H).

Mixture of 11-noraustrodorenes 591-593.

A solution of dimethyl sulfoxide (1.33 mL, 18.66 mmol) in dichloromethane (9 mL) was added dropwise to a stirred solution of oxalyl chloride (0.8 mL, 9.34 mmol) in dichloromethane (15 mL) cooled to –60 °C. After 3 min of stirring at this temperature, a solution of noraustrodorol **590** (1.22 g, 6.22 mmol) in dichloromethane (10 mL) was added dropwise. After 20 min of stirring (–60 °C) DIPEA (7.57 mL, 43.54 mmol) was added to the reaction mixture, and after another 15 min the cooling bath was removed and water (25 mL) was added at room temperature. After separation of the phases, the aqueous phase was extracted with dichloromethane (3×25 mL) and the combined organic phase was subsequently washed with a 20% sulfuric acid solution, a saturated sodium hydrogencarbonate solution, brine, and dried with sodium sulfate. Evaporation of the solvent under reduced pressure gave the crude dehydration product, which was purified by FC. Elution with 5% EtOAc in PE gave 810 mg (4.55 mmol, 73%) of hydrocarbons **591-593** and elution with 15 % EtOAc in PE gave 110 mg (9%) of unreacted starting material. ^{1}H NMR (KV-107) ($CDCl_3$, 300 MHz, selected peaks) δ 5.28-5.32 (m, 0.7H), 4.54-4.58 (m, 2H), 0.962 (s, 2.5H), 0.955 (s, 3.9H), 0.938 (s, 3.9H), 0.901 (s, 3.1H), 0.880 (s, 8.7H), 0.823 (s, 2.3H).

11-Noraustrodor-10-ol 594.

The mixture of hydrocarbons **591-593** (40 mg, 0.22 mmol) was dissolved in 1 ml dry THF and was treated at 0ºC with BH_3-DMS complex (0.1 ml, 1 mmol). After 5 hrs of stirring at r.t., the reaction mixture was treated with 7.5 ml NaOH (3N) and 7.5 ml H_2O_2 (30%) at 0 ºC. Stirring continued overnight at r.t., followed by careful quenching with dilute sulfuric acid to neutral and extraction with diethyl ether (3x30ml). The etheric extract was washed successively with sat. sodium bicarbonate and brine, then dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave 55 mg of crude product which was submitted to FC. Elution with 15% EtOAc in PE gave 41 mg mixture of primary and secondary alcohols **594** and **595**. ^{1}H NMR ($CDCl_3$, 300 MHz, selected peaks) δ 4.22-4.16 (m, 0.2H), 3.89-3.83 (m, 0.6H), 3.71-3.66 (m, 1H), 3.54-3.48 (m, 1H), 3.30-3.24 (m, 0.2H), 0.89 (s, 1H), 0.86 (s, 1.6H), 0.85 (bs, 5.3H), 0.84 (s, 2.8H), 0.73 (s, 2.5H), 0.66 (s, 1.8H).

(+)-11-Nor-austrodor-9-al 588.

The mixture of alcohols **594** and **595** (35 mg, 0.18 mmol) was dissolved in 1 ml DCM and treated at r.t. with 58 mg PCC (0.27 mmol). The reaction mixture was stirred for 1.5 hrs at r.t., then diluted with 25 ml diethyl ether. The formed sediment of chromium compounds was decanted and washed with two 10 ml portions of diethyl ether. The combined etheric fractions have been percolated through a bed of Celite, then the solvent was distilled under reduced pressure. The crude was submitted to FC (Kieselgel 40-60 mkm). Elution with 5% EtOAc in PE gave 14 mg of pure aldehyde **588**, 10 mg of pure ketone **596**, along with 7 mg of mixture of both (89%).

(+)-11-Noraustrodor-9-al 588: R_f = 0.65 (15% ethyl acetate/PE). $[\alpha]_D^{25}$ = +88.7 (c = 1.0, $CHCl_3$). IR (film): ν = 2924, 2712, 1717, 1460, 1387, 1102 cm^{-1}. ^1H NMR (KV-344) ($CDCl_3$, 300 MHz) δ=9.75 (d, J=2Hz, 1H), 2.24 (bt, J=8Hz, 1H), 1.98 (t.d., J_t=3Hz, J_d=1Hz, 0.5H), 1.94 (t.d., J_t=3Hz, J_d=1Hz, 0.5H), 1.0-1.8 (m, 10H), 0.87 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (KV-344) (75.5 MHz, $CDCl_3$): δ=205.3(0); 64.3(+); 62.4; 58.5(+); 44.9(0); 41.38(–); 39.19(–); 33.42(+); 33.2(0); 21.35(–); 20.7(+); 19.99(–); 19.44(–); 15.36(+). HREI-MS: 194,1671. Calculated for $C_{13}H_{22}O$: 194.1671.

(-)-11-Noraustrodor-7-one 596: R_f=0.6 (15% ethyl acetate/PE). $[\alpha]_D^{25}$ = -200 (c = 2.0, $CHCl_3$). IR (film): ν = 2926, 1740, 1461, 1153, 1036 cm^{-1}. ^1H NMR (KV-134) ($CDCl_3$, 300 MHz) δ=2.07 (d, J=7Hz, 0.4H), 2.27 (d, J=7Hz, 0.6H), 1.99 (s., 0.3H), 1.95 (s., 0.3H), 1.94 (s., 0.3H), 1.91 (s., 0.3H), 1.89 (d., J1.5 Hz, 0.6H), 1.54-1.78 (m., 5H), 1.1-1.3 (m., 2H), 0.92 (s, 3H), 0.90 (bs., 4.5H), 0.88 (s, 1.5H), 0.75 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=219.8(0); 59.62(+); 53.82(+); 42.38(0); 41.38(–); 38.05(–); 35.51 (–); 33.49 (+); 32.24 (0); 20.71 (+); 19.40(–); 13.87(+); 7.41. HRMS: 194,1673. Calculated for $C_{13}H_{22}O$: 194.1671.

Coupling of (+)-11-noraustrodor-9-al 588 and (1R,5S,6S)-3,6-diisopropyl-4-bromo-2-oxabicyclo[3.1.0]hex-3-ene-3,6-dicarboxylate 597.

42 ml of Trapp (THF:Et_2O:Pentane, 4:1:1) mixture were thermostated at -115 ºC, then the bromide **597** (1.542 g, 4.63 mmol) dissolved in 12 ml of Trapp mixture was added dropwise,

concomitantly with 6.0 ml 1.7 M sln. t-BuLi (10.2 mmol, 2.2 equiv., freshly opened bottle). After 7 min of stirring at this temperature, the solution of aldehyde **588** (336 mg, 1.73 mmol) in 6 ml of Trapp mixture was added dropwise, the reaction mixture was stirred for 15 min at -115 °C, then was left to reach -40 °C over 30min. Removal of cooling bath and dilution with sat. NH_4Cl was followed by usual workup. The crude product was submitted to flash chromatography (20% EtOAc/PE), to provide the coupling product (467 mg, 1.04 mmol, 60%, calculated on the bases of R-CHO) as a mixture of alcohols **598**. Major diastereomer. R_f = 0.25 (30% EtOAc/PE); $[\alpha]_D^{25}$ = -75 (c = 0.5, $CHCl_3$). IR (film): ν = 3500 (b.), 2954, 1714, 1467, 1374, 1297, 1177, 1103, 1009, 930 cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$) δH = 5.16 (p., J=6H, 1H), 5.01 (sept., J=6Hz, 1H), 4.9-5.0 (b.m., 2H), 2.993 (dd, J1=5Hz; J2=4Hz, 1H), 2.7 (b.s., 1H), 1.240 (d., J=6Hz, 6H), 1.235 (d., J=6Hz, 6H), 0.861 (s., 3H), 0.848 (s., 6H). ^{13}C-NMR (150 MHz, $CDCl_3$) δC =171.35; 159.96; 141.83; 135.96; 69.66; 68.44; 66.69; 65.96; 57.91; 57.41; 42.29; 41.47; 39.55; 34.00; 33.47; 33.05; 23.58; 22.40; 21.85; 21.83; 21.75; 21.71; 20.74; 20.53; 19.66; 14.41. HRMS: 448,2835. Calculated for $C_{26}H_{40}O_6$: 448.2825.

Synthesis of the mixture of 8α-acetoxy-16-norlabda-12,14-dienes 602 and 603.

Triphenylphosphonium allyl bromide (2.20 g, 5.72 mmol) was suspended in 15 mL of dry THF and treated with 3.5 mL of BuLi solution in hexanes (1.6 M, 5.72 mmol) at 0 °C under argon. The obtained solution was gradually warmed to room temperature over 30 min, then cooled to –30 °C, and a solution of 561 mg (1.91 mmol) of aldehyde **601** [172] in 12 mL of THF was added dropwise. Stirring was continued at r.t. for 2h, after which TLC analysis showed no remaining starting material. Usual work-up included dilution of the reaction mixture with H_2O (50 mL), followed by extraction with diethyl ether (3x25 ml), washing the organic phase successively with diluted sulfuric acid, saturated sodium bicarbonate solution and brine to bring the pH to neutral. Drying the etherial extract over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure gave the crude product which was submitted to column chromatography over silica gel. Elution with 5% EtOAc in petroleum ether gave 400 mg of a mixture of **602** and **603** as an oil, in a 7:3 ratio. ^{1}H NMR (500 MHz, $CDCl_3$, selected): δ_H=0.807 (s), 0.811 (s), 0.87 (s), 0.89 (s), 0.90 (s) – all 9H; 1.48 (s), 1.50 (s) – all 3H; 1.91 (s), 1.92 (s) – all 3H; 4.94 (d, J=10 Hz, 0.4H); 5.07 (d, J=10 Hz, 0.4H), 5.09 (d, J=16.5 Hz, 0.6H); 5.18 (d, J=16.5 Hz, 0.6H); 5.51 (m, 0.6H); 5.75 (m, 0.4H); 5.91 (t, J=11 Hz, 0.6H); 6.01 (dd, J=10, 15 Hz, 0.4H); 6.31 (dt, J=10, 17 Hz, 0.4H); 6.73 (dt, J=10, 17 Hz, 0.6H). IR (cm^{-1}): 1250; 1728; 2933.

Synthesis of 8α-hydroxy-16-norlabda-12Z,14-diene 600.

A mixture of acetates **602** and **603** (260 mg, 0.82 mmol) was treated with a solution of KOH (448 mg, 8 mmol) in EtOH (5 mL) for 2h at gentle reflux. Dilution with H_2O and usual workup gave a mixture of **600** and its corresponding *E*-isomer. This mixture was submitted to HPLC separation on a Phenomenex Luna 5 μm C18 semi-preparative column (9:1 MeOH-H_2O) to provide pure **600** (yellow liquid). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H=0.81 (s, 3H); 0.86 (s, 3H); 0.88 (s, 3H); 1.20 (s, 3H); 5.13 (d, J=10 Hz, 1H); 5.21 (d, J=17 Hz, 1H); 5.61 (m, 1H); 5.96 (t, J=11 Hz, 1H); 6.77 (dt, J=6, 5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=15.61 (C-17); 18.78 (C-2); 20.53 (C-1); 21.77 (C-18); 23.84 (C-11); 24.54 (C-16); 33.49 (C-4); 33.67 (C-19); 36.53 (C-10); 40.42 (C-6); 42.05 (C-7); 44.38 (C-3); 56.31 (C-5); 62.42 (C-9); 74.39 (C-8); 117.35 (C-15); 128.04 (C-13); 132.37 (C-14); 135.79 (C-12). IR (cm^{-1}): 598; 903; 1122; 1387; 1462; 2928; 3336.

Preparation of bishomodrim-8α,12-oxi-13-ol 605.

Diene **600** (10 mg, 0.036 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and treated with 1.5 mL of a saturated ozone solution in CH_2Cl_2 at 0 ºC for 10 min. Removal of excess ozone with a stream of argon was followed by addition of excess $NaBH_4$ and stirring was continued at r.t. for 2 h. Usual work-up gave the crude product which was submitted to column chromatography over silica gel. Elution with 25% EtOAc in petroleum ether gave 6 mg of **605** (yellow liquid). ^{1}H NMR (500 MHz, $CDCl_3$, selected): δ_H=0.84 (s, 3H); 0.85 (s, 3H); 0.88 (s, 3H); 1.16 (s, 3H); 3.56 (dd, J=7.5, 15 Hz, 1H); 3.67 (dd, J=3.5, 10 Hz, 1H); 4.15 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C=15.73 (C-17); 18.61 (C-2); 21.12 (C-1); 21.24 (C-15); 25.07 (C-14); 25.41 (C-11); 33.30 (C-4); 33.72 (C-16); 36.53 (C-10); 40.20 (C-7); 40.60 (C-6); 42.65 (C-3); 57.28 (C-5); 60.90 (C-9); 67.20 (C-13); 79.30 (C-12); 81.10 (C-8). IR (cm^-1): 827; 912; 1009; 1376; 2921; 3430.

Ozonolysis of sclareol 247 to sclareoloxide 611.

Sclareol **247** (5 g, 16 mmol) was dissolved in 70 ml acetone, and a solution of lead diacetate trihydrate (0.6 g, 1.6 mmol) was added as a solution in 30 ml water. The reaction mixture was treated with ozone at 0 ºC until the TLC showed disappearance of starting material. Excess ozone was removed by nitrogen sparkling for 3 minutes. Acetone was distilled from the reaction mixture under reduced pressure (bath temperature +40 ºC) and the residue was extracted with petroleum ether (3 x

50 ml). The combined organic extract was washed with brine to a neutral pH (2 x 10 ml), then dried over sodium sulfate. Distillation of the solvent under reduced pressure provided the crude sclareoloxide **611** (4.2 g), identified by GC-MS at 98 % purity level.

Synthesis of alcohol 616.

Alcohol **616** was obtained according to the described methodology [261] involving epoxidation of ester **343**, followed by $Al(OiPr)_3$ - mediated epoxide opening.

Synthesis of methyl-16α-(3-iodo)-benzoylscalar-17(20)-enoate 618.

167 mg of 3-iodobenzoic acid (0.672 mmol) were treated with 1.5 mL $SOCl_2$ under reflux for 1 h. Cooling to the room temperature was followed by addition of 3 drops of DMF and refluxing continued for further 30 min. Evaporation of the excess $SOCl_2$ under reduced pressure provided the crude acyl chloride, to which 90 mg of alcohol **616** (0.224 mmol) were added, dissolved in 3 mL of benzene and 0.5 mL of pyridine. After 4 h of reflux, TLC showed no starting material. Usual work-up provided the crude reaction product, which was submitted to Si-gel flash chromatography. Elution with 2% EtOAc in petroleum ether provided 140 mg (0.222 mmol, 99%) of ester **618**. Colorless viscous liquid; $[\alpha]_D^{25}$ -32.4 (c 0.36, $CHCl_3$); IR ν_{max} (liquid film) 1732, 1716 cm^{-1}; ^1H NMR (400 MHz) δ_H: 8.37 (1H, s, H-2'); 7.99 (1H, d, *J*=7.8 Hz, H-6'); 7.91 (1H, d, *J*=7.9 Hz, H-4'); 7.23 (1H, dd, *J*=7.8 and 7.9 Hz, H-5'); 5.66 (1H, m, H-16); 5.29 (1H, bs, H-20a); 5.09 (1H, bs, H-20b); 3.65 (3H, s, -OMe); 3.21 (1H, s, H-18); 1.99 (1H, m, H-15a); 1.77 (1H, m, H-15b); 1.70 (2H, m, H-1a and H-7a); 1.65 (1H, m, H-2a); 1.60 (2H, m, H-6a and H-12a); 1.53 (1H, m, H-14); 1.50 (2H, m, H_2-11); 1.45 (1H, m, H-12b); 1.40 (2H, m, H-2b and H-6b); 1.35 (1H, m, H-3a); 1.12 (1H, ddd, *J*=13.3, 13.4 and 4.0 Hz, H-3b); 1.07 (3H, s, H_3-25); 0.90 (1H, bd, *J*=10.6 Hz, H-9); 0.86 (3H, s, H_3-24); 0.82 (6H, s, H_3-21 and H_3-23); 0.81 (2H, m, H-5 and H-1b); 0.79 (3H, s, H_3-22). ^{13}C NMR (75.5 MHz) δ_C: 171.4 (C-19), 163.6 (CO-phenyl), 141.7 (C-4'), 139.8 (C-17), 138.6 (C-2'), 132.7 (C-1'), 130.1 (C-5'), 128.7 (C-6'), 115.1 (C-20), 93.8 (C-3'), 76.2 (C-16), 61.2 (C-9), 58.8 (C-18), 56.5 (C-5), 53.7 (C-14), 51.0 (-OMe), 42.1 (C-3), 41.8 (C-7), 40.3 (C-12), 39.8 (C-1), 39.6 (C-13), 37.7 (C-8), 37.6 (C-10), 33.3 (2C, C-4 and C-21), 27.4 (C-15), 21.3 (C-22), 18.6 (C-2), 18.1 (C-6); 17.5 (C-11), 17.1 (C-24), 16.3 (C-23), 14.2 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 655.2276 (655.2260 calculated for $C_{33}H_{45}O_4INa$).

Synthesis of methyl-16α-(3-iodophenyl)-acetylscalar-17(20)-enoate) 619.

3-Iodophenylacetic acid (149 mg, 0.567 mmol) was treated with $SOCl_2$ (2 mL) under reflux for 1 h. Cooling to the room temperature was followed by addition of 3 drops of DMF and refluxing continued for 30 min. Evaporation of the excess $SOCl_2$ under reduced pressure provided the crude acyl chloride, to which 114 mg of alcohol **616** (0.284 mmol) were added, dissolved in 4 ml of benzene and 0.4 mL of pyridine. After 4 h of reflux, TLC showed no starting material. Usual work-up provided the crude reaction product, submitted to flash chromatography on Si gel. Elution with 3% EtOAc in petroleum ether provided 181 mg (0.28 mmol, 99%) of ester **619**. Colorless viscous liquid; $[\alpha]_D^{25}$ -22.6 (c 0.12, $CHCl_3$); IR ν_{max} (liquid film) 1747, 1732 cm^{-1}; ^1H NMR (300 MHz) selected values δ_H: 7.73 (1H, s, H-2'); 7.63 (1H, d, *J*=7.9 Hz, H-6'); 7.28 (1H, d, *J*=8.7 Hz, H-4'); 7.06 (1H, dd, *J*=7.9 and 8.7 Hz, H-5'); 5.39 (1H, m, H-16); 5.17 (1H, bs, H-20a); 5.00 (1H, bs, H-20b); 3.67 (3H, s, -OMe), 3.55 (2H, ABq, *J*=14.2 Hz, H_2-benzyl); 3.02 (1H, s, H-18); 0.98 (3H, s, H_3-25); 0.89 (3H, s, H_3-24); 0.79 (3H, s, H_3-23); 0.78 (3H, s, H_3-21); 0.75 (3H, s, H_3-22). ^{13}C NMR (75.5 MHz) δ_C: 171.4 (C-19), 169.5 (CO-benzyl), 140.0 (C-17), 138.5 (C-4'), 136.7 (C-1'), 136.2 (C-2'), 130.3 (C-5'), 128.7 (C-6'), 114.3 (C-20), 94.4 (C-3'), 75.8 (C-16), 60.8 (C-9), 58.5 (C-18), 56.0 (C-5), 52.9 (C-14), 51.1 (-OMe), 42.2 (C-3), 41.8 (C-7), 41.4 (CH_2-benzyl); 40.2 (C-12), 39.8 (C-1), 39.5 (C-13), 37.5 (C-8), 37.3 (C-10), 33.4 (2C, C-4 and C-21), 27.0 (C-15), 21.3 (C-22), 18.7 (C-2), 18.0 (C-6); 17.4 (C-11), 17.1 (C-24), 16.3 (C-23), 14.1 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 669.2405 (669.2417 calculated for $C_{34}H_{47}O_4INa$).

Radical Relay Halogenation of ester 618. Methyl-16α-hydroxy-scalar-5(6),17(20)-dienoate 620.

17 mg (0.12 mmol) of K_2CO_3 were added to a deoxygenated solution of ester **618** (15 mg, 0.024 mmol) in 2.5 mL of a mixture dichloromethane/*tert*-butanol (2:1). The resulting suspension was treated on stirring with 9.75 mg (0.036 mmol) of iodophenyldichloride [265]. The reaction mixture was irradiated at room temperature for 2 h with two filament lamps (200W+100W) on stirring. Following distillation of the solvent under reduced pressure provided a crude residue, which was treated with a mixture of dioxane (1.5 mL) and 10% KOH in methanol (1.5 mL) at 80ºC for one hour. Usual work-up provided the crude product, which was submitted to flash chromatography on Si-gel. Elution with 10% EtOAc in petroleum ether provided 5 mg (0.013 mmol, 52%) of ester **620**. Colorless viscous liquid; $[\alpha]_D^{25}$ -50.7 (c 0.15, $CHCl_3$); IR ν_{max} (liquid film) 1725 cm^{-1}. ^1H NMR (400 MHz) δ_H:

5.39 (1H, m, H-6); 5.06 (1H, bs, H-20a); 4.86 (1H, bs, H-20b); 4.40 (1H, m, H-16); 3.66 (3H, s, -OMe); 3.32 (1H, s, H-18); 1.99 (1H, dd, *J*= 17.2 and 5.5 Hz, H-7a); 1.84 (1H, m, H-1a); 1.80 (1H, m, H-2a); 1.77 (1H, m, H-7b); 1.70 (2H, m, H_2-15); 1.63 (1H, m, H-12a); 1.60 (1H, m, H-14); 1.52 (2H, m, H_2-11); 1.48 (1H, m, H-12b); 1.47 (1H, m, H-3a); 1.45 (1H, m, H-2b); 1.22 (1H, m, H-3b); 1.18 (1H, m, H-9); 1.11 (3H, s, H_3-22); 1.09 (3H, s, H_3-23); 1.05 (3H, s, H_3-21); 1.04 (3H, s, H_3-25); 0.92 (1H, m, H-1b); 0.85 (3H, s, H_3-24). ^{13}C NMR (75.5 MHz) δ_C: 171.7 (C-19); 148.1 (C-5); 145.1 (C-17); 116.4 (C-6); 111.5 (C-20); 72.9 (C-16); 57.4 (C-18); 56.1 (C-9); 50.9 (2C, -OMe and C-14); 42.6 (C-7); 41.8 (C-3); 41.1 (C-1); 39.6 (2C, C-12 and C-13); 37.8 (C-10); 36.3 (C-8); 34.8 (C-4); 33.2 (C-21); 29.4 (2C, C-15 and C-22); 20.3 (C-23); 18.9 (C-11); 18.6 (C-2); 17.9 (C-24); 13.4 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 423.2867 (423.2875 calculated for $C_{26}H_{40}O_3Na$).

Radical Relay Halogenation of ester 619.

A solution of 83 mg (0.129 mmol) of ester **616** and 3.1 mg (0.013 mmol) dibenzoylperoxide in 12 mL CCl_4 was treated with 12.4 mL (0.154 mmol) SO_2Cl_2 and the reaction mixture refluxed for 5 h. Following distillation of the solvent under reduced pressure provided a crude residue, which was treated with a mixture of dioxane (1.5 mL) and 10% KOH in methanol (1.5 mL) at 80°C for 1 h. Usual work-up provided the crude product, which was submitted to flash chromatography on Si gel. Elution with 10% EtOAc in petroleum ether provided 8 mg (0.02 mmol, 16%) of ester **620**.

Acetylation of 620. **Methyl-16α-acetoxy-scalar-5(6),17(20)-dienoate 621.**

Compound **620** (7 mg) was dissolved in pyridine (1 mL) and treated with acetic anhydride (0.3 mL). After 12 h at room temperature, usual work-up provided pure acetate **621**. Colorless viscous liquid; $[\alpha]_D^{25}$ -49.5 (c 0.10, $CHCl_3$); IR ν_{max} (liquid film) 1739 cm^{-1}. ^{1}H NMR (400 MHz) δ_H: 5.44 (1H, m, H-16); 5.39 (1H, m, H-6); 5.20 (1H, bs, H-20a); 5.01 (1H, d, *J*=0.5 Hz, H-20b); 3.66 (3H, s, -OMe); 3.14 (1H, s, H-18); 2.05 (3H, s, -OAc); 1.97 (1H, dd, *J*= 17.3 and 5.5 Hz, H-7a); 1.82 (1H, m, H-1a); 1.80 (2H, m, H-2a and H-15a); 1.70 (1H, m, H-15b); 1.65 (1H, m, H-7b); 1.62 (1H, m, H-12a); 1.54 (2H, m, H_2-11); 1.48 (1H, m, H-3a); 1.47 (1H, m, H-2b); 1.46 (1H, m, H-14); 1.37 (1H, m, H-12b); 1.22 (1H, m, H-3b); 1.17 (1H, m, H-9); 1.12 (3H, s, H_3-22); 1.09 (3H, s, H_3-23); 1.06 (3H, s, H_3-21); 1.05 (3H, s, H_3-25); 0.92 (1H, m, H-1b); 0.85 (3H, s, H_3-24). ^{13}C NMR (75.5 MHz) δ_C: 171.2 (C-19); 170.1 (-OAc); 149.0 (C-5); 140.2 (C-17); 116.2 (C-6); 114.4 (C-20); 74.9 (C-16); 58.4 (C-

18); 56.1 (C-9); 52.0 (C-14); 51.0 (-OMe); 42.6 (C-7); 41.8 (C-3); 41.2 (C-1); 39.7 (C-12); 39.4 (C-13); 37.8 (C-10); 36.3 (C-8); 34.8 (C-4); 33.1 (C-21); 29.3 (C-22); 27.5 (C-15); 21.5 (-OAc); 20.3 (C-23); 18.9 (C-11); 18.6 (C-2); 17.8 (C-24); 13.6 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 465.2958 (465.2981 calculated for $C_{28}H_{42}O_4Na$).

Allylic oxidation of acetate 621. Methyl-7-oxo-16α-acetoxy-scalar-5(6),17(20)-dienoate 622.

Compound **621 (**5 mg, 0.011 mmol) was dissolved in 0.5 mL acetonitrile and treated on stirring with a catalytic amount of CuI and 20 mL of a solution of *t*-butyl hydroperoxide in nonane. After stirring for 20 h at +50 ºC under nitrogen, the reaction mixture was diluted with a sat. solution of Na_2SO_3 (5 mL) and worked-up as usual. The crude product was submitted to flash chromatography affording 3 mg (0.007 mmol, 58%) of keto-diester **622**. Colorless viscous liquid; $[\alpha]_D^{25}$ -64.9 (c 0.16, $CHCl_3$). IR ν_{max} (liquid film) 1738, 1668 cm^{-1}. ^1H NMR (400 MHz) δ_H: 5.76 (1H, s, H-6); 5.47 (1H, m, H-16); 5.21 (1H, bs, H-20a); 4.95 (1H, d, *J*=0.7 Hz, H-20b); 3.66 (3H, s, -OMe); 3.25 (1H, s, H-18); 2.84 (1H, m, H-15a); 2.10 (3H, s, -OAc); 2.05 (1H, dd, *J*=12.5 and 2.2 Hz, H-14); 1.96 (1H, m, H-1a); 1.87 (1H, m, H-2a); 1.67 (1H, m, H-15b); 1.62 (2H, m, H-3a and H-12a); 1.61 (1H, m, H-9); 1.60 (3H, m, H_2-11 and H-2b); 1.35 (2H, m, H-3b and H-12b); 1.27 (3H, s, H_3-23); 1.20 (3H, s, H_3-22); 1.14 (3H, s, H_3-21); 1.13 (3H, s, H_3-24); 1.10 (3H, s, H_3-25); 1.03 (1H, ddd, *J*=13.0, 12.7 and 3.8 Hz, H-1b). ^{13}C NMR (75.5 MHz) δ_C: 205.7 (C-7), 171.2 (2C, C-5 and C-19); 169.9 (-OAc); 140.4 (C-17); 121.4 (C-6); 114.5 (C-20); 74.7 (C-16); 58.8 (C-18); 56.4 (C-9); 51.0 (-OMe); 46.7 (C-8); 44.1 (C-14); 41.0 (C-1); 40.7 (C-3); 39.8 (C-10); 39.4 (C-13); 38.9 (C-12); 37.2 (C-4); 32.3 (C-21); 30.1 (C-15); 28.6 (C-22); 21.5 (-OAc); 20.4 (C-23); 18.6 (C-2); 18.3 (C-11); 16.2 (C-24); 15.1 (C-25). HRESIMS: *m/z* $(M+Na)^+$ 479.2756 (479.2773 calculated for $C_{28}H_{40}O_5Na$).

5.5. Conclusions to chapter 5

The natural product austrodoral **637** has been successfully used to synthesize a bicyclic perhydrindanic fragment **705,** common to a whole family of rearranged spongiane terpenoids of marine origin. The synthetic strategy was based on a degradation-oxidation approach and following connection of the obtained perhydrindane with a highly oxygenated fragment was demonstrated [232],[233].

A new method for the synthesis of substituted tetrahydrofurans has been demonstrated. The procedure based on a tandem ozonolysis-cyclization reaction provides an excellent yield of the heterocyclic compound, possessing a lateral chain for further functionalization [235].

Ozonolytic degradation was used in order to develop a new catalytic process of sclareoloxide preparation. The catalyst can be conveniently recycled with minimal harm to the environment [9],[250],[251].

The ring B functionalization of a sesterterpene scalarane has been achieved by using a short and straightforward remote functionalization procedure. The Radical Relay Halogenation method has been used here for the first time on terpenes. The obtained functionalized scalaranes **736-738** could be further transformed to be used for structure-activity relationship studies [155],[259].

OVERALL CONCLUSIONS AND RECOMMENDATIONS

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

- Direct oxidative functionalization of open chain terpenoids was efficient in the case of mono- and sesquiterpenes [119],[120],[121],[124]. Van Tamelen epoxidation procedure has been demonstrated in the case of a diterpenic substrate [125]. Two natural products with relevant properties have been obtained by direct oxidation, namely 8-acetoxygeranylacetate **427** - a component of the pheromone of the Australian predaceous bug *Oechalia schellenbergii* and *trans*-16-hydroxygeranylgeraniol **451** – an inhibitor of peroxide formation in macrophagous cells isolated from the fungus *Boletinus cavipes*.

- Higher terpenoids (di-, sester- and triterpenes) have been assembled predominantly via oligomerization protocols [122],[123]. Fragment coupling has been performed successfully basing on monoterpenic α,ω-bifunctional substrates and other building blocks of diverse complexity, including both open chain and cyclic systems. Allylic phenylsulfones represented convenient substrates for generation of donor synthons on lithiation. As coupling partners both allylic halogenides and carbonyl compounds have been used. The obtained adducts represent examples of functional groups integration both at chain extremities and middle of the chain.

- An alternative oligomerization procedure based on a $C_3 + C_2$ strategy was shown effective for different substrates, including those with steric hindrances. The tricyclic skeleton **410** and **411** of natural cheilanthanes was assembled in optically active form [135].

- Performing terpene functionalization before cyclization step allowed to control the selectivity of this challenging step. Selective initiation of cyclization cascade from an internal double bond has been achieved when the open chain substrate contained oxygenated functional group at both α- and ω-ends. Superacidic cyclization of such substrates of sesquiterpenic series led to monocyclic compounds with terminal pendant prenylation of *seco*-eudesmanic structure **475** and **476** [124]. Diterpenic α,ω-bifunctionalized substrates have been cyclized into bicyclic compounds with terminal pendant prenylation of sacculatane family **480** and **481**. It was the first reported biomimetic synthesis of sacculatanes [125].

- Intercalation of a specific functional group into the terpenic chain resulted in selective control over superacidic cyclization process, leading to a suspension of the cyclization sequence. The results included formation of partially cyclic compounds with the head units pendant. Open chain sesterterpenic substrates with a *cis*-configured internal double bond have been cyclized to cheilanthanes of regular **488** and rearranged **489** structure in racemic form [146], [147]. Bicyclic sesterterpenes of the same configuration in the lateral chain allowed access to above mentioned compounds in optically active form [152]. Using the readily available bicyclic diterpenoid sclareol under this scenario resulted in the elaboration of an integrated process for the synthesis of sesterterpenes of both tetracyclic scalarane and tricyclic cheilanthane structure [155].

- Selective suspension of the cyclization cascade was achieved on the intercalation in the terpenic chain of a phenylsulfonyl functional group [120],[121].

- Ionic liquids of methyl,butyl-imidazolinium series have been shown to represent suitable media for superacidic induced biomimetic like cyclizations [159],[160].

- A ring contraction biomimetic process of a homodrimanic epoxide has been applied as the key step for the synthesis of austrodoric acid **521** – a secondary metabolite isolated from the nudibranch *Austrodoris Kerguelenensis* [164],[165].

- A ring contraction biomimetic process of a drimanic epoxide has been applied as the key step for the synthesis of austrodoral **522** – a secondary metabolite isolated from the nudibranch *Austrodoris Kerguelenensis* [173].

- Selective rearrangement of a homodrimanic epoxide resulted in the synthesis of compounds possessing the bicyclic skeleton of *ent*-halimanes **558** – **561** [188].

- Intercalation of two electron-withdrawing functional groups into the linear chain of a bicyclic triterpenic substrate resulted in a total inhibition of three double bonds under superacidic cyclization conditions. A very selective skeletal rearrangement was achieved leading to a bicyclic compound **564** - congener of the bicyclic family of natural neopolypodatetraenes [123].

- Oxidative degradation procedures have been applied for the synthesis of the bicyclic perhydrindane fragment **522** of norrisolide – a rearranged member of spongiane diterpenoids. The potential application of this fragment was demonstrated on its coupling with a highly oxygenated cycloropanated furan on the way to natural norrisolide synthesis [232],[233].

- Ozonolytic degradations have been shown as useful tools for terpene functionalization. An unusual ozonolysis of a diene system led to the formation of a functionalized furan **605** via a hypothetical mechanism based on the Criegee's intermediates [235],[236].

- Ozonolytic degradation of sclareol under catalytic conditions in an aqueous solvent allowed for an efficient preparation of sclareoloxide – **611**. This degraded diterpene was successfully used as ingredient of various aromatic compositions for tobacco products [9],[251],[252].

- Functionalization of scalaranic framework has been achieved by a free radical process. The synthesis of cycle B – functionalized scalaranes **620** – **622** has been reported for the first time [155],[259].

To summarize, the current work presents application if a new concept in the biomimetic synthesis of terpenoids. It is based on the random combination of the chemical processes that mimic

the known biosynthetic steps. As a result of this concept implementation it was possible to build in a flexible way diverse terpenic substances with a high complexity and functionalization pattern. The starting building blocks have been simple open chain substrates, as well as more complex, but still available cyclic structures, including those bearing chirality.

The flexible combination of the oligomerization-functionalization-cyclization-isomerization processes allows exploring the reactivity of terpenic substrates in a very unusual and unexpected mode. As the result, diverse classes of terpenic compounds with complex structure have been obtained. These represent a relevant interest as carriers of relevant bioactivities, being in the same time hardly available from natural sources.

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

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

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ANNEXES

ANNEX. 1. THE LIST OF PUBLICATIONS LINKED TO THE THESIS*

Book chapters

1. Kulciţki V., Ungur N. Synthesis of scalarane sesterterpenoids. In *Recent Res. Dev. Org. Chem.*, 2003, p. 241–258 (**Review**, *Citations: 2*).

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2. Kulciţki V., Harghel P., Ungur N. Unusual cyclic terpenoids with terminal pendant prenyl moieties: from occurrence to synthesis. In: *Nat. Prod. Rep.*, 2014, vol. 31, nr. 12, p. 1686–1720. (**Review**, IF: 10.986, *Citations: 1*).
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8. Grinco M. et al. Synthesis of 16-hydroxygeranylgeraniol and its derivatives from geraniol. In: Chem. Nat. Compd., 2007, vol. 43, nr. 3, p. 277–281 (IF: 0.473, *Citations: 1*).
9. Kulciţki V. et al. Superacid cyclization of (2E,6E,10E,14 E)-8- phenylsulfonylgeranylfarnesol tetrahydropyranyl ether. In: Chem. Nat. Compd., 2007, vol. 43, no. 3, p. 268–273 (IF: 0.473, *Citations: 2*).
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17. Kulciţki V. et al. Superacidic cyclization of omega-oxygeraniol diacetate and benzyl ether of omega-acetoxygeraniol. In: Russ. Chem. Bull., 1999, vol. 48, no. 1, p. 135–137 (IF: 0.579, *Citations: 1*).
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19. Grinco M. et al. Molecular rearrangements of highly functionalized terpenes. An unique reactivity of bicyclic framework and polyenic chain inhibition under superacidic treatment. In: Chem. J. Mold. Gen. Ind. Ecol. Chem., 2013, vol. 8, no. 2, p. 94–100.
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21. Kulciţki V., Sîrbu T., Ungur N. On the peculiarities of the ring contraction reaction of homodrimanes via acid mediated epoxide rearrangement. In: Chem. J. Mold. Gen. Ind. Ecol. Chem., 2011, vol. 6, no. 1, p. 110–112.

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22. Kulciţki V., Harghel P., Ungur N. Unusually pendant-prenylated cyclic terpenoids – an emerging class of natural products with a broad spectrum of biological activity. In: *The International Conference dedicated to the 55th anniversary from the foundation of the Institute of Chemistry of the Academy of Sciences of Moldova*, abstracts of communication, Chisinau, Moldova, May 28 - 30, 2014, p. 46-47.
23. Kulciţki V. Contributions to the biomimetic synthesis of terpenoids. In: *Phytochemical Society of Europe meeting "Phytochemicals in Medicine and Pharmacognosy,"* abstracts of communication, Piatra Neamt, Romania, April 27-30, 2014, p. 97.
24. Kulciţki V. Biomimetic approaches in the synthesis of complex natural products. In: *Cooperation and Networking of Universities and Research Institutes – study by doing research, NANO-2011*, abstracts of communication, Chisinau, Republic of Moldova, October 6-10, 2011, p. 24.
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26. Harghel P. et al. Valorisation of *Salvia Sclarea* wastes. Efficient synthesis of sclareoloxide by sclareol ozonolysis in aqueous Solvent System. In: Phytochemical Society of Europe meeting

"Phytochemicals in Medicine and Pharmacognosy", abstracts of communication, Piatra Neamt, Romania, April 27-30, 2014, p. 44.
27. Sîrbu T. et al. Advanced oxidation processes based on ozonolysis. Application to renewable raw material processing. In: The V International Conference-Symposium Ecological Chemistry, abstracts of communication, Chisinau, Republic of Moldova, March 2-3, 2012, p. 96.
28. Kulciţki V., Wittmann S., Reiser O. Synthetic routes towards rearanged spongiane diterpenoids. In: Netzwerktagung der Alexander von Humboldt-Stiftung, abstracts of communications, Darmstadt, Germany, October 8–10, 2008, p. 51.
29. Grinco M. et al. Efficient synthesis of 16-hydroxy-all- trans -geranylgeraniol from geraniol. In: *The II-nd International Conference of the Chemical Society of Republic of Moldova (ICOCSM-II) "Achievements and Perspectives of Modern Chemistry,"* abstracts of communications, Chisinau, Moldova, October 1-3, 2007, p. 124.
30. Grinco M. et al. Low temperature superacidic cyclization of (2E,6E,10E,14E)-8-phenylsulfonylgeranylfarnesol tetrahydropyranyl ether to bicyclic sesterterpenic compounds. In: *The II-nd International Conference of the Chemical Society of Republic of Moldova (ICOCSM-II) "Achievements and Perspectives of Modern Chemistry,"* abstracts of communications, Chisinau, Moldova, October 1-3, 2007, p. 125.
31. M. Grinco, V. Kulciţki, N. Ungur, P. F. Vlad, M. Gavagnin, F. Castelluccio, and G. Cimino, "Synthesis and Superacidic Cyclization of alfa, omega-Bifunctional Diterpenoids. A Straight Path Towards Sacculatanic Compounds," In: *International Symposium on Advanced Science in Organic Chemistry*, abstracts of communications, Sudak, Ukraine, June 26–30, 2006, p. C-041.
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35. Kulciţki V. et al. Synthesis of functionalized scalaranes by radical relay halogenation. In: The XXIX-th Romanian Chemistry Conference, abstracts of communications, Călimăneşti-Căciulata, Vâlcea, România, 2006, p. 30.
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37. Kulciţki V. et al. Synthetic studies towards marine natural products. Elaboration of a precursor for the preparation of C12-functionalized scalaranes," in *The Ist International Conference of the Moldavian Chemical Society "Achievements and perspectives of modern chemistry,"* abstracts of communications, Chisinau, Moldova, 2003, p. 180.
38. Kulciţki V. et al. A short stereospecific synthesis of austrodoric acid, a nor-sesquiterpene with a new carbon skeleton from the marine dorid Austrodoris kerguelenensis. In: International Symposium "Chemistry & Biology of marine Organisms," abstracts of communications, Kolympari, Crete, Greece, 2003, p. 172.
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Patents

40. Patent of the Republic of Moldova. 2253, MD. Aromatization product for smoking tobacco, procedures for its production, aroma composition (variants), procedure for production of composition for tobacco products (variants) / Porcescu P. et al. (MD). Application of 30.09.2002, BOPI, 2003, 9, p. 16-17.
41. Patent of the Republic of Moldova. 2349, MD. Aroma composition for smoking tobacco and procedure for production of tobacco products aroma composition / Postovoi A. et. al. (MD). Application of 30.01.2003, BOPI, 2004, 1, p. 21-22.
42. Patent of the Republic of Moldova. 4209, MD. Process for producing sclareoloxide / Kulciţki V. et. al. (MD). Application of 30.03.2012, BOPI, 2013, 3, p. 20-21.

DECLARATION ON THE ASSUMPTION OF RESPONSIBILITY

I, the undersigned, Veaceslav KULCIȚKI, 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.

Veaceslav KULCIȚKI

Date:

Signature:

AUTHOR'S CV

I. Personal data

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II. Education

12/1993-12/1996	Ph.D.-studies, Academy of Sciences of Moldova, Chişinău, Moldova;
09/1986-06/1992	Department of Chemistry, Moldova State University, Chişinău, Moldova (interrupted by military service *07/1988-09/1989*);
09/1980-06/1984	Primary musical school with honors. Specialty – accordion;
09/1976-06/1986	Secondary school with gold medal award, Olişcani, Moldova.

III. All academic degrees and titles obtained

09/2006	Associate Professor in Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Compounds, The National Council of Accreditation and Attestation, Moldova;
10/1998	Ph.D. in Bioorganic Chemistry, Institute of Chemistry, Academy of Sciences of Moldova. Thesis title: "Synthesis of Functionalized Cyclic Terpenoids by Superacidic Cyclization";
07/1992	M.Sci. in Organic Chemistry, Moldova State University, Chemistry Department, Chişinău, Moldova.

IV. Postdocs

01/2008-07/2009	Professor Oliver Reiser, University of Regensburg, Germany;
02/2005-04/2005	Professor Daniel Baden, Center for Marine Science, University of North Carolina at Wilmington, USA;
05/2004-10/2004	Professor Guido Cimino, Istituto per la Chimica di Molecole di Interesse Biologico, Napoli, Italy.

V. Employment (last three years)

11/2015-curent	Coordinating scientific researcher, Laboratory of Natural and Biologically Active Product Chemistry, Institute of Chemistry, Academy of Sci., Chişinău, Republic of Moldova;
11/2013-11/2015	Postdoctoral student, University of Academy of Sciences of Moldova;

04/2012-11/2013 Director, Advisory Expertise Council, Academy of Sci., Chişinău, Republic of Moldova.

VI. Area of scientific activity

Synthetic organic chemistry, modern analytical chemistry, chemistry of natural compounds.
ResearcherID: A-7991-2010 / ORCID ID: orcid.org/0000-0002-9363-1615.

VII. Teaching experience

09/2002-Prezent Strategy of Organic Synthesis, Stability of Pharmaceuticals, Quality Management, Philosophy and Methodology of Scientific Research, History of chemistry.

VIII. Scientific publications

More then 30 papers in peer-reviewed journals, including reviews, book chapters and 3 patents.
H index – 8 (scholar.google.com). Average citation per article – 6.50 (Researcher ID). Recent relevant contributions:

1. Grinco, M.; Girbu, V.; Gorincioi, E.; Barba, A.; Kulciţki, V.; Ungur, N. The first biomimetic synthesis of a diterpenoid with the ent-verrucosin A/B skeleton. *Tetrahedron Lett*. **2016**, 57 (19), p. 2084-2086.
2. Kulcitki, V.; Harghel, P.; Ungur, N. Unusual cyclic terpenoids with terminal pendant prenyl moieties: from occurrence to synthesis. *Nat. Prod. Rep.*, **2014**, *31*, p. 1686-1720.
3. Koval'skaya, S.S.; Kozlov, N.G.; Kulciţki, V.; Arîcu, A.; Ungur, N. Transformation of Sclareol under Ritter Reaction Conditions. *Russ. J. Org. Chem.*, **2013**, *49*(2), p. 303−311.
4. Kulcitki, V.; Duca, Gh.; Ungur, N.; Sirbu, T.; Colta, M.; Golosov, I. Process for production of sclareol oxide. Patent of Republic of Moldova. Nr 4209, *BOPI*, **2013**, (3), p. 20.
5. Ungur, N.; Kulcitki, V.; Chetraru, O.; Grinco, M.; Vlad, P. Synthesis of natural atisanic diterpenoids by retro-biomimetic transformations. *Helv. Chim. Acta*, **2013**, *96*, p. 864-871.

IX. Workshops and training

09/2007-12/2007 Intensive German language course, Goethe Institute, München, Germany;
02/1999 Training program on Quality Management. Organized by Human Dynamics (Austria). Chisinau. Moldova;
06/1998 International Workshop on Modern Spectroscopic Techniques in Biophysics, Neptun, Romania;
05/1997 International Workshop on Nuclear Magnetic Resonance Spectroscopy and Imaging, Braşov, Romania.

X. Awards and honors

04/2015 STCU research project. Kiev, Ukraine;
04/2014 SCOPES bilateral project. Swiss National Science Foundation;
01/2011 Bilateral Moldovan-Italian cooperative grant. ASM-CNR;
07/2007 Alexander von Humboldt Foundation scholarship award;
11/2006 Diploma award for remarkable results in the promotion of research in Moldova, Academy of Sciences of Moldova;
01/2005, 09/2005 MRDA-CRDF travel fellowship/follow-up grant;
11/2003 INTAS individual advanced doctoral fellowship award;

09/2000, 05/2004 NATO fellowship awards;
10/1997 European Fellowship Fund EFS-15/97.

XI. Hobbies

Photography, travelling, biking, music.