Studies Towards Synthesis of Biologically Active Guaianolides: Enantioselective Total Synthesis of (+)-Arglabin

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Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

For my parents & teachers.....

"Research is to see what everybody else has seen, and to think what nobody else has thought"

- Albert Szent-Gyorgyi
1937 Nobel Prize for Medicine

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STUDIES TOWARDS SYNTHESIS OF BIOLOGICALLY ACTIVE GUAIANOLIDES: ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-ARGLABIN

1. Introduction

1.1 Natural products as an important source of drugs

Natural products are bioactive secondary metabolites that are isolated from all kingdoms of life and have proven to be a rich source of disease modulating drugs throughout the history of medicinal chemistry and pharmaceutical drug development.[1] For many centuries drugs were entirely of natural origin and composed of herbs, animal products, and inorganic materials. Early therapeutics has combined these ingredients with witchcraft, mysticism, astrology, or religion, and those treatments that were effective were subsequently recorded and documented leading to the early herbals. The science of pharmacognosy, i.e. the knowledge of drugs, grew from these records to provide a disciplined, scientific description of natural materials used in medicine.[2] Herbs formed the bulk of these remedies. As chemical techniques improved, the active constituents were isolated from plants, structurally characterized, and in due course many were synthesized in the laboratory. Sometimes more active or better tolerated drugs were produced by chemical modifications (semi-synthesis), or by total synthesis of analogues of the active principles. Gradually synthetic compounds superseded many of the old plant drugs, though certain plant derived agents were never surpassed and remain as valued medicines to this day. The shown below (Fig. 1) are some of the representative natural product derived medicinal compounds from past to present.

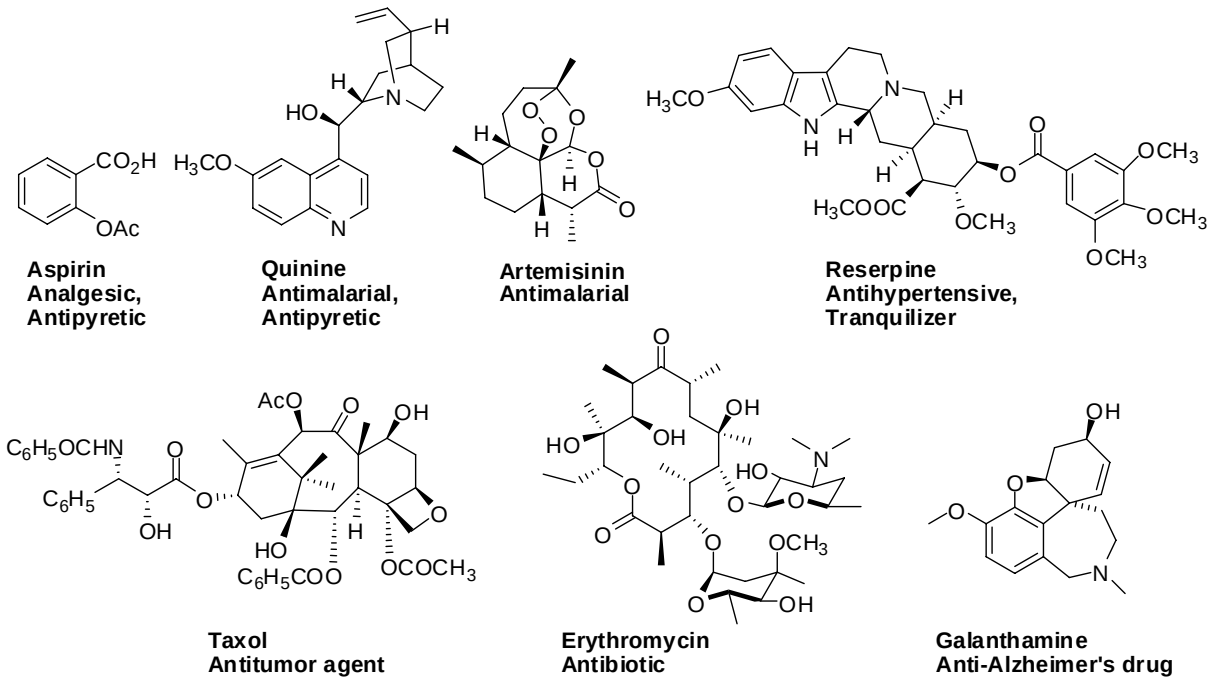


Figure. 1. Examples of natural product based drugs from past to present.

There is currently a renewed interest in pharmacologically active natural products, be they from plants, microorganisms, or animals, in the continued search for new drugs, particularly for disease states where our present range of drugs is less effective than we would wish. Natural products play a highly significant role in the drug discovery and development process. Especially this was apparent in the areas of cancer and infectious diseases. It was revealed that above 60% and 75% of these drugs were to be of natural origin. In a recent survey conducted by National Cancer Institute, among the new 877 small-molecule chemical entities introduced as drugs worldwide during 1981–2002, 61% were found to be inspired by natural products.[3] These include natural products (6%), natural product derivatives (27%), synthetic compounds with natural-product-derived pharmacophores (5%), and synthetic compounds designed on the basis of knowledge gained from a natural product (that is, a natural product mimic; 23%). The pronounced biological activity of natural products has been rationalized by the fact that during biosynthesis, and while participating in their biological role, they interact with multiple proteins as substrates and targets.[4] Natural products are evolved to perform a function that is achieved by binding to proteins or DNA. Therefore, they are capable to penetrate biological barriers and make their way into certain cells or organs in which they will exert the effect. Thus, most natural products already are biologically validated to reach and bind specific proteins. In the plant itself, natural products as secondary metabolites often serve to defend against or poison pathogens or insect predators. In humans, these compounds can be used to protect against, ameliorate, or cure some of our deadlier diseases often by acting as specific toxins against the causal organisms, aberrant cells, or a physiology out of whack.[5]

1.2 Total synthesis of natural products as a tool for drug discovery

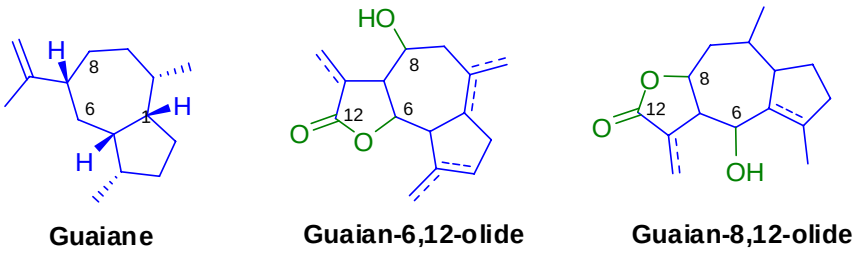
Every natural product type isolated from the seemingly limitless chemical diversity in nature provides a unique set of research opportunities deriving from its distinctive three-dimensional architecture and biological properties. For the past century, the total synthesis of natural products has served as the flagship of chemical synthesis and the principal driving force for discovering new chemical reactivity, evaluating physical organic theories, testing the power of existing synthetic methods, and enabling biology and medicine.[6a] A handful of past and current “miracle drugs” from plants can easily illustrate the importance of total synthesis of natural products in drug discovery — from quinine to Taxol, from aspirin to the birth control pill. Many if not most of these have been tremendous challenges to the medicinal chemist to make in the laboratory, much less scale up to factory-level production. The development of powerful and highly selective methodologies that have control of reactions in chemo-, regio-,

stereo-, and enantio-selectivity have extended the frontiers of total synthesis to near the conceivable limit. The thalidomide episode[6b] in 1960 (different isomers of thalidomide showing differing pharmacological activities, (*R*)-thalidomide has desired sedative properties, while (*S*) enantiomer is teratogenic and induces fetal malformations) perhaps serves as a sad reminder of the enormously difficult and often unpredictable problem of biological activity elicited by enantiomeric substances, and it highlights the utmost importance of access to enantiomerically pure compounds. With the advent of new techniques such as High Throughput Screening (HTS), Computer-aided drug design, Structure based drug design, and Quantitative structure activity relationship (QSAR) the screening of drug candidates can be done more efficiently leading to cost reduction and shortening of development time.

1.3 Biologically active guaianolides and dimeric guaianolides

1.3.1 Guaianolides: Structural features and bioactivity

Guaianolides, consisting of tricyclic 5,7,5-ring system, represent one of the largest subgroup of naturally occurring sesquiterpene lactones exhibiting significant biological activity.[7, 8] Plants containing different guaianolides as the active principles have been used in traditional medicine throughout history for treating conditions ranging from rheumatic pains, increase of bile production to pulmonary disorders. As the name itself indicates, the core structure of the guaianolides is derived from Guaiane, a natural product with a *cis*-fused 5,7-bicyclic hydroazulene ring system (Fig. 2).

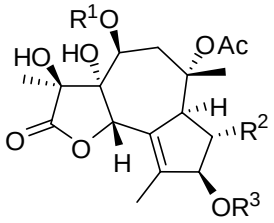


Guaiane **Guaian-6,12-olide** **Guaian-8,12-olide**

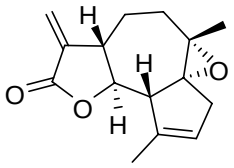
Figure 2. Skeletal relationships: Two classes of guaianolide skeleton.

The guaianolide skeleton along with the 5,7-bicyclic hydroazulene ring system often contains a third ring, an unsaturated α-methylene-γ-lactone, fused to the seven membered ring. Guaianolides exist in two forms namely, guaian-6,12-olides and guaian-8,12-olides (Fig. 2). These two classes differ in their site of annulation of the γ-butyrolactone motif and can simply be termed as angular and linear guaianolides respectively. The γ-butyrolactone ring is *trans*-annulated in approximately 85% of all known guaianolides, while in few guaianolides, the hydroazulene core is also *cis*-fused in the 5,7,5-tricyclic carbon skeleton.[9] Along with the

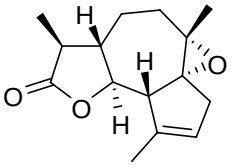
structural diversity, guaianolides exhibit a broad range of biological activity and stimulate the development of research in their total synthesis. Some guaianolides have been reported to possess high antitumor, antihistosomal, anthelminthic, contraceptive, root-growth stimulatory and germination inhibitory activities.[10] This diverse bioactivity of guaianolides makes them attractive synthetic targets since the availability of these compounds from natural sources is very limited. The representative members shown below (Fig. 3) exemplify the structural diversity found within this class of compounds. Among the prominent members of guaianolides are the Thapsigargins isolated from root of *Thapsia garganica*, exhibiting Ca^{2+} modulating properties in subnanomolar concentrations. When applied to intact cells, Thapsigargin can severely alter cellular Ca^{2+} levels, leading to disrupted cell growth and function, and in many cases to programmed cell death.[11] (+)-Arglabin, another prominent member of guaianolides, was isolated from *Artemisia glabella*[12] and shows promising antitumor activity and cytotoxicity against different tumor cell lines (Human tumor cell lines IC_{50}= 0.9-5.0 μg/ml).[13] Arglabin is of interest to the medical community in the recent years as it is currently being tested clinically against breast, colon, ovarian and lung cancer.[14, 15] Intrigued by its biological activity and structural features, we aimed towards the enantioselective total synthesis of (+)-Arglabin and this was successfully accomplished.[16]



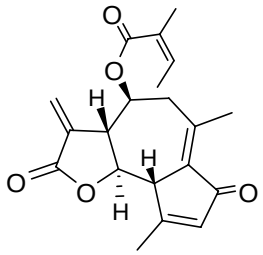
Thapsigargins
Isolated from Thapsia garganica
Exhibits potent Ca^{2+}-modulating properties.



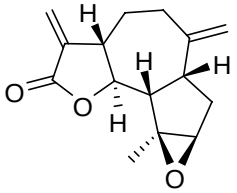
(+) Arglabin
Isolated from *Artemisia glabella*
Inhibits farnesyl transferase and exhibits antitumor activity.



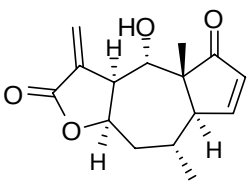
Arborescin
Isolated from *Artemisia arboresces*
insecticidal and contraceptive activity.



Moxartenolide
Isolated from *Artemisia Sylvatica*
Potent inhibitor of NF-kB.



Estafiatin
Isolated from *Artemisia mexicana*
Exhibits antihelminthic activity.

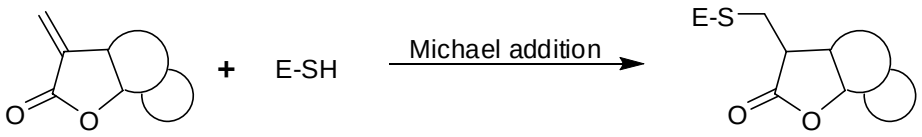


Helenalin
Isolated from *Helenium automnale*
Potent anti-inflammatory agent and inhibitor of NF-kB.

Figure 3. Some representative examples of guaianolides exhibiting structural diversity**.**

1.3.2 Biological properties of sesquiterpene lactones

Many of the α-methylene sesquiterpene lactones show cytotoxic, antitumor, and bactericidal properties, while few of them cause an allergenic contact dermatitis or affect plants by inhibition of growth.[17] The structure-activity relationship (SAR) of α-methylene sesquiterpene lactones was intensively studied.[18-22] It has been shown that these compounds can react by conjugate addition of various biological nucleophiles such as L-cysteine or thiol-containing enzymes (E-SH) (Scheme 1). Further evidences shows that these lactones inhibit the incorporation of selected amino acids into proteins, i.e., they inhibit the metabolism at the cellular level, but do not alkylate DNA.[20, 23-28] Apparently, the residual molecule and its lipophilicity also determine the specificity and the site of the activity.



Scheme 1. Michael addition on α-methylene sesquiterpene lactones.

Based on the SAR studies it has been shown that almost all known cytotoxic sesquiterpene lactones possess an α, β-unsaturated lactone structure, and that the conjugated double bond must be exocyclic.[23] A cyclopentenone or an additional α-methylene lactone moiety or a hydroxy group enhances the cytotoxic activity. The high cytotoxicity of sesquiterpene lactones can be attributed to the inhibition of DNA synthesis and/or transcription.[28a] A large number of active sesquiterpene lactones isolated from plant extracts show tumor inhibiting activity.[29] A few of them such as Vernolepin and Elephantopin (Fig. 4) show promising *in vivo* antitumor activity against the Walker 256 intramuscular carcinosarcoma in rats.[23] Despite of having very good antitumor activity, the considerable cytotoxicity of sesquiterpene lactones has prevented them so far from any useful medicinal application.[28b]

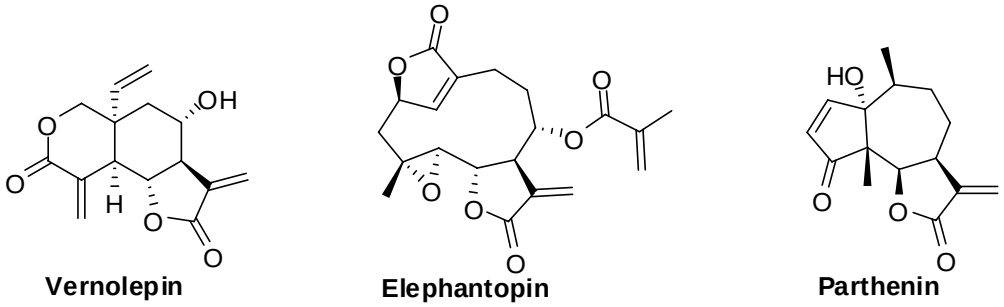


Figure 4. Representative members of α-methylene sesquiterpene lactones showing diverse biological properties.

In addition to cytotoxic and antitumor properties, certain sesquiterpene lactones show allergenic, phytotoxic and antimicrobial activities. Sesquiterpene lactones, which are sometimes present in the pollen, can cause allergic contact dermatitis, even when carried by the wind. For example, Parthenin (Fig. 4) present in *Parthenium hysterophoros*, is a primary allergen and the allergy thus caused represents a serious dermatological problem in India and neighbouring countries.[30] The α-methylene lactones present in the common sunflower (*Helianthus annuus L.*) are know to be stress metabolites, i.e. they are formed during attack by pests, during periods of dryness or overexposure to sunlight and heat, and probably act mainly as chemical defences against pests, especially microorganisms.[31]

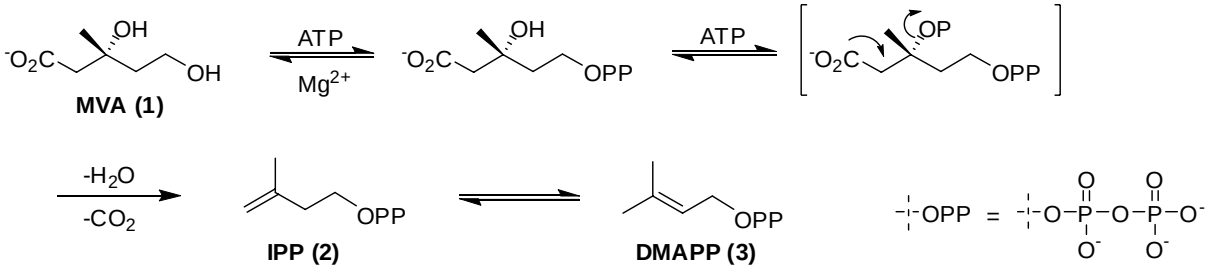
1.4 Biogenesis of sesquiterpene lactones

1.4.1 The MVA pathway

In the early history of natural product chemistry, many strongly odorous plant compounds were observed to be formed from C_5 units called isopentenyl or isoprene units. These compounds were termed terpenes. They are classified according to the number of isoprene units present in the molecule such as monoterpenes, C_{10}; sesquiterpenes, C_{15}; diterpenes, C_{20}; etc. They are hypothetically derived from isoprene by joining two or more units from either end the head or the tail, known as the isoprene rule proposed by *Wallach* in 1887.[32] The "isoprene rule" deduced from these observations can only be regarded as a working hypothesis, since it fails to be true in all cases but has proven to be very useful in the majority of cases. In present-day terms, terpenes are classified according to the 'biogenetic isoprene rule' proposed by *Ruzicka* in 1953.[33] It is based on the biogenesis of terpenes and states that each member of a terpenoid subgroup was derived from a single parent compound that was unique to that group, and that the various parents were related in a simple homologous fashion. Accordingly, all sesquiterpenoids were derived from the parent compound farnesyl pyrophosphate (FPP) by a sequence of straight forward cyclizations, functionalizations and sometimes rearrangements that are well known from mechanistic organic chemistry.

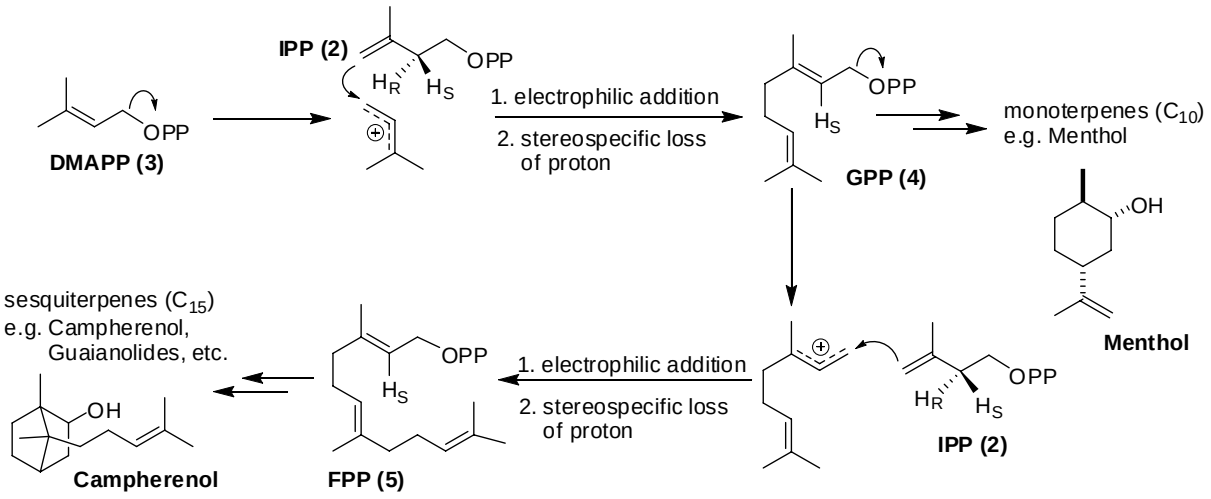
The parent of the terpenoids is 3*R*-(+)-mevalonic acid (MVA, **1;** Scheme 2) which was isolated in 1956 as a metabolite of a *Lactobacterium* species and was found to be potent growth factor for yeast.[34, 35] Isoprene itself does not function as the reactive biogenetic species, but isopentenyl and dimethylallyl pyrophosphates are the reactive species involved in the formation of terpenes. These important precursors are formed from mevalonic acid (MVA, **1**; Scheme 2) by phosphorylation followed by ATP-assisted loss of water and carbon dioxide to give isopentenyl pyrophosphate (IPP, **2**). Isomerization of the double bond gives

dimethylallyl pyrophosphate (DMAPP, **3**) (Scheme 2).[36] The biochemical pathways leading to the formation of these precursors have been extensively studied over the last 50 years and are generally accepted as mevalonate (MVA) biosynthesis pathway of terpenes in organisms.[37] More recently a second biosynthetic route known as mevalonate independent pathway or methylerythritol-phosphate pathway (MEP) was discovered in plants also leading to the formation of IPP (**2**) and DMAPP (**3**) as the final products.[38]



Scheme 2. MVA pathway for the synthesis of IPP (**2**) and DMAPP (**3**).

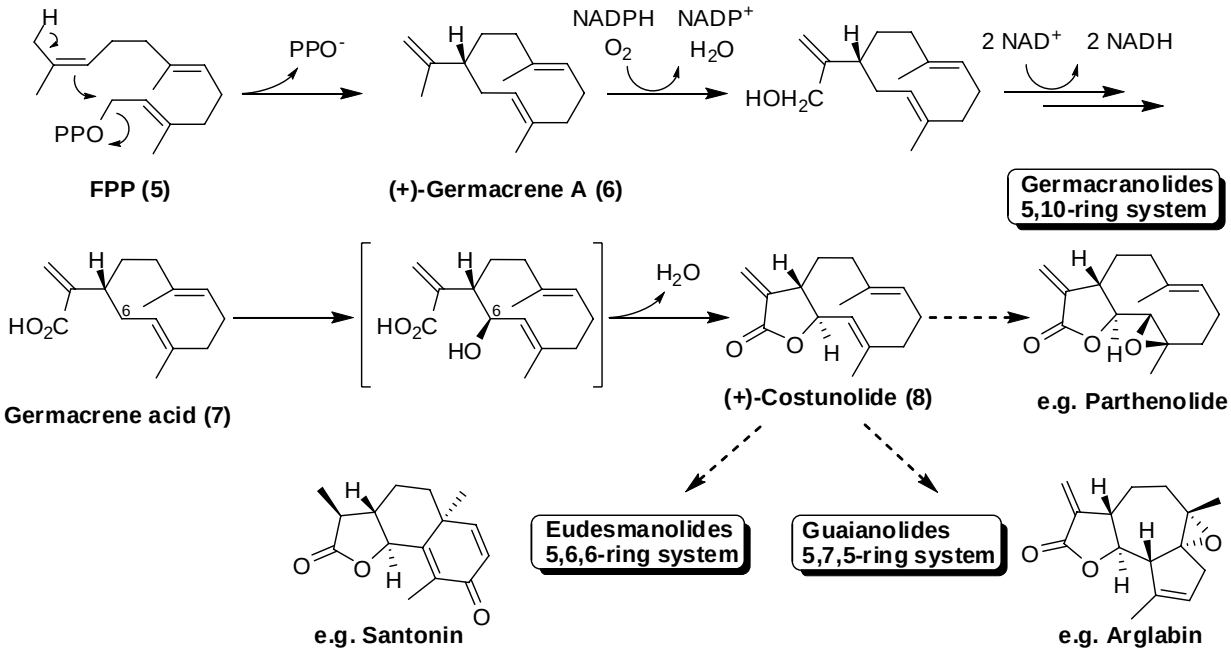
IPP (**2**) and its isomer DMAPP (**3**) together represent the equivalent of the isoprene unit. The joining of these two units in a head to tail fashion by prenyltransferases leads to the construction of basic backbones of terpenes (Scheme 3). The isomerase that interconnects IPP (**2**) and DMAPP (**3**) abstracts stereoselectively the pro-(***R***) hydrogen from the C_2 position of IPP (**2**) to result in a *trans* substituted double bond and releases geranylpyrophosphate (GPP, **4**). The GPP (**4**) formed in this process acts as a fundamental precursor for the synthesis of monoterpenes (e.g. menthol). Addition of further C_5-IPP (**2**) to the C_{10}-skeleton of GPP (**4**) according to the isoprene rule gives rise to the formation of farnesylpyrophosphate (FPP**, 5**), the precursor for linear, cyclic sesquiterpenes (e.g. campherenol) and also sesquiterpene lactones such as guaianolides.



Scheme 3. Biosynthesis of sesquiterpenes *via* the formation of FPP (**5**).

1.4.2 Biogenesis of guaianolides

Sesquiterpene lactones are a major class of plant secondary metabolites that are mainly found in the *Asteraceae* but also occur in other high plant families and lower plants.[39] The majority of more than 4000 known different structures have a guaiane, eudesmane, or germacrane framework. *Chicory* (*Cichorium intybus*), also known as French endive, is known to contain guaianolides, eudesmanolides, and germacranolides. The biosynthesis of these sesquiterpene lactones in *Chicory* has been investigated by *de Kraker et al*. and is also reasonable to validate the same for other plant species.[40-43] Accordingly, the studies with the *Chicory* roots have shown that its sesquiterpene lactones are derived from (+)-Germacrene A (**6**; Scheme 4). Thus cyclization of FPP (**5**) yields (+)-Germacrene A (**6**) which undergoes further enzymatic oxidations to afford Germacrene acid (**7**). Formation of (+)-Costunolide (**8**) from Germacrene acid (**7**) is postulated to occur *via* hydroxylation at the C_6-position by a cytochrome P450 enzyme, after which lactonization yields (+)-Costunolide (**8**).[40] Further rearrangements and oxidative modifications of (+)-Costunolide (**8**) give rise to structurally diversified classes of compounds such as germacranolides, guaianolides and eudesmanolides (Scheme 4).



Scheme 4. Biosynthesis of germacranolides, guaianolides and eudesmanolides.

A number of stereospecific biomimetic transformations leading to the formation of eudesmanolides and guaianolides from germacranolides and their derivatives have been reported in literature.[44-45]

1.5 Dimeric guaianolides

1.5.1 Structural features and biological properties

Dimeric guaianolides are structurally more complex guaianolides derived through the dimerization of two monomeric guaianolides, presumably *via* a [4+2] cycloaddition. Dimeric guaianolides isolated from plants, also known as disesquiterpene lactones, belong to a little studied type of sesquiterpenes, although their initial molecules, the mono guaianolides, have been studied in more detail both under chemical and stereo chemical aspects.[46] Members of the *Artemisia* genus are important medicinal plants found throughout the world. Artemisinin (see Fig. 1) isolated from *Artemisia annua* L. is a potent antimalarial agent. Dimeric sesquiterpene lactones isolated from *Artemisia sylvatica* exhibit a wide range of biological activities. Arteminolide A (Fig. 5) isolated from *Artemisia sylvatica* inhibits recombinant rat FPTase with IC_{50} of 360 nM and appears to be selective for FPTase. It did not inhibit rat squalene synthase (IC_{50} >> 200 μM) and recombinant rat geranyl-geranyl protein transferase I (IC_{50} >> 200 μM).[47, 48] These results suggest that Arteminolides are novel inhibitors of FPTase and could be used as antitumor agents against *ras*-mutated human cancers or a wide array of human cancers. Arteminolides B-D (Fig. 5) are new farnesyl protein transferase inhibitors isolated together with known Arteminolide A from the aerial parts of *Artemisia argyi*.[49] These new series inhibited a recombinant human FPTase with IC_{50} values of 0.76 μM (Arteminolide B), 0.95 μM (Arteminolide C), and 1.1 μM (Arteminolide D).

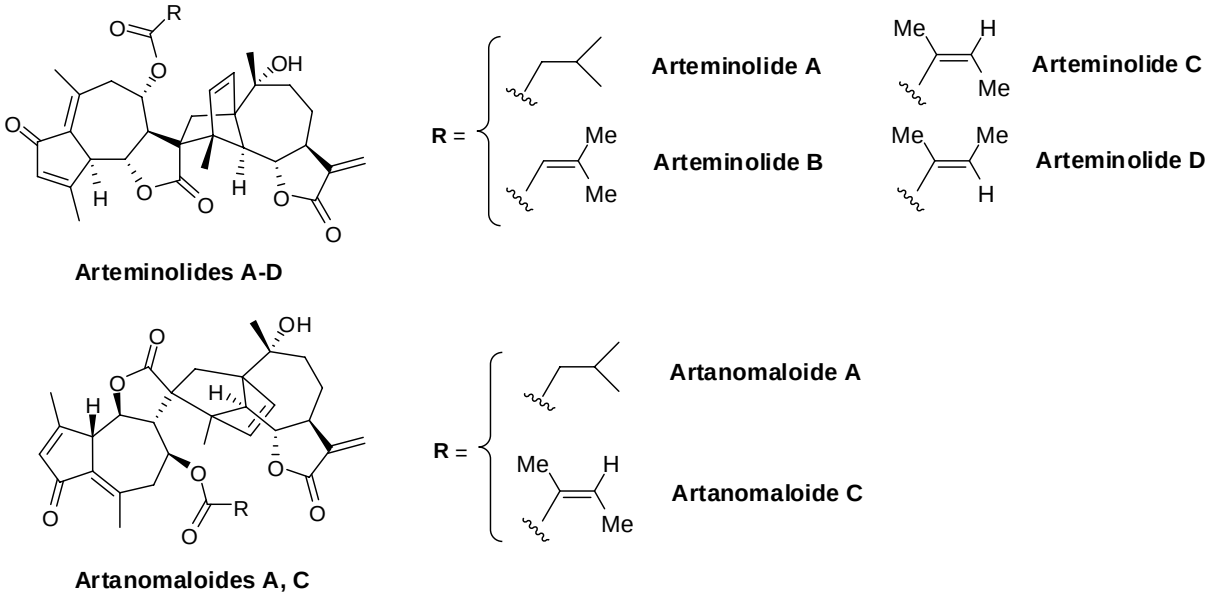
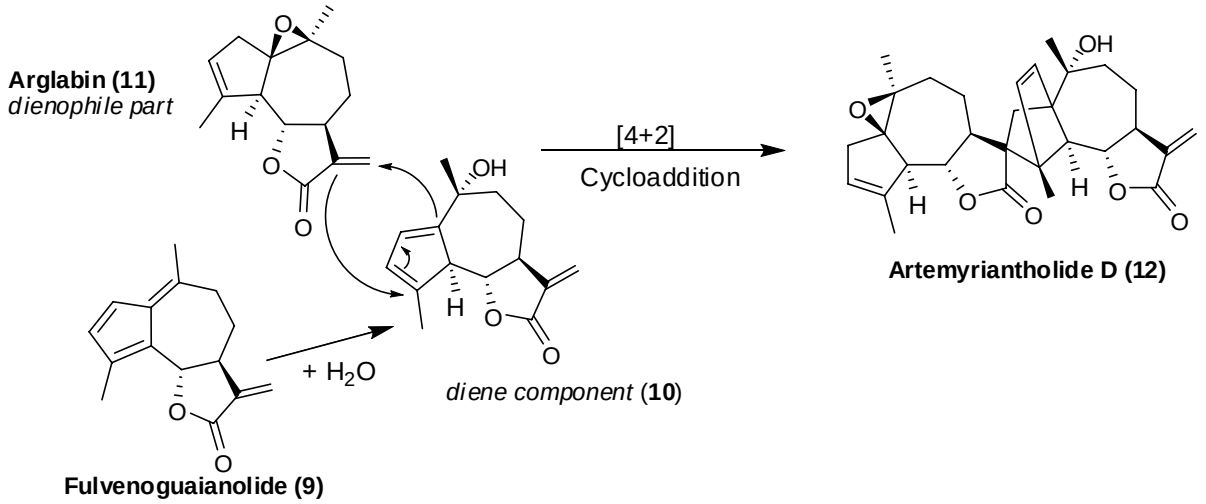


Figure 5. Structural features of dimeric guaianolides, Arteminolides and Artanomaloides.

Artanomaloides A, C (Fig. 5) were also isolated from *Artemisia argyi* and are configurational isomers of Arteminolides A, C respectively. Interestingly, these configurational isomers show poor enzyme inhibition with IC_{50} values of 105 μM (Artanomaloide **A**) and 150 μM (Artanomaloide C) compared to Arteminolides A, C respectively.[49] This result indicates that the stereochemistry at the site of spiro-ring fusion is highly important for the biological activity of dimeric guaianolides.[50]

1.5.2 Biosynthesis of dimeric guaianolides

Dimeric guaianolides are biosynthetically derived from the mono guaianolides presumably via a Diels-Alder reaction. Diels-Alder reactions have been postulated as key steps in a number of biosynthetic conversions. However, until now there is no case known where the corresponding enzyme system, that would be the Diels-Alder-ase, could be detected.[51] Recently, Oikawa, Ishihara et al. published experimental evidence that the two phytotoxins "solanapyrones" produced by the pathogenic fungus *Alternaria solani* are probably formed by an enzyme-catalyzed [4+2] cycloaddition.[52] In case of dimeric guaianolides, the evidence comes from the fact that these compounds appear to undergo spontaneous retro Diels-Alder reactions in the mass spectrometer under a variety of ionization techniques. The daughter ion(s) formed by such fragmentation generally had half the mass of the parent dimer. Artemyriantholide D (**12**) (Scheme 5) is a dimeric guaianolide isolated from *Artemisia myriantha* and is postulated to derive biosynthetically from a Diels-Alder reaction, in which new carbon-carbon bond formation take place between electron-deficient carbon-carbon double bond of the α,β- unsaturated lactone of a molecule of Arglabin (**11**) and a guaianolide (**10**) containing cyclopentadiene functionality derived from a fulvenoguaianolide (**9**).[53]



Scheme 5. Proposed biosynthesis of dimeric guaianolide Artemyriantholide D (**12**) via Diels-Alder reaction.

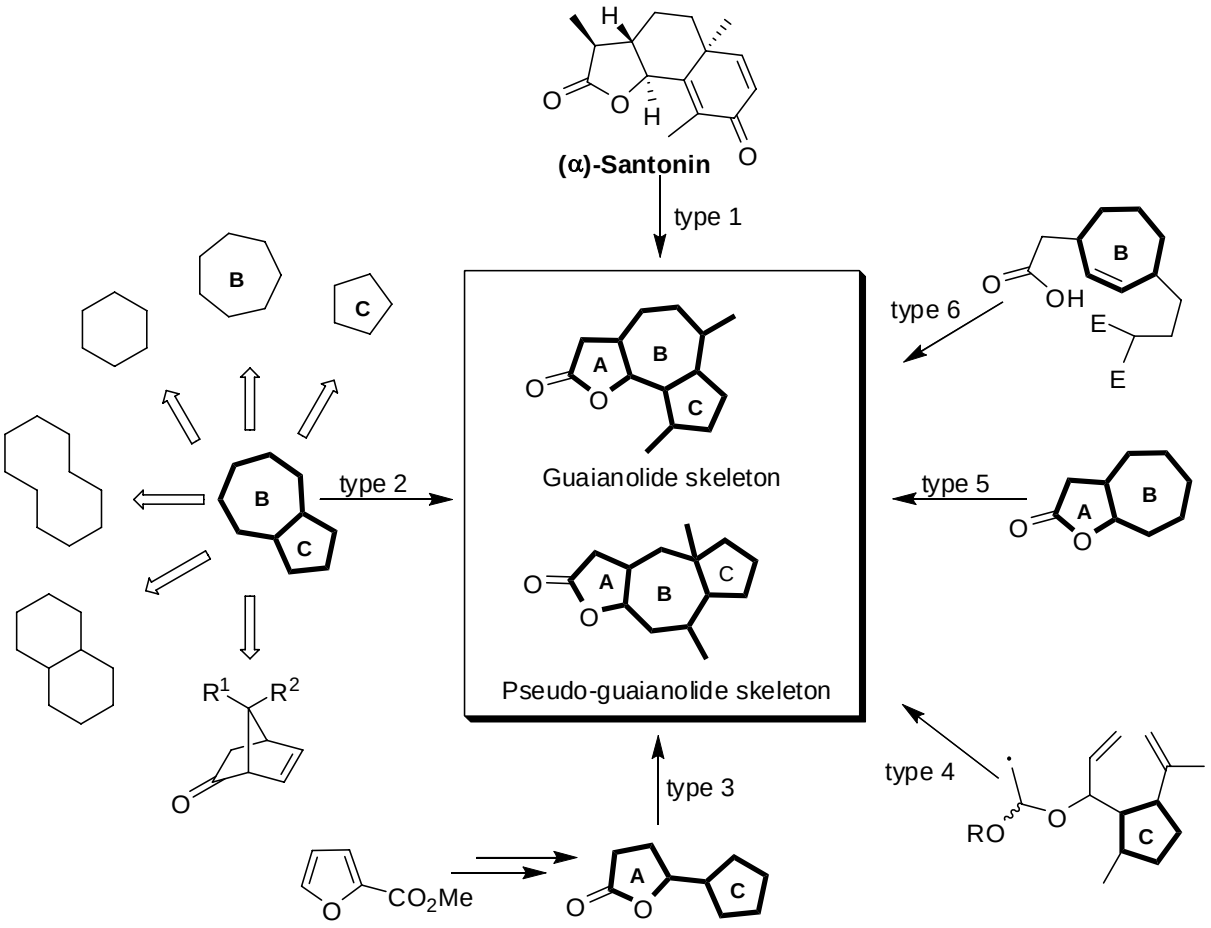
The isolation of Fulvenoguaianolide (**9**) in substantial amounts from *Artemisia myriantha* and the existence of Arglabin (**11**) as most abundant guaianolide in this species add support to the fact that this type of intermolecular Diels-Alder reaction can take place between them before isolation leading to the formation of dimeric guaianolides such as Artemyriantholide D (**12**). An *exo* Diels-Alder transition state is required in order to account for the stereochemistry of the dimeric linkage in Artemyriantholide D (**12**). This orientation of approach is unusual for Diels-Alder additions, which normally adopt an *endo* transition state, in which the possibility of secondary orbital overlap between frontier orbitals of the diene and dienophile reactants is maximized. This unusual orientation may be the result of steric avoidance and of favorable hydrogen bonding in the transition state between the lactone carbonyl of the dienophile (Arglabin (**11**)) and the hydroxyl group adjacent to the diene (**10**), which determine both the regio and stereoselectivity of the reaction.[53]

1.6 Synthesis of guaianolides and dimeric guaianolides

1.6.1 Various approaches towards the synthesis of guaianolides

The biosynthesis of guaianolides in conjunction with the recent developments in the total synthesis of various biologically active guaianolides has been recently reported by *Reiser et al.*[54] Many of these synthetic approaches towards guaianolides and pseudo- guaianolides which are either racemic or stereoselective can be broadly classified into six types as shown in Scheme 6.[55]

A classical semi-synthesis involves the transformation of naturally occurring α-Santonin to the 5,7,5-tricyclic ring system of the guaianolides via photochemical rearrangement or a solvolytic rearrangement (Type 1).[56] The second type involves the annulation of the γ-butyrolactone ring on the hydroazulene scaffold, which is pre constructed using a variety of laboratory starting materials and methods.[57] In the third type, the construction of the seven membered ring (B ring) takes place on the preexisting AC rings by means of a radical cyclization or by ring closing metathesis (RCM). This approach forms a basis for studies towards the total synthesis of various guaianolide natural products from our group. The concerted formation of AB ring system on a functionalized C-ring via radical cyclization stands for type 4 transformation. The annulation of C-ring on the preexisting AB ring system accounts for type 5, while the concerted annulation of A and C-rings on the B-ring accounts for type 6 approach (Scheme 6).

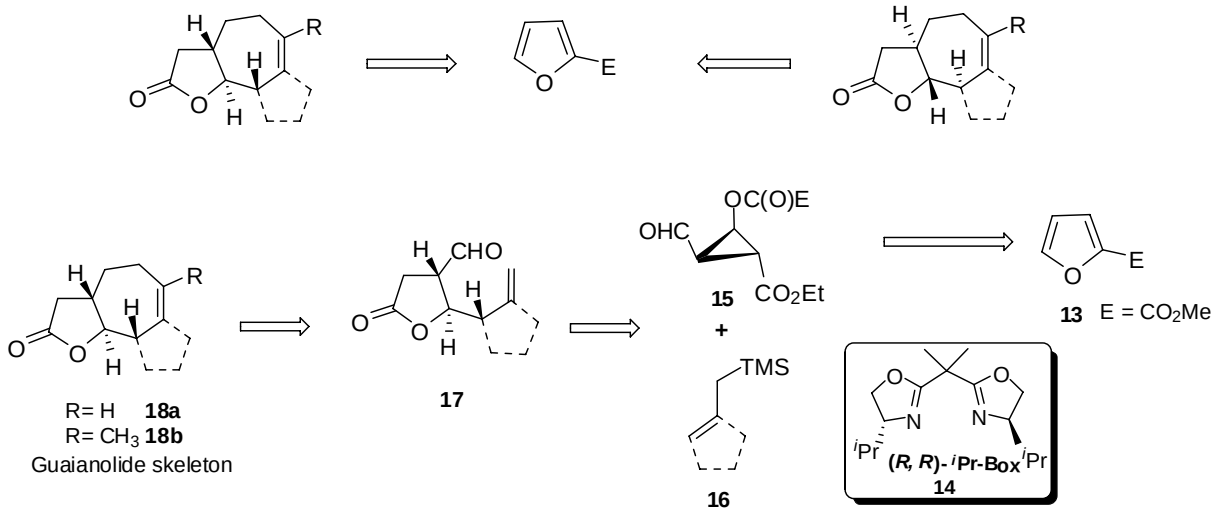


Scheme 6.Various approaches towards the synthesis of guaianolides and pseudo-guaianolides.

1.6.2 Stereoselective synthesis of guaianolides starting from simple aromatics

The laboratory synthesis in the Reiser group involves the transformation of simple aromatics into functionalized 2,3-*anti*-disubstituted γ-butyrolactones that are capable of elaborating to guaianolide skeletons.[58] The shown below retrosynthetic approach (Scheme 7) outlines the key steps that are involved in transforming simple aromatic starting materials to guaianolide scaffolds. At first the application of asymmetric catalysis as a means of transforming simple achiral starting materials into useful chiral building blocks is utilized to a greater extent in our approach. Thus asymmetric cyclopropanation of a simple aromatic starting material such as furoic ester **13**, followed by the ozonolysis of the unreacted double bond delivers enantiomerically pure cyclopropylcarbaldehyde **15** in good yield. The use of chiral bis (oxazoline) ligand such as (*R*,*R*)-^{i}Pr-box **14** sets the regio and stereoselectivity of the reaction. Cyclopropylcarbaldehyde intermediates such as **15** are very reactive towards cyclic or acyclic allylsilane **16** under Sakurai allylation conditions, leading to the formation of an adduct which

on subjecting to a retroaldol/lactonization cascade results in the formation of 2,3-*anti*-disubstituted γ-butyrolactone **17**.



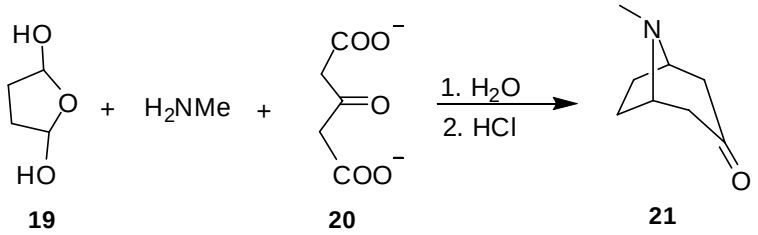
Scheme 7. Retrosynthetic outline towards the synthesis of guaianolide scaffolds.

The *anti*-disubstituted γ-butyrolactone is a key structural motif of guaianolides, and can be elaborated to the tricyclic core **18** of various guaianolide natural products either by ring closing metathesis (RCM) or by radical cyclizations as key steps. Interestingly, the use of appropriate chiral bis(oxazoline) ligand in the first step, i.e. in asymmetric cyclopropanation, can alter the whole sequence leading to the corresponding enantiomer of γ-butyrolactone **17**. Thus, the approach is flexible enough in transforming simple aromatic starting materials to either of the enantiomerically pure guaianolide scaffolds. The application of this strategy was successfully utilized in the first enantioselective total synthesis of a novel antitumor guaianolide (+)-Arglabin.[16] Further extension of this strategy to the total synthesis of Moxartenolide (see Fig. 3) is currently under investigation.

1.6.3 Biomimetic approach towards the synthesis of dimeric guaianolides

The appealing beauty of the routes that nature uses to build natural products is amazing and the quest for laboratory syntheses that mimic these routes is longstanding.[59] The importance of biomimetic synthesis in natural product synthesis can be illustrated in the words of Skyler and Heathcock[60] as *"For all natural products, there exists a synthesis from ubiquitous biomolecules. The inherent interconnectivity of natural products implies that a truly biomimetic total synthesis represents a general solution not to the preparation of a compound but to the preparation of all similarly derived natural products (discovered and undiscovered)."* The concept of biomimetic synthesis was coined by Robinson in 1917,

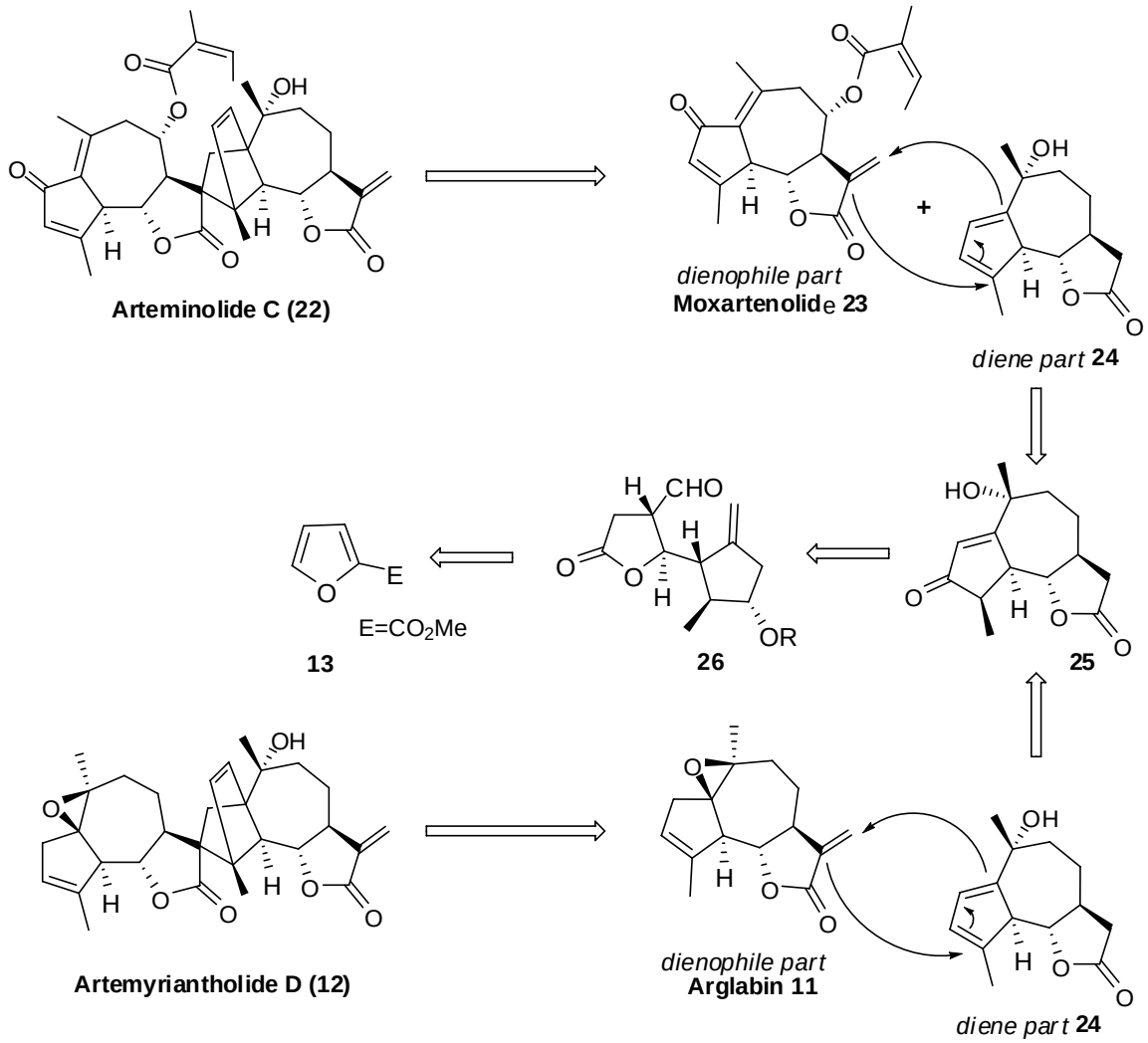
following his straightforward synthesis of tropinone **21** from succinaldehyde **19**, methylamine, and acetone dicarboxylic acid **20** (Scheme 8).[61]



19 **20** **21**

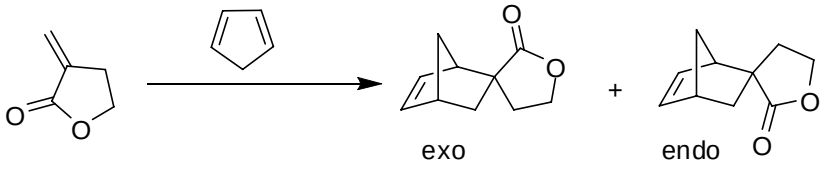
Scheme 8. Robinson's one pot synthesis of Tropinone (**21**), first example of biomimetic synthesis

As described in the biosynthesis of dimeric guaianolides, their biogenesis involves a [4+2] cycloaddition reaction between two mono guaianolides; the mimic of this process in the laboratory can lead us to the total synthesis of dimeric guaianolides. The target dimeric guaianolides chosen for this purpose are Artemyriantholide D (**12**) and Arteminolide C (**22**) (Scheme 9).



Scheme 9. Retrosynthetic strategy towards the synthesis of dimeric guaianolides Arteminolide C (**22**) and Artemyriantholide (**12**)

As outlined in the above retrosynthetic scheme (Scheme 9), the dimeric linkage between the two mono guaianolides, i.e. the dienophile part and the diene part is planned to assemble through a Diels Alder reaction. Thus, for both the cases Artemyriantholide D (**12**) and Arteminolide C (**22**) the diene component **24** is the same while the dienophile partner varies accordingly (**11** and **23** respectively). The diene component **24** is accessible from the intermediate **25**, which in turn can be synthesized from functionalized 2,3-*anti*-disubstituted γ-butyrolactone such as **26**. Interestingly, the mono guaianolide Arglabin **11** needed as dienophile for the synthesis of Artemyriantholide D (**12**) has already been synthesized, while the Moxartenolide **23** needed for the synthesis of Arteminolide C (**22**) is yet to be synthesized. The stereochemistry of the dimeric linkage in both the dimeric guaianolides Artemyriantholide D (**12**) and Arteminolide C (**22**) is a result of an *exo* transition state of a [4+2] cycloaddition reaction. This type of transition state is unusual for Diels-Alder additions taking place in a reaction flask, but *Buono et al.* [62] has shown that high exoselectivity occurs in the Diels-Alder additions of α-methylene-γ-butyrolactones to cyclopentadiene under kinetically controlled as well as thermal conditions (Scheme 10). This offers an example of a substrate which violates the prevalent Alder-Stein principle.[63] The high exoselectivity observed is a result of conformationally rigid cyclic cisoid dienophile and is highly related to the α-substitution of the dienophile.[62]



conditions	exo : endo
1. Toluene, reflux	92 : 8
2. $ZnCl_2$ (10 mol%) CH_2Cl_2, rt	93 : 7
3. $AlCl_3$, (10 mol%) CH_2Cl_2, -15 ^oC	94 : 6

Scheme 10. Diels-Alder reaction between α-methylene-γ-butyrolactone and pentadiene showing *exo* selectivity.

Thus, the existence of such literature precedence for high *exo* selectivity prompted us to investigate and apply the same conditions in order to achieve the proposed *exo* selectivity in the biomimetic synthesis of these natural products. Also the successful application of above described biomimetic approach forms a basis to support the proposed biogenetic hypothesis.

1.7 Conclusions

Guaianolides exhibit a broad range of biological activity and stimulate the development of research in their total synthesis. The diverse bioactivity of guaianolides makes them attractive synthetic targets since the availability of these compounds from natural sources is very limited. As there are more and more members of the guaianolide family discovered, the full evaluation of their biological activity is still of current interest. Although the high toxicity of some of the guaianolides prevents them from any useful medicinal application, attempts to control the cytotoxicity by chemical modifications and synthesizing the derivatives would be of great value. In case of dimeric guaianolides, the biomimetic approach would help us to validate the proposed biogenetic hypothesis involving a [4+2] cycloaddition reaction. Therefore the total synthesis of guaianolides plays an important role in inventing new, efficient and flexible ways to synthesize this class of natural products and their derivatives.

2. Aim of this work

2.1 Studies towards the total synthesis of (+)-Arglabin and (+)-Moxartenolide

The aim of this work was to achieve the enantioselective total synthesis of novel antitumor guaianolide (+)-Arglabin (**11**) by applying the strategy of transforming simple aromatic starting materials to guaianolide skeletons. The work was further extended towards the enantioselective total synthesis of (+)-Moxartenolide (**23**) and dimeric guaianolides such as Artemyriantholide D (**12**) (Fig. 6)

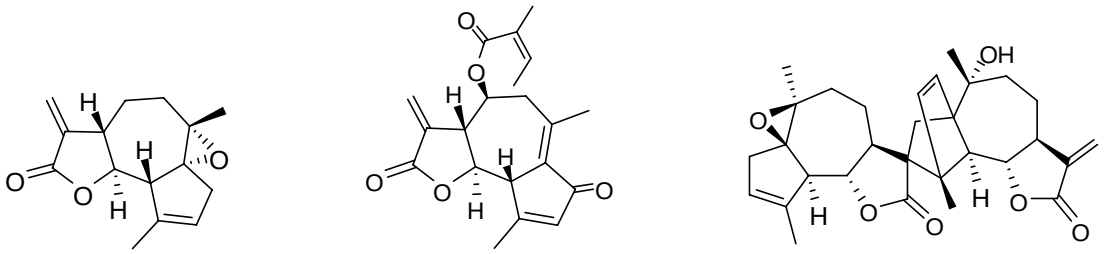
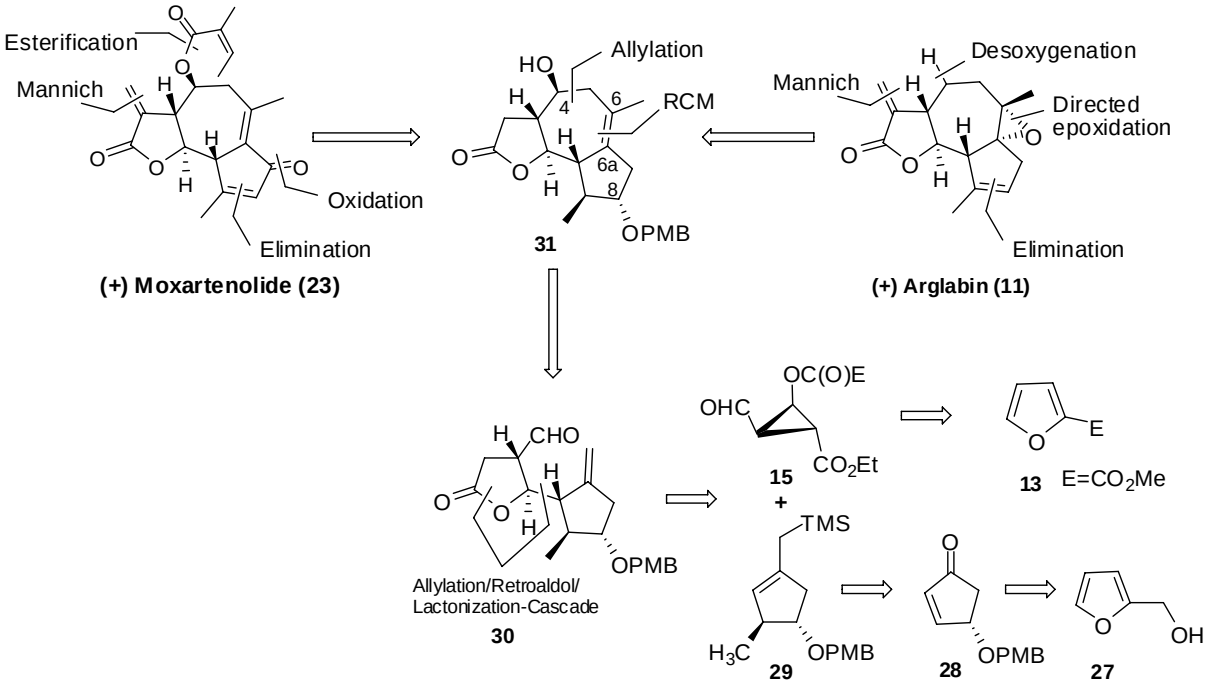


Figure 6. Target guaianolides aimed for total synthesis.

The general retrosynthetic strategy shown below outlines the approach to achieve the target guaianolides. The total synthesis of both Arglabin (**11**) and Moxartenolide (**23**) was planned to achieve from a common synthetic intermediate of type **31** (Scheme 11).

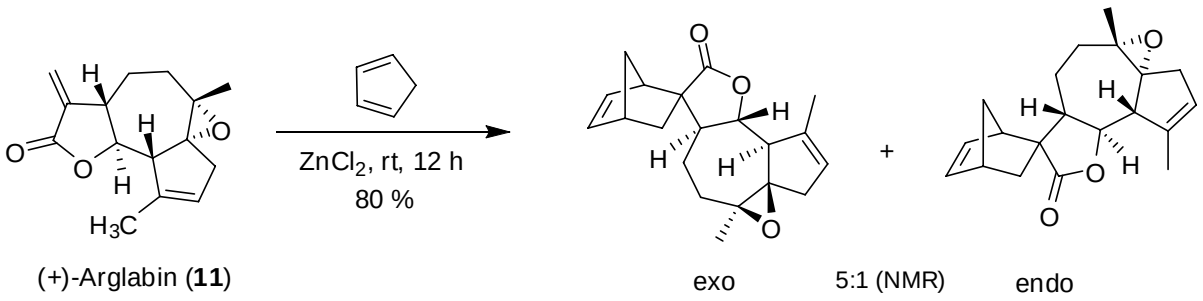


Scheme 11. Retrosynthetic approach towards the total synthesis of Arglabin (**11**) and Moxartenolide (**23**).

The *exo* methylene group responsible for biological activity of both the guaianolides was incorporated by means of Mannich reaction. In case of (+)-Arglabin **11**, the C6/C6a double bond has to be stereoselectively epoxidized, for which a study of directed epoxidation using the free hydroxy group at C8 position in **31** was extensively investigated. The C4 stereogenic centre in **31** can be utilized for esterification purpose in case of Moxartenolide (**23**), while it has to be subjected to desoxygenation for the total synthesis of Arglabin (**11**). The key intermediate **31** having all the necessary functional groups and capable of transforming into target molecules was readily obtained from lactone aldehyde **30** by allylation/ring closing metathesis sequence. The transformation of aromatic starting materials into functionalized 2,3-*anti*-disubstituted γ-butyro-lactones is a standard protocol which was employed in the synthesis of **30**. The chiral allyl silane **29** that accounts for the lower five membered ring of the target guaianolides was synthesized in a enantiomerically pure manner starting from furfuryl alcohol **27** via the intermediate 4-hydroxy protected 2-cyclopentenone **28.**

2.2 Model studies towards total synthesis of dimeric guaianolides

As described in the retrosynthetic strategy of Artemyriantholide D (**12**) (see Introduction, Scheme 9) that a Diels-Alder reaction is required as key step between Arglabin (**11**) and diene component of type **24** with high exoselectivity. To validate the high exoselectivity reported in the Diels-Alder additions of α-methylene-γ-butyrolactones to cyclopentadiene (see Introduction, Scheme 10), a model study was conducted between Arglabin (**11**) and cyclopentadiene under different reaction conditions (Scheme 12). Also the effect of bis (oxazoline) ligand (BOX) in complexation with $Cu(OTf)_2$ as a chiral Lewis acid was studied these types of Diels-Alder reactions was examined.



Scheme 12. Diels-Alder reaction between Arglabin (**11**) and cyclopentadiene showing high exoselectivity.

3. Enantioselective Total Synthesis of (+)-Arglabin

3.1 Isolation and bioactivity

Guaianolides are a member of one of the largest groups of naturally occurring sesquiterpene lactones. One of the prominent members of this widely distributed class of guaianolides is (+)-Arglabin (**11**) (Fig. 7). It's a sesquiterpene γ-lactone isolated from the aerial part of *Artemisia glabella*, a species of wormwood endemic to the Karaganda region of Kazakhstan. (+)-Arglabin was isolated as a crystalline compound with composition $C_{15}H_{18}O_3$, and its structural elucidation was carried out by NMR studies and confirmed by X-ray analysis.[12]

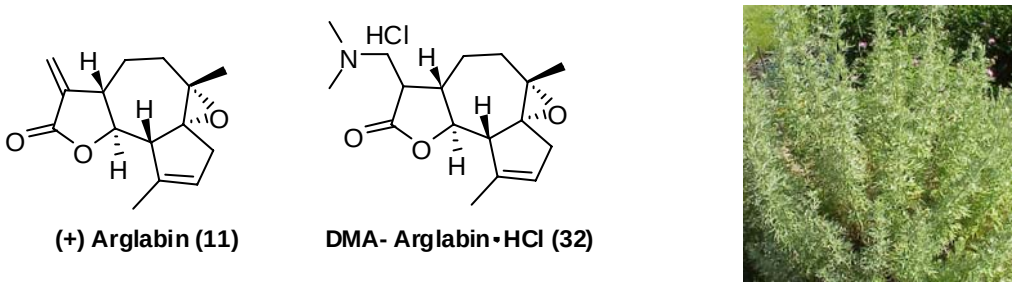


Figure 7. Structures of Arglabin (**11**), DMA-Arglabin-HCl (**32**) and picture of *Artemisia glabella*

(+)- Arglabin (**11**) shows promising antitumor activity and cytotoxicity against different tumor cell lines (Human tumor cell lines IC_{50} = 0.9-5.0 μg/ml).[13] The antitumor activity of Arglabin is known to occur *via* its inhibition of farnesyltransferase which leads to the activation of RAS proto-oncogene, a process that is believed to play a pivotal role in 20-30% of all human tumors. The transformation of Arglabin (**11**) to its dimethylamino hydrochloride salt (**32**) will lead to increase of its bioavailability and has been successfully used in Kazakhstan for treatment of breast, colon, ovarian and lung cancer, and is currently under clinical evaluation.[64, 65]

3.2 Farnesyltransferase inhibitors (FTIs) as novel therapeutic agents

One of the aspects being extensively investigated in anticancer drug development is the intracellular signal transduction pathway. Rational therapies that target the RAS pathways might inhibit tumor growth, survival and spread. Several of these new therapeutic agents are showing promise in the clinic and many more are being developed. The RAS proteins are members of a large super family of low molecular weight GTP binding proteins, which can be divided into several families according to the degree of sequence conservation. The RAS family controls cell growth and the three members of the RAS family namely, HRAS, KRAS and NRAS, are found to be activated by mutation in human tumors.[66] The normal function of RAS proteins requires them to be post-translationally modified. The purpose of this is primarily to

localize them to the correct sub cellular compartment, principally the inner face of the plasma membrane. RAS proteins that are mislocalized at other sites in the cell are inactive, probably because they cannot recruit their target enzymes.[67] The fact that correct post-translational modification of RAS is required for its biological activity has made the enzymes involved in this processing very attractive targets for therapeutic intervention.[68] The steps in the normal post-translational processing of RAS are well described in literature[69] and can be shown in a schematic picture (Figure 8). Farnesyltransferase (FTase) catalyses the transfer of the 15-carbon isoprenoid chain from farnesyl pyrophosphate (FPP, F) to a cysteine residue that is close to the carboxyl terminus (C186 in human HRAS) (step a, Fig. 8). This results in RAS associating with intracellular membranes via its farnesyl group (F). Farnesyltransferase inhibitors (FTIs) block this farnesylation, so RAS remains in the cytosol and is unable to stimulate its downstream targets. However, when FTase is inhibited, KRAS and NRAS, but not HRAS, can be geranylgeranylated, an alternative 20-carbon isoprenylation is added, and this is catalyzed by geranylgeranyltransferase (GGTase), resulting in rescue of processing of these RAS isoforms. Following isoprenylation, several other processing steps occur (steps b, c, d, Fig. 8) before transportation to the plasma membrane. The greatest drug discovery effort has gone into developing inhibitors of FTase, but other steps in the pathway might be worth pursuing. The failure of FTIs to block KRAS processing has proved to be a notable problem as KRAS is the most commonly mutated RAS isoform in human tumors.

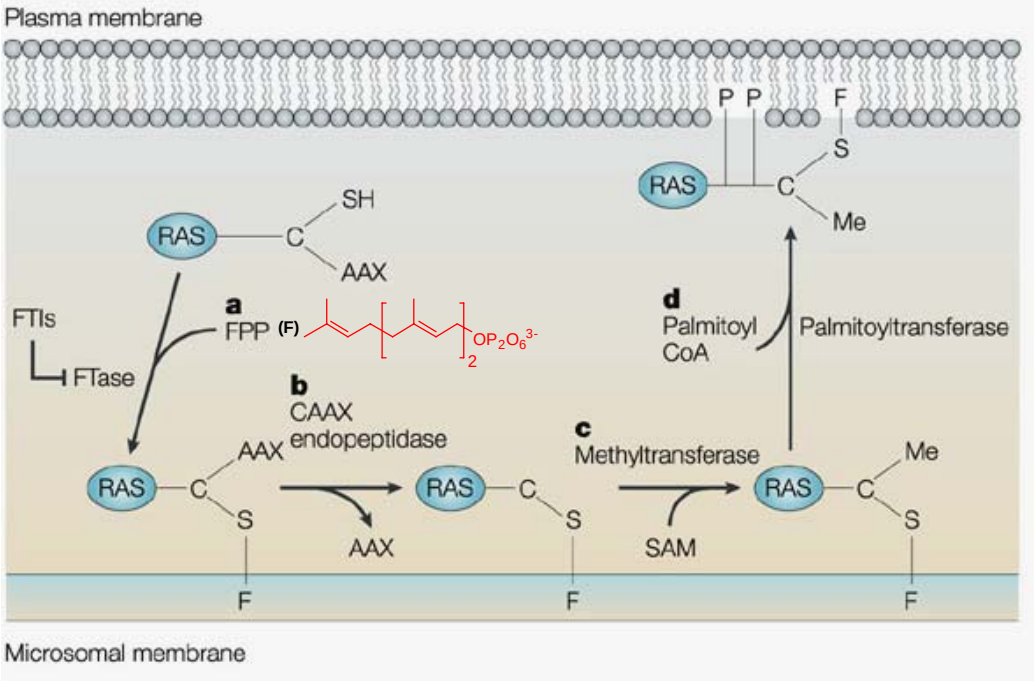
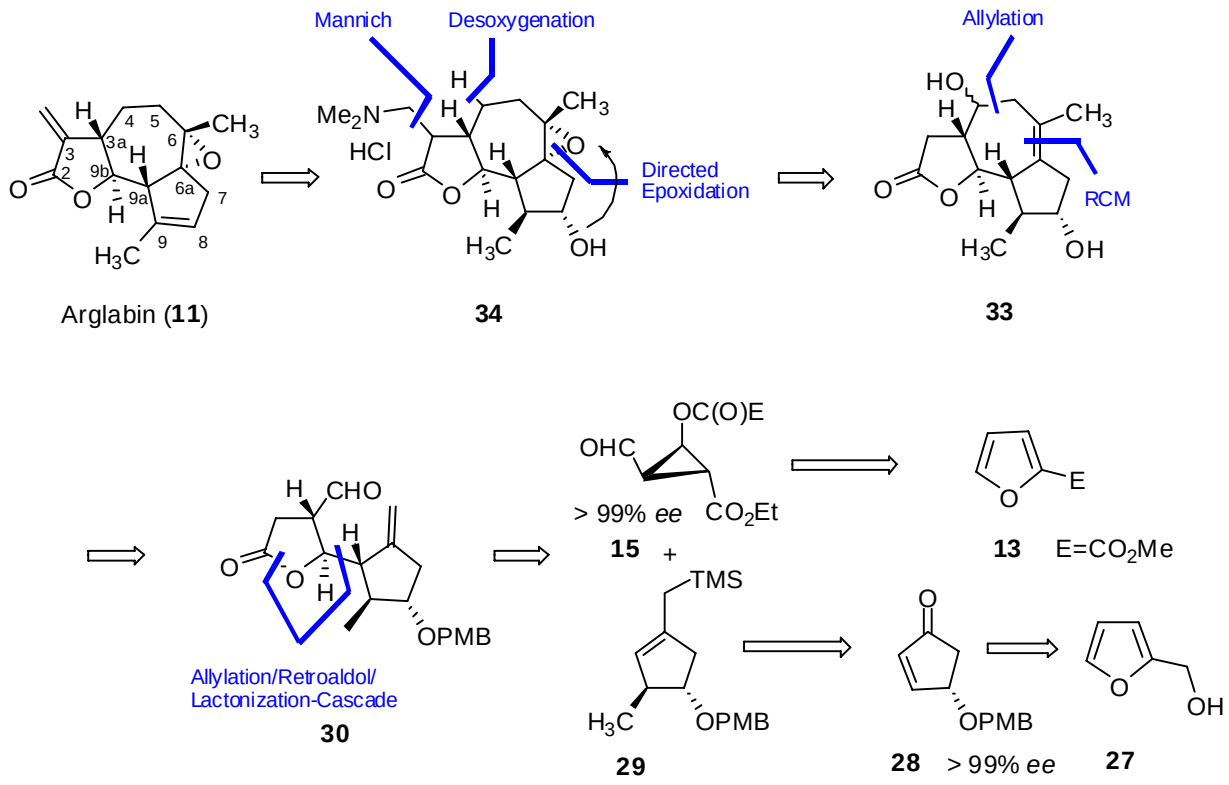


Figure 8. Post-translational processing of RAS proteins. (Modified from Ref. 67)

3.3 Retrosynthetic strategy

In our retrosynthetic analysis the main focus was to achieve the stereo selective epoxidation of the C6/C6a double bond present in the natural product **11** (Scheme 13). To achieve this it was envisioned that the presence of a hydroxyl group at C8 position in the intermediate **34** can give rise to directed epoxidation to install the right stereochemistry of the epoxide. The C8 hydroxyl group can in turn be eliminated in an E1-type fashion leading to the installation of C8/C9 double bond. The *exo* methylene group at C3 can be incorporated by means of a Mannich reaction employing Eschenmoser's salt. The C6/C6a double bond in the intermediate **33** was planned to install via ring closing metathesis (RCM) of the allylation product derived from **30**. Following a strategy developed in our research group for the enantioselective synthesis of *trans*-4,5-disubstituted γ-butyro-lactones,[58, 70] the key lactone aldehyde **30** can be synthesized readily from enantiomerically pure intermediates such as cyclopropylcarbaldehyde **15** and allylsilane **29**. The synthesis of these chiral precursors can be achieved starting from simple aromatic starting materials such as **13** and **27** respectively (Scheme 13).

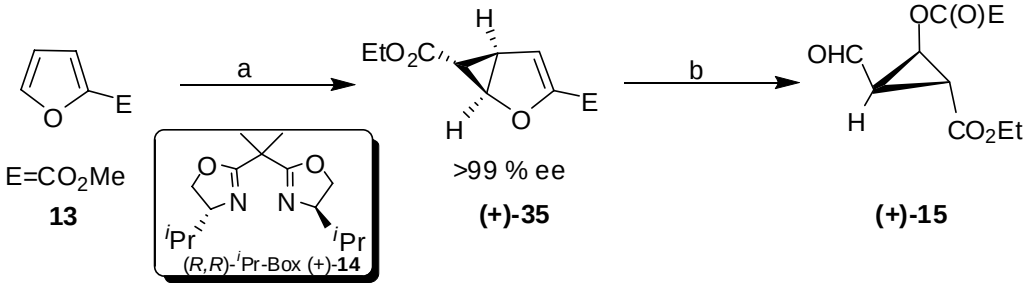


Scheme 13. Retrosynthetic outline for (+)-Arglabin (**11**).

4. Synthesis of chiral precursors

4.1 Synthesis of cyclopropylcarbaldehyde via asymmetric cyclopropanation

Cyclopropanes are an important class of compounds because of their occurrence in numerous natural products, drugs and also because of their value as synthetic building blocks in organic synthesis.[71] Cyclopropanes vicinally substituted with donor and acceptor moieties are particularly useful, since they easily undergo ring opening, giving rise to reactive intermediates, which can be intra- or intermolecularly trapped.[72] Highly functionalized 1,2,3-trisubstituted cyclopropylcarbaldehyde such as **15** can be synthesized in enantiomerically pure form in a two step sequence starting from methyl-2-furoate (**13**) (Scheme 14).[70, 72-74] Thus upon a Cu(I)-mediated asymmetric, regio and diastereoselective cyclopropanation of methyl-2-furoate (**13**) using ethyl diazoacetate in the presence of chiral ligand (*R*,*R*)-^{i}Pr-Box (+)-**14** resulted in (+)-**35** with high enantioselectivity of 85-90% *ee*, which was improved to >99% *ee* upon recrystallization. The ozonolysis of the unreacted double bond under standard conditions followed by reductive workup afforded enantiomerically pure cyclopropylcarbaldehyde (+)-**15** in good yield. The whole sequence can be scaled up to 50-100 g with out significant drop in enantiomeric excess of products.



Scheme 14. Conditions: a) (i) ethyl diazoacetate (2.67 eq.), $Cu(OTf)_2$ (0.66 mol%), (*R*,*R*)-^{i}Pr-box (+)-**14** (0.84 mol %), $PhNHNH_2$ (0.70 mol %), CH_2Cl_2, 0 ^{o}C, 54%, 85-90% *ee*; (ii) recrystallization (pentane) >99% *ee*, 38%. b: (i) O_3, CH_2Cl_2, –78 ^{o}C (ii) dimethylsulfide (4 eq.), 22 h, –78 ^{o}C to rt, 94%.

The stereochemical outcome and high enantioselectivities of the cyclopropanated product during asymmetric cyclopropanation depends on the stereochemistry of the bis(oxazoline)-ligand (BOX) **14** used in the reaction (Fig. 9). The use of other enantiomer of BOX ligand, i.e.

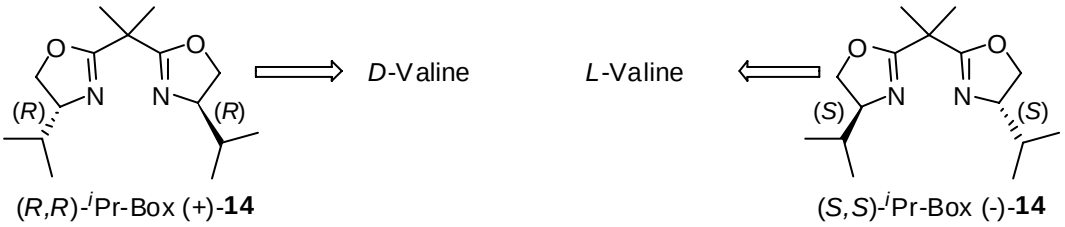
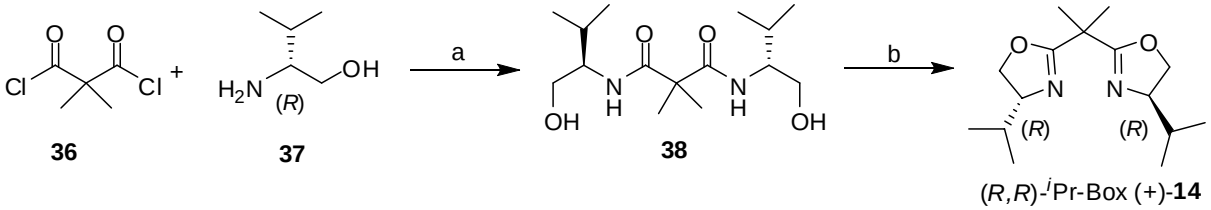


Figure 9. Two enantiomers of BOX-ligand.

(-)-**14** in the above sequence gives rise to the synthesis of (-)-**15**. Thus with the choice of appropriate chiral ligand, the synthesis of either of the enantiomers of cyclopropylcarbaldehyde **15** can be achieved. Both enantiomers of the chiral BOX-ligand **14** were prepared from D or L-valinol **37** derived from the corresponding amino acids by sodium borohydride reduction and iodine (Scheme 15). The procedure is well standardized in our laboratory and also reported in literature.[75, 76]



Scheme 15. Synthesis of chiral BOX-ligand. Conditions: a) valinol (2.0 eq.), NEt_3 (2.5 eq.), CH_2Cl_2, 0 °C - RT, 70 min, 84%; b) DMAP (10 mol %), NEt_3 (4.0 eq.), TsCl (2.0 eq.), CH_2Cl_2, RT, 27 h, 83%.

The regio, diastereo, and high enantio-selectivities observed during the cyclopropanation step can be explained by applying the models suggested by Pfaltz[77] and Andersson[78] for the asymmetric cyclopropanation of alkenes. The reactive complex **39** involved in the reaction can be accessed by reacting partner **13** in two ways (Fig. 10). Out of the two possible approaches, an approach from the right side is more favored, since an attack from left side shows strong repulsive interaction between **13** and ^{i}Pr group of the ligand (+)-**14**. In the subsequent cyclopropanation the less substituted and presumably more electron rich double bond of **13** is attacked.

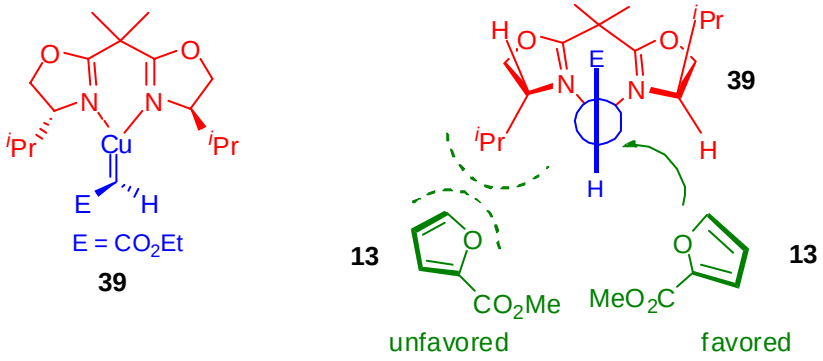
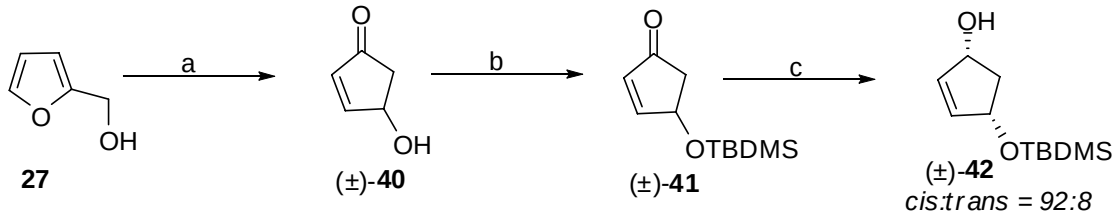


Figure 10. Model for asymmetric cyclopropanation explaining the observed selectivities. (Reprinted from Ref. 75)

4.2 Synthesis of chiral allylsilane

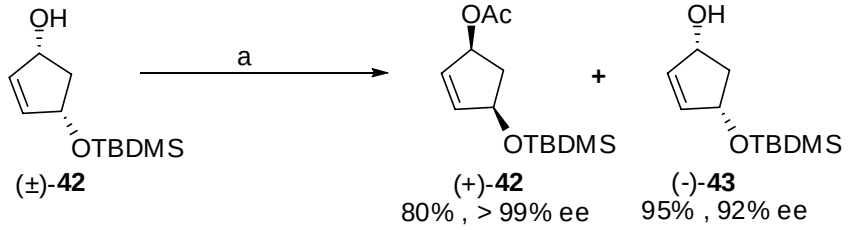
Allylsilanes have proven to be versatile building blocks in organic chemistry, especially for the mild and highly selective Hosomi-Sakurai allylation.[79, 80] As described in the retrosynthetic outline of Arglabin (**11**) (see Scheme 13), the allylsilane of type **29** is required to construct the lower five membered ring of the natural product. The synthesis of chiral allylsilane **29** can be

achieved from enantiomerically pure cyclopentenone **28**, which in turn is obtained starting from furfuryl alcohol **27**. Thus the synthesis of cyclopentenone **28** was first carried out following a well established route reported by *Curran et al.* for large quantity preparation of optically active *cis*-2-cyclopenten-1,4-diols.[81a, b] The synthesis starts with the rearrangement of furfuryl alcohol **27** to racemic 4-hydroxy cyclopent-2-enone (±) **40** in a moderate yield (Scheme 16). The mechanism of this rearrangement is an interesting feature to study and reported in literature.[81c, d] The protection of the free hydroxy group in (±) **40** with a bulky protecting group helps the subsequent LAH reduction of (±) **41** to occur in a highly diastereoselective fashion delivering the *cis*-substituted product (±) **42** in a good yield.



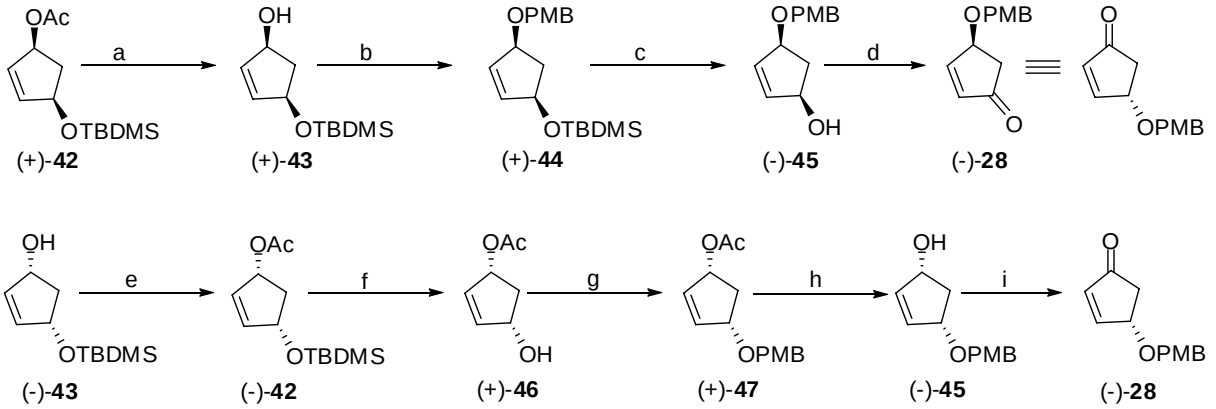
Scheme 16. Synthesis of precursor for enzymatic resolution. Conditions: a) KH_2PO_4, pH = 4.1, H_2O, reflux, 2 d, 40%; b) TBDMSCl (1.15 eq.), NEt_3 (1.50 eq.), DMAP (5 mol%), THF, 0 °C - RT, 89%; c) $LiAlH_4$ (0.70 eq.), LiI (0.50 eq.), Toluene/TBME, -30 °C, 3 h, 85% (*cis/trans* 92:8).

The racemate of (±)-**42** was then subjected to a kinetic enzymatic resolution using porcine pancreas lipase (PPLE).[82] This resulted in the separation of two enantiomers (+)-**42** and (-)-**43** by simple chromatography on silica gel, and interestingly both the enantiomers can be used in the further synthesis providing the important feature of not to loose material in this kinetic resolution (Scheme 17).



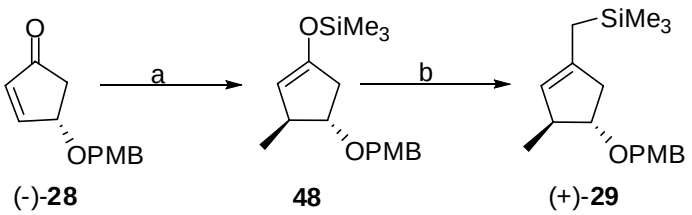
Scheme 17. Enzymatic resolution. Conditions: a) Porcine Pancreas Lipase PPLE, vinylacetate (4.50 eq.), NEt_3 (0.68 eq.), TBME, RT, 48 h, (-)-**43** (95%, 92% *ee)*, (+)-**42** (80%, >99% *ee*).

Having separated both the enantiomers by kinetic resolution, both the enantiomers were now converted to a single chiral intermediate 4-hydroxy protected cyclopent-2-enone (-)-**28** by means of protection-deprotection sequence reported from *Reiser* group.[55, 75] The sequential steps leading to these transformations are outlined in Scheme 18. The transformations (a-d) on (+)-**42** leads to PMB-protected cyclopent-2-enone (-)-**28**, while transformations (e-i) on (-)-**43** also leads to the same intermediate (-)-**28** with good enantiopurity and yield.



Scheme 18. Transformations on kinetically resolved enantiomers (+)-**42** and (-)-**43** leading to same intermediate (-)-**28**. Conditions: a) LiOH (1.2 eq.), THF: MeOH: H_2O (3:1:1), RT, 2 h, 96%; b) NaH (1.25 eq.), NaI (1.00 eq.), *p*-methoxybenzylbromide (1.3 eq.), THF, RT, 5 h, 86%; c) TBAF (1.00 eq.), Et_3N (0.10 eq.), THF, RT, 24 h, 85%. d) PCC (1.2 eq.), 4 Å MS, CH_2Cl_2, RT, 24 h, 86%; e) Et_3N (2.0 eq.), Ac_2O (4.5 eq.), RT, 6 h, 97%; f) TBAF (1.0 eq), NEt_3 (0.1 eq.), THF, RT, 2 h, 95%; g) *p*-methoxybenzyltrichloroacetimidate (1.67 eq.), $Cu(OTf)_2$ (5 mol%), CH_2Cl_2, 0 °C - RT, 24 h, 83%; h) LiOH (1.2 eq.), THF/MeOH/H_2O (3:1:1), Rt, 2 h, 92%. i) PCC (1.2 eq.), 4 Å MS, CH_2Cl_2, RT, 24 h, 85%

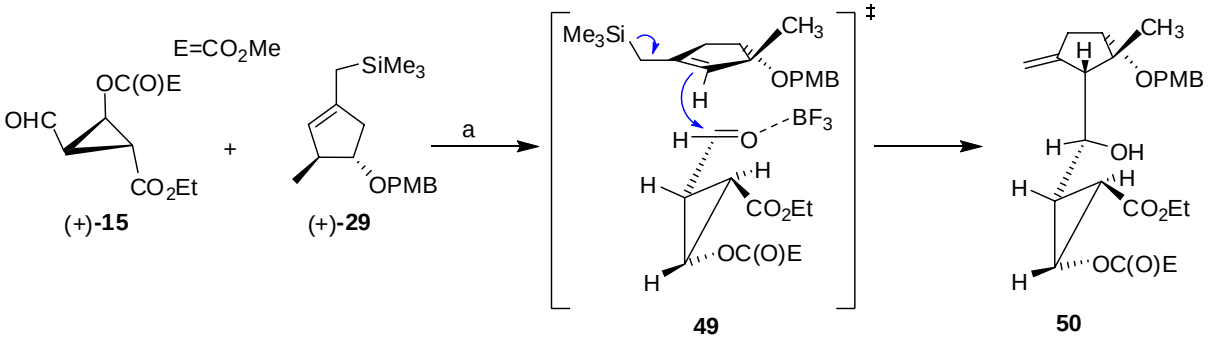
Having synthesized the key intermediate **28** in enantiomerically pure form, the further task is to convert it to the corresponding allylsilane (+)-**29**. This is achieved by subjecting **28** to a highly diastereoselective 1,4-addition using appropriate cuprate reagent followed by trapping of the resulting enolate as corresponding silylenolether **48** (Scheme 19). The bulky PMB-protecting group in (-)-**28** shields the lower half space making the cuprate addition proceed highly diastereoselective from the upper face resulting in the desired *anti*-substitution on the cyclopentane ring. The silylenolether **48** is very sensitive to heat and traces of acid. Therefore, purification by distillation or chromatography was not possible, however, after extensive extraction the products possessed sufficient purity to carry on with the next steps. The transformation of silylenolether **48** to the allylsilane **29** was achieved by using the Kumada coupling conditions reported by *Kumada et al.*[83] Accordingly, the use of $Ni(acac)_2$ catalyzes the coupling of silylenolether **48** with appropriate Grignard reagent to afford the desired allylsilane **29** in moderate yield.



Scheme 19. Synthesis of allylsilane. Conditions: a) LiCl (0.3 eq.), CuI (0.15 eq.), TMSCl (4.0 eq.), MeMgCl (3M in THF) (4.5 eq.), THF, -78 °C, 3 h, 90%, *dr* >99:1; b) $Ni(acac)_2$ (0.15 eq.) Me_3SiCH_2MgCl (2 N in Et_2O) (2.0 eq.), Et_2O, reflux, 16 h, 62%.

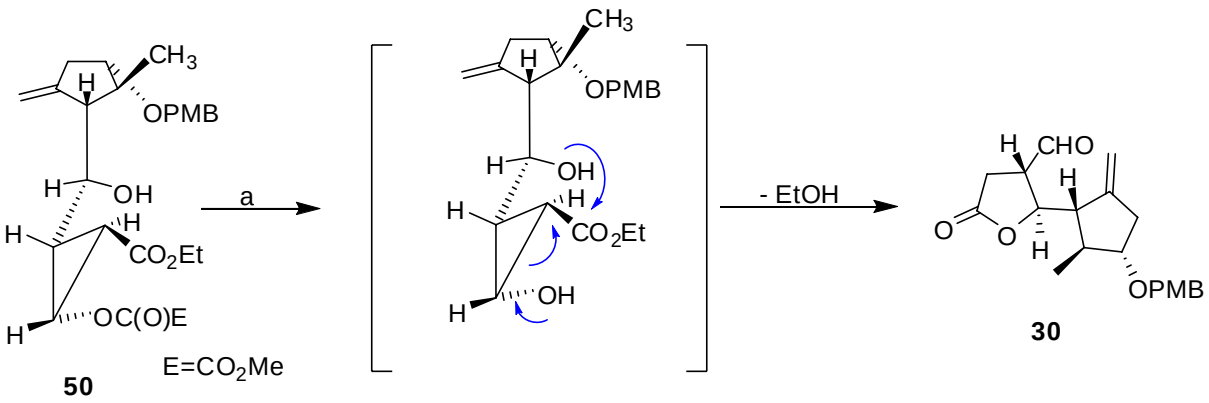
5. Synthesis of *trans*-4,5-disubstituted γ-butyro-lactone

Having synthesized the key intermediates cyclopropylcarbaldehyde (+)-**15** and allylsilane (+)-**29** in enantiomerically pure form, the next step was addition of allylsilane (+)-**29** to cyclopropylcarbaldehyde (+)-**15**. The stereocontrol additions on a cyclopropyl-substituted carbonyl compound such as **15** can be explained by analyzing the conformational preferences and applying the Felkin-Anh-model[84] in combination with the Curtin-Hammett-principle.[85] Thus Borontrifluoride mediated addition of allylsilane (+)-**29** to cyclopropylcarbaldehyde (+)-**15** proceeded with excellent double stereocontrol, in which the attack of the allylsilane **29** takes place in accordance with Felkin-Anh paradigm (Scheme 20). The stereochemical outcome of this reaction can be explained by the proposed transition state **49**. In this case, the nucleophile attacks the *s-cis*-conformation of the carbonyl group in *anti*-orientation to its methyl substituent leading to the experimentally observed *trans*-Felkin-Anh-product **50**.



Scheme 20. Conditions: a) $BF_3 \cdot OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 16 h, 80% (crude), *dr* >99:1.

Without isolation, the adduct **50** was directly subjected to base which results in the saponification of the labile oxalic ester group. As a result, the now unmasked donor-acceptor cyclopropane[86] undergoes a cascade of ring opening (retroaldol) and lactonization to afford **30** as single stereoisomer (Scheme 21).



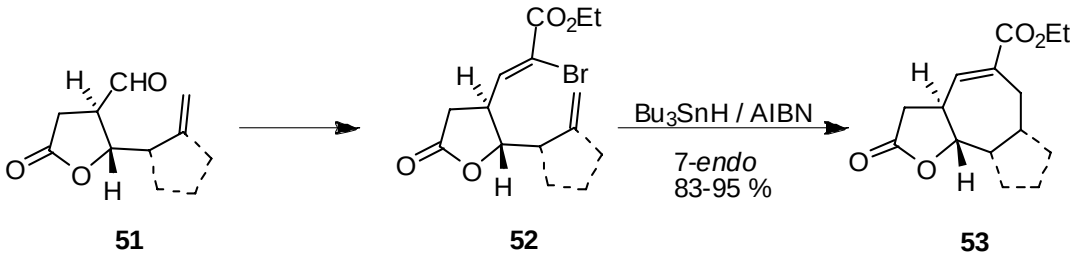
Scheme 21. Retroaldol-lactonization. Conditions: a) $Ba(OH)_2 \cdot 8H_2O$ (0.55 eq.), MeOH, RT, 2 h, 62% (over two steps), *dr* >99:1.

6. Construction of the tricyclic core

The *trans*-4,5-disubstituted γ-butyro-lactone **30** with its stereo centers incorporated as required in the natural product Arglabin (**11**) is a key building block for the synthesis of many other guaianolide natural products having *anti*-disubstituted lactone motif. The annulation of the seven membered rings on the lactone aldehyde **30** can be achieved in two different ways.

6.1 Radical cyclization approach

It has been earlier reported from *Reiser* group that precursors of the type **51** can be transformed into bi-and tricyclic sesquiterpene lactone scaffolds **53** via radical cyclization (Scheme 22).[73] Thus alkenylation of **51** by modified Horner-Wadsworth-Emmons (HWE) reaction gave rise to **52**, which upon treatment with Bu_3SnH and AIBN gave rise to scaffolds **53** in good yields.

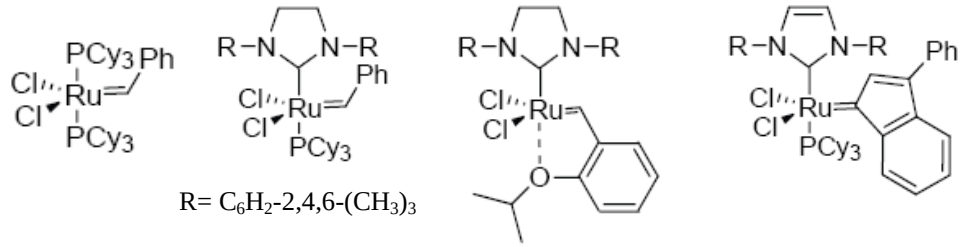


51 **52** **53**

Scheme 22. Radical cyclization approach towards the construction of tricyclic core.

6.2 Ring closing metathesis (RCM) approach

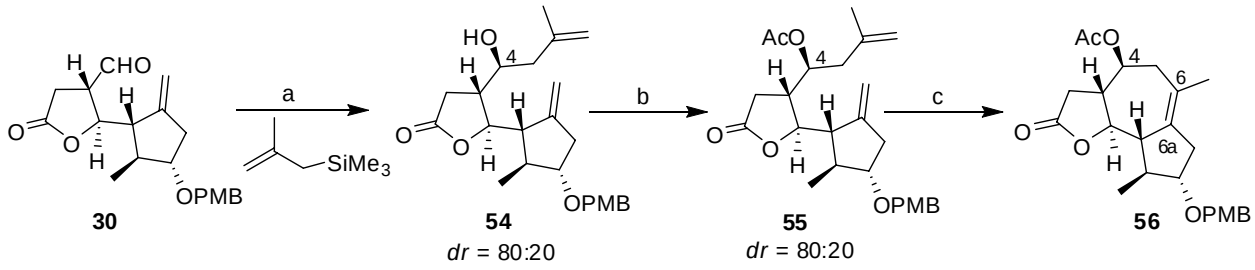
Over the past decade, olefin metathesis has emerged as a powerful carbon-carbon bond-forming reaction that is widely used in organic synthesis and polymer science.[87] In the recent years it has been utilized to a greater extent for the synthesis of complex organic molecules and natural products. Various ruthenium based metathesis catalysts developed during the course of time are shown in Figure 11.



Grubbs' 1st gen 1995 **Grubbs' 2nd gen 1999** **Hoveyda-Grubbs' 2000** **catMETium® ImesPCy degussa.**

Figure 11. Various ruthenium based metathesis catalysts known in the literature.

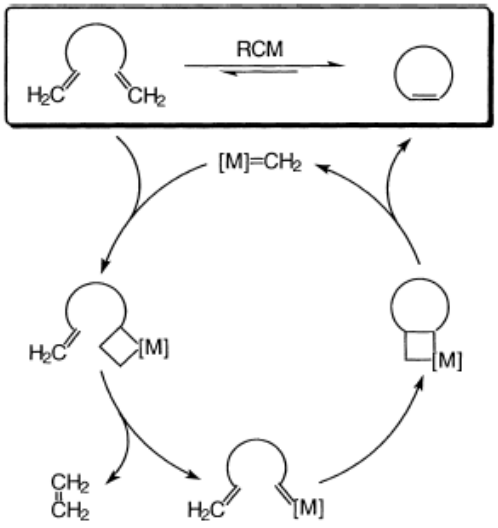
RCM is a versatile tool in organic chemistry and has already proven to be suitable for the formation of medium size rings and also for unusual ring sizes. The recent development of enantioselective metathesis catalysts based on ruthenium is expected to expand dramatically the scope and utility of this reaction in enantioselective total synthesis of natural products.[88] In the present total synthesis of (+)-Arglabin (**11**), it was planned to install the C6/C6a double bond through RCM. For the application of RCM, a diene system is needed, which is constructed by a Hosomi-Sakurai allylation[79, 80] of the lactone aldehyde **30**. Thus Sakurai allylation of **30** with 2-methylallylsilane yielded **54** as a 4:1 mixture of C-4-epimers (Scheme 23). The latter is in principle without consequences, since the newly created hydroxyl group had to be removed at a latter point in the sequence for the synthesis of target Arglabin (**11**). Based on earlier experiments and reports from our group on similar unsubstituted structures, [89] the new free hydroxy functionality is known to perturb the subsequent ring closing metathesis. Therefore to overcome this known problem, it is necessary to protect the free hydroxy group in **54**. Thus Acylation of **54** set the stage for ring closing metathesis which was carried out by using Grubbs' 2nd generation catalyst (see Fig.11) with inert gas sparging at a reaction temperature of 95 °C. To achieve complete conversion of the starting material **55** the catalyst (15 mol%) was split in three portions of 5 mol% each and employed with a time interval of 2 hours. Under these conditions the desired **56** and its C-4-epimer *epi*-**56** in a total of 86% yield. The use of Grubbs' 1st generation catalyst or Hoveyda-Grubbs' catalyst (see Fig. 11) were not suitable for this transformation, while the use of catMETium®[90] catalyst gave a better yield (90%) of the desired product.



Scheme 23. Construction of the tricyclic core via RCM. Conditions: a) $BF_3 \cdot OEt_2$, -78 °C, 16 h, 70% (4:1 epimeric mixture at C-4); 2. Ac_2O, Et_3N, DMAP, RT, 24 h, 85% (4:1 epimeric mixture at C-4); b) Grubbs' 2nd gen cat. (3x5 mol %), toluene, sparging with Ar, 95 °C, 6 h; followed by separation of C-4 epimers by chromatography: **56** (70%), *epi*-**56** (16%).

The generally accepted mechanism for metathesis reaction is the *Chauvin* mechanism[91] which consists of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkene, metal carbenes and metallocyclobutane intermediates (Scheme 24). All the steps of the catalytic cycle are reversible; an equilibrium mixture of olefins is obtained. The forward process is entropically driven because RCM cuts one substrate molecule into two products, and if one of

them is volatile (ethene, propene, etc.) the desired cycloalkene will accumulate in the reaction mixture.[87c]

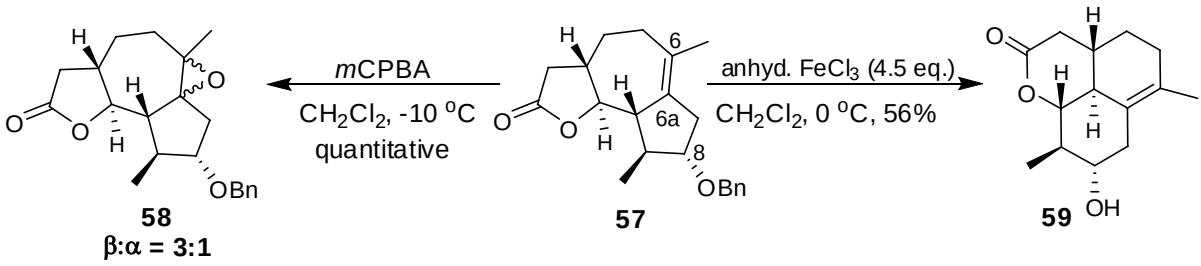


Scheme 24. Basic catalytic cycle of RCM. All the individual steps are reversible.

7. Stereoselective epoxidations

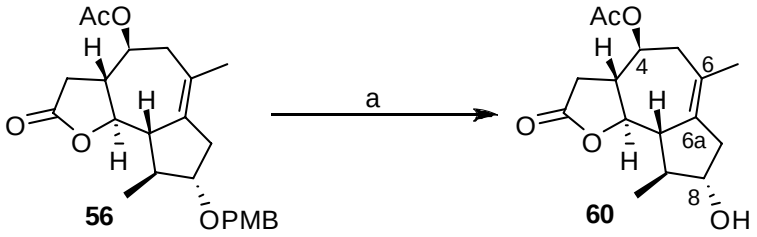
7.1 The peracid method

One of the major tasks in the total synthesis of (+)-Arglabin (**11**) was to stereoselectively epoxidize the C6/C6a double bond and gets the right stereo chemistry of the epoxide. Early investigations on such stereoselective epoxidations from our group on substrates similar to the intermediate **56** were unsuccessful in delivering the right stereo chemistry of the epoxide.[55] Thus the epoxidation of the substrate **57** with *m*CPBA gave mixture of diastereomeric epoxides **58** in the ratio of 3:1 (β:α), the α-epoxide being the required one. So it was thought the presence of a free hydroxyl group at C8 position in **57** can give rise to directed epoxidation and improve the diastereoselectivity of the reaction. But attempts to deprotect the benzyl protecting group in **57** led to unexpected rearrangement of the guaianolide skeleton to 6,6,6-tricyclic δ-valerolactone skeleton **59** (Scheme 25).[55] The inherent problem associated with the standard debenzylation conditions (Pd/C, H_2) in the presence of C6/C6a double bond led to the use of anhydrous $FeCl_3$ as deprotection agent in this reaction.



Scheme 25: Earlier reports on stereoselective epoxidations from *Reiser* group. [55]

Taking the above experiences into consideration, for the total synthesis of Arglabin (**11**), it was envisioned that the choice of appropriate protection group at C8 position will help us to give better diastereoselectivity by means of directed epoxidation. For this purpose the PMB-group was chosen as the choice, since it can be deprotected under mild conditions using DDQ without perturbing other functionalities. Thus the deprotection of PMB group in **56** took place smoothly to deliver **60** as a crystalline solid in a good yield (Scheme 26). A single crystal X-ray analysis of **60** confirmed that all the stereo centers created so far are in right configuration as required in the natural product (Fig. 12).



Scheme 26. Deprotection of PMB. Conditions: a) DDQ, CH_2Cl_2, 4 h, RT, 90%.

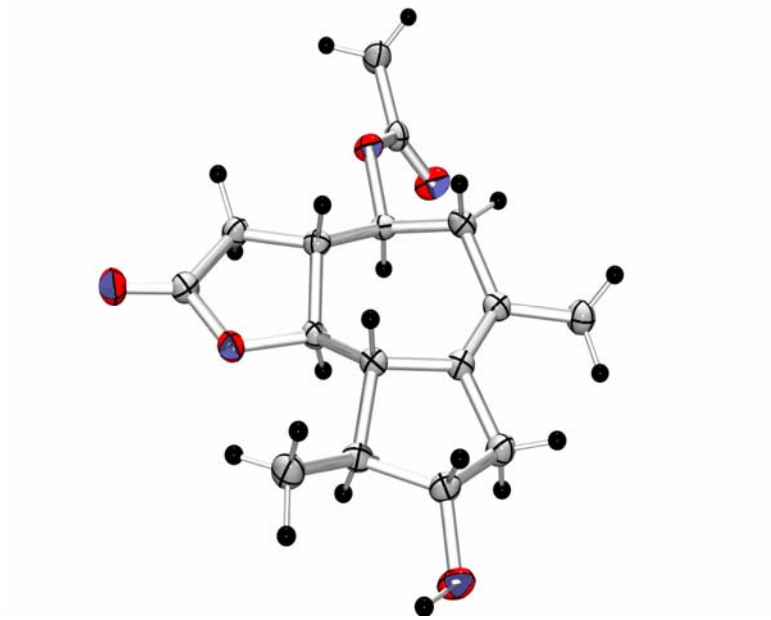
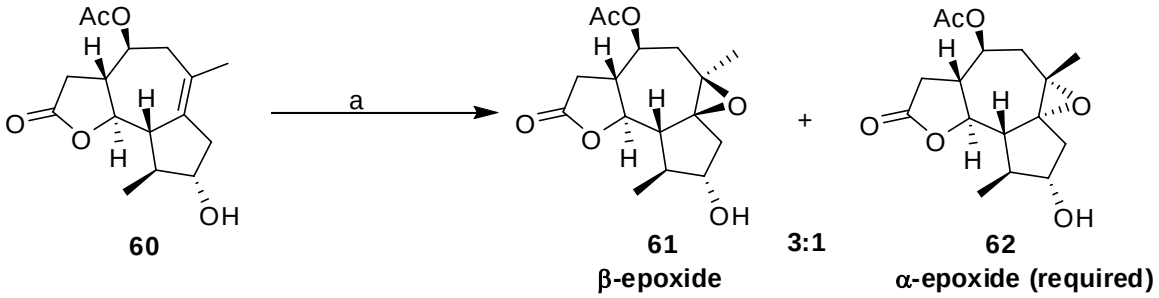


Figure 12. X-ray structure of **60**.

Having the key intermediate **60** in hand, it was subjected to stereoselective epoxidation conditions using variety of known methods in the literature.[92] The X-ray structure of **60** (Fig. 12) revealed that both faces of the seven-membered ring for the subsequently planned epoxidation are equally exposed. In particular, it became clear that for the desired attack from the α face (bottom), the upward but pseudoequatorial-pointing acetoxy group at C-4 would provide a little steric shielding. Moreover, the hydroxy group at C-8 that was envisioned to serve as a directing substituent. Such directing effect is known not only for the epoxidation of the allylic alcohols but also for homoallylic alcohols.[93] Also from the X-ray structure it was evident that the C-8 hydroxyl group was oriented rather unfavorably in a pseudoequatorial position and pointed away from the double bond that was to be attacked. Furthermore, epoxidation from the β face (top) delivers the product with the more stable *cis* annulation between the five and seven-membered ring. With all these observations in mind, the epoxidation with *m*CPBA under standard conditions gave the diastereomeric mixture of epoxides **61** (β-epoxide) and **62** (α-epoxide) in the ratio of 3:1 respectively, the α-epoxide

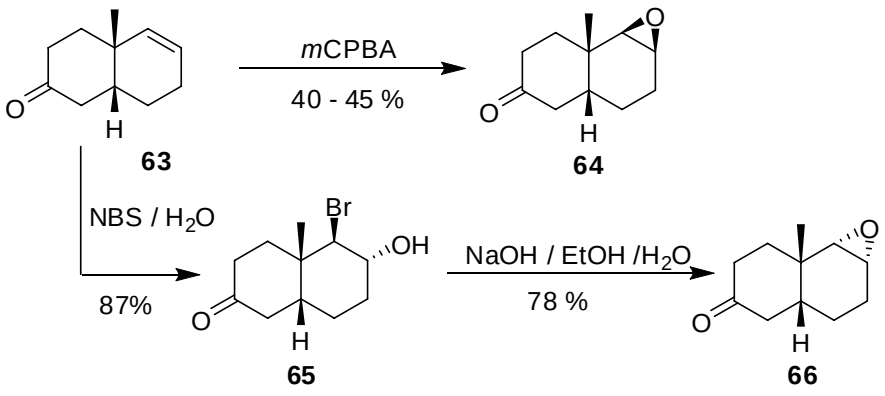
being the required one (Scheme 27). Disappointingly, *m*CPBA, which is known to be directed by homoallylic alcohols, still gave the β-epoxide preferentially, which again demonstrates the preference for the *cis* annulation of the five- and seven-membered rings.[94]



Scheme 27. Conditions: a) *m*-CPBA, CH_2Cl_2, -10 °C to RT, 6 h, 85 %.

7.2 The halohydrin approach

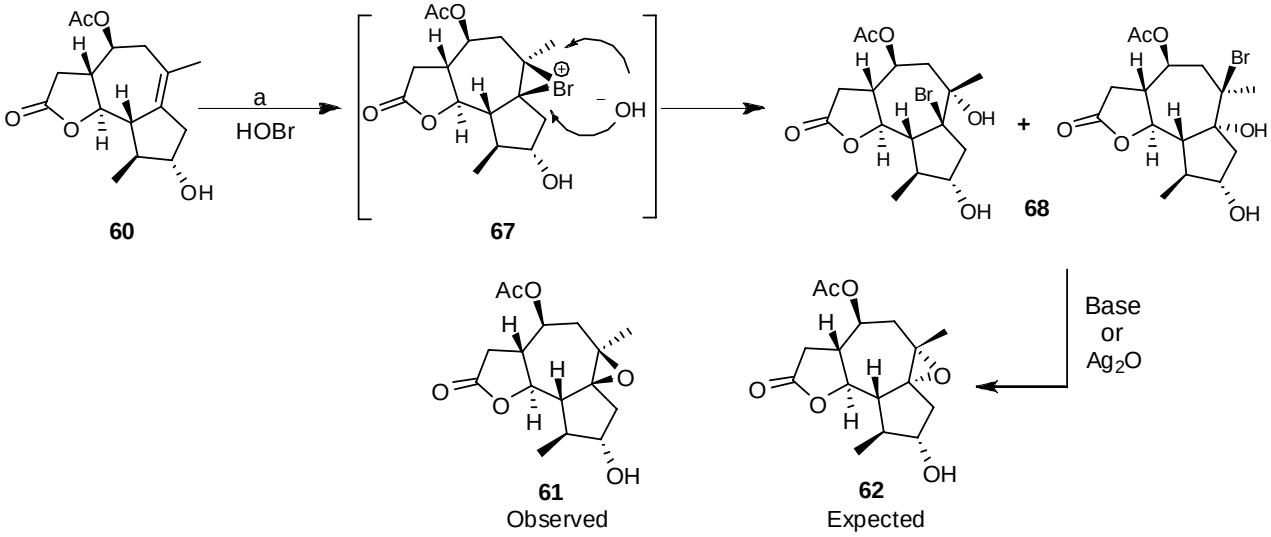
Halohydrins derived from halohydroxylation of double bond are versatile synthetic intermediates and their principal synthetic application is incontestably the preparation of epoxides.[95] The reaction has been used extensively in organic synthesis and still a good complement to the direct epoxidation of alkenes. The stereochemistry of the epoxide derived from a two step halohydrin process is usually complementary to that of *m*CPBA mediated epoxidation. Thus for instance, the *m*CPBA oxidation of the *cis*-decalin **63** is known to occur selectively *exo* to afford **64**, while the two step epoxidation through the bromohydrin intermediate **65** gives exclusively the *endo* epoxide **66** (Scheme 28).[96]



Scheme 28. Differences in the stereochemistry of epoxide derived through peracid and halohydrin strategies.

The above results prompted us to investigate the halohydrin strategy on the key intermediate **60**. The use of mild conditions that involves the *in situ* generation of hypobromous acid from

the combination of $NaBrO_3$ and $NaHSO_3$ were employed to carry out this reaction (Scheme 29).[97] The reaction was expected to proceed via the formation of bromonium ion **67** which in principle can be attacked by the nucleophile (OH^-) in two different ways leading to the formation of regiomeric mixture of bromohydrins **68**. Nevertheless both the regio isomers can be transformed into desired product **62** by treatment with base or Ag_2O. Indeed, by using this strategy, the overall epoxidation took place in high yields without the isolation of intermediates, and gave only one product, although unfortunately again the unwanted β–epoxide **61** exclusively (Scheme 29). Crystallization of the isolated β–epoxide **61** from pentane-CH_2Cl_2 mixture afforded crystalline compound which on single crystal X-ray analysis proved the stereochemistry of β-epoxide (Fig. 13).



Scheme 29. Halohydrin strategy. Conditions: a) $NaBrO_3$ / $NaHSO_3$ (1:2), CH_3CN/H_2O (1:2), 48 h, RT, 80%.

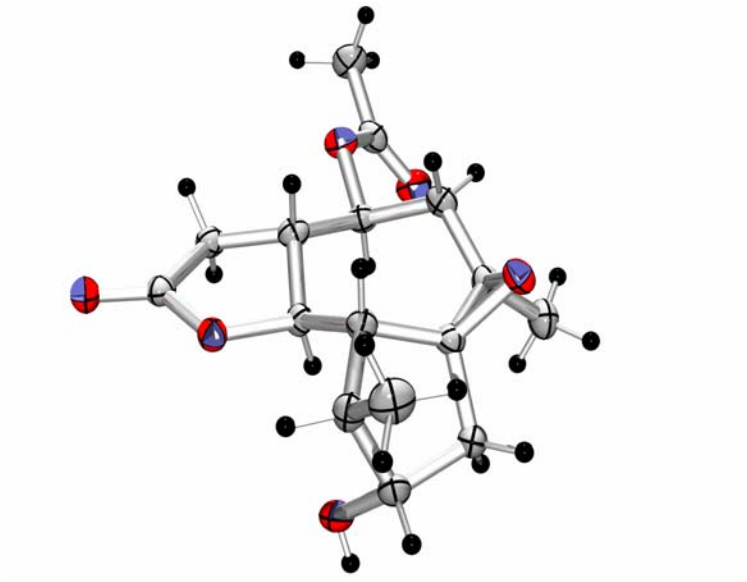
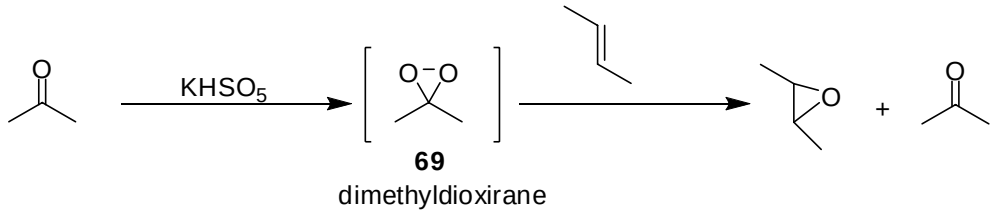


Figure 13. X-ray structure of **61**.

The use of different system such as NBS-H_2O to generate *in situ* hypobromous acid did not alter the out come of reaction, resulting again unwanted β–epoxide **61** exclusively.

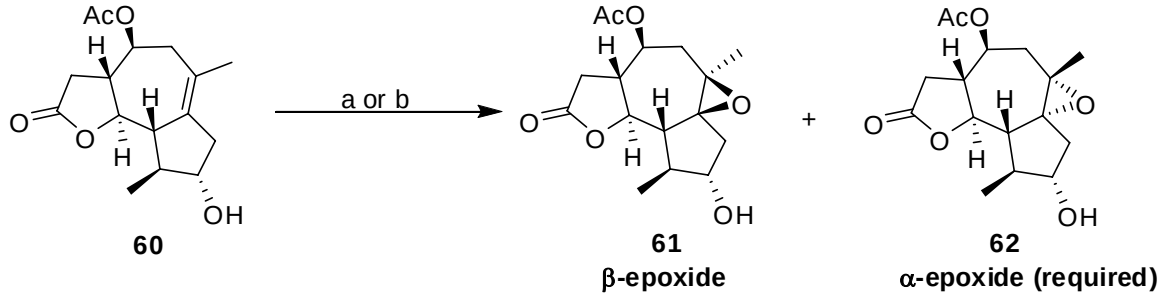
7.3 The dioxirane method

Dioxiranes are known to be important and versatile oxidants, which are generated *in situ* from potassium monoperoxysulfate ($KHSO_5$, commercially known as oxone) and ketones (Scheme 30). Dimethyldioxirane **69**, a dioxirane generated from acetone as a ketone, is particularly useful as an oxidation reagent with a broad scope of synthetic applications.[98] The *Shi* epoxidation that is described in literature as an asymmetric epoxidation of olefins involves the use of dioxirane generated from oxone and a fructose-derived ketone.[99] It is reported that dioxiranes as oxidants usually give rise to opposite selectivity in comparison to the *m*CPBA mediated epoxidations.[100]



Scheme 30. Synthesis of dimethyldioxirane and its utility as epoxidizing agent.

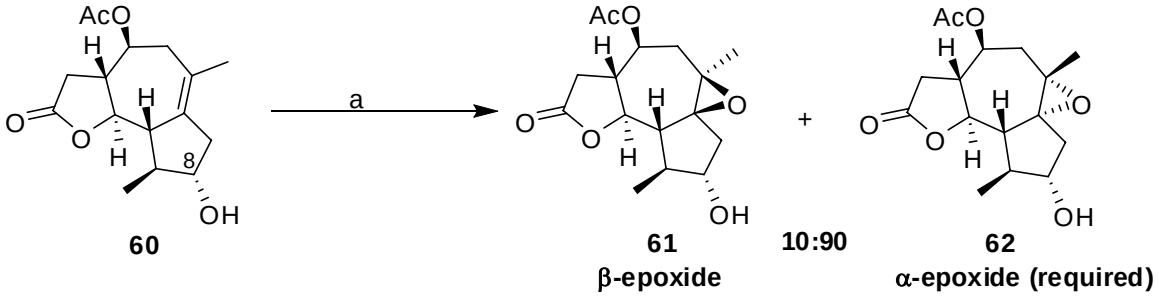
Treatment of **60** with *in situ* generated dimethyldioxirane **69** under biphasic conditions (CH_2Cl_2-H_2O solvent system) resulted in the epoxidation with preference of 7:1 of the corresponding β-epoxide **61** and α-epoxide **62** respectively (Scheme 31). The use of monophasic conditions (Acetone-H_2O solvent system) also resulted in the epoxidation with preference to β-epoxide **61**.



Scheme 31. Dioxirane method of epoxidation. Conditions: a) $KHSO_5$ / Acetone, CH_2Cl_2/H_2O, pH 7.2 buffer, 18-crown-6, 0 °C, 6 h, 65%, *dr* = 88:12 (**61**: **62**). b) $KHSO_5$, Acetone-H_2O (4:1), $NaHCO_3$, 0 °C to RT, 6 h, 70%, *dr* = 84:16 (**61**:**62**).

7.4 Transition metal catalyzed epoxidation of homoallylic alcohols

The use of transition metal catalysts such as vanadium and molybdenum for the epoxidation of olefins by alkyl hydroperoxides is well known in literature,[101] and it has been employed to a greater extent in the area of complex molecule synthesis in the recent years. It was shown that these transition metal-hydroperoxide reagents exhibit remarkable reactivity toward olefinic alcohols and give high stereo- and regioselectivities. The widely used catalysts for this purpose are $VO(acac)_2$ and $Mo(CO)_6$. The vanadium and molybdenum catalyzed epoxidations of the allylic alcohols and even the homoallylic alcohols are essentially stereospecific compared to the peracid method. The use of $VO(acac)_2$ in combination with TBHP served to a greater extent in getting the desired α-epoxide in the present system.[102] Thus employing catalytic amounts of $VO(acac)_2$ and tert-butylhydroperoxide TBHP as the stoichiometric oxidant in the epoxidation of **60** gave the desired α-epoxide **62** with a preference of 9:1, which demonstrates the extraordinary affinity for precoordination of the vanadium reagent to the C8 hydroxyl group before the epoxidation occurs. The desired α-epoxide **62** was isolated in 78% yield after chromatographic separation from the minor β-epoxide product **61** (Scheme 32).



Scheme 32. Transition metal mediated epoxidation. Conditions: a) $[VO(acac)_2]$ (2 mol %), TBHP, CH_2Cl_2, 0 °C to RT, 16 h, 78% (yield of purified **62**).

The high selectivity observed during the V^{5+}/TBHP epoxidation could be explained by a proposed vanadate ester transition state in which the metal coordinates tetrahedrally and exists in a preferred chair form (Fig. 14). This nicely accounts for the selectivities observed in case of many acyclic homoallylic alcohols.[102, 103]

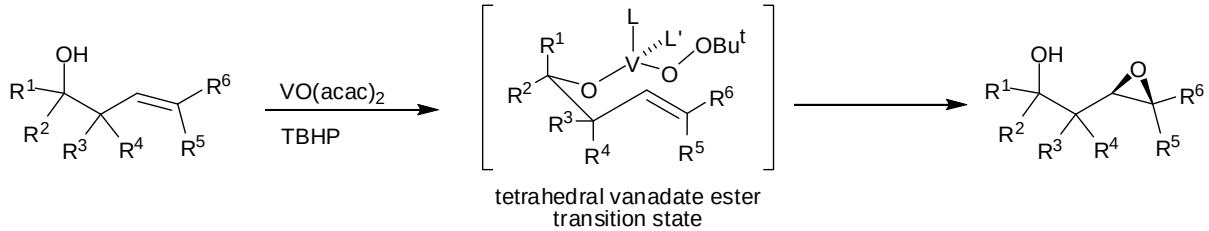
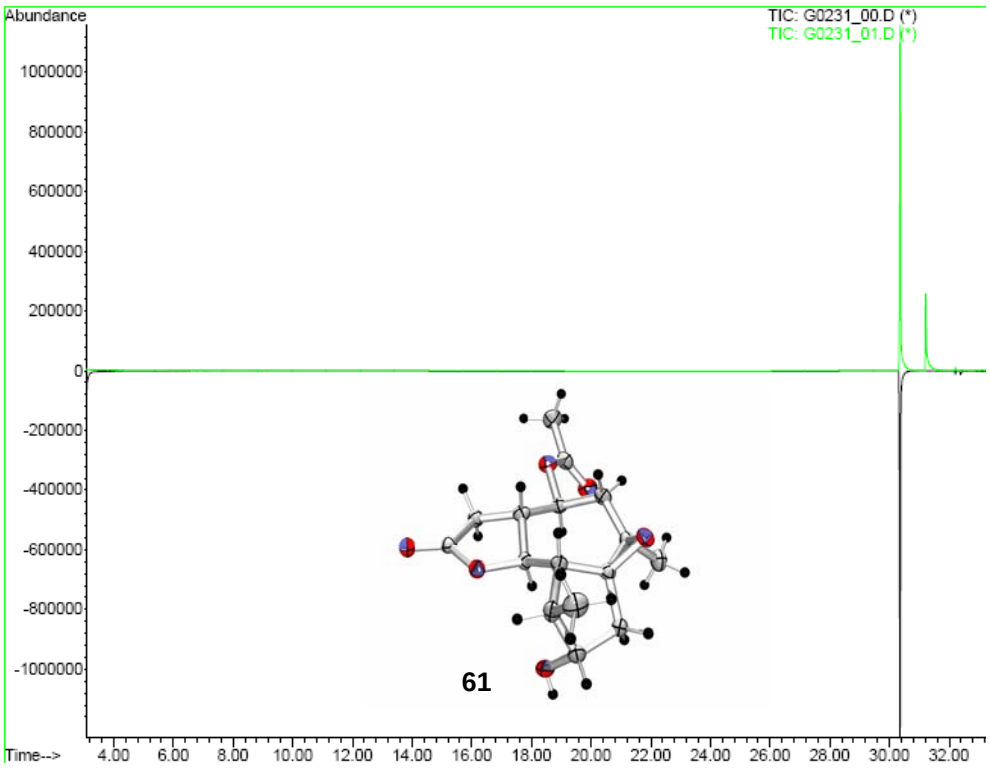


Figure 14. Proposed transition state to explain observed selectivities in V^{5+} / TBHP epoxidation.

The whole epoxidations exploited on substrate **60** can be summarized as shown in Table 1.

entry	method	conditions	ratio **61**/**62** [a] (β:α)	yield (%) [b]
1	dimethyl-dioxirane	$KHSO_5$,acetone DCM- H_2O, pH 7.2 buffer, 18-crown-6, 0 ^oC ,6 h	88:12	65
2	dimethyl-dioxirane	$KHSO_5$, $NaHCO_3$ acetone / H_2O (4:1) 0 ^oC to Rt , 6 h	84:16	70
3	halohydrin	$NaBrO_3$ / $NaHSO_3$ (1:2),CH_3CN / H_2O (1:2), > 48 h, Rt	>99:1	80
4	halohydrin	NBS, THF / H_2O (2:1), 15 h, Rt	>99:1	72
5	peracid	mCPBA, CH_2Cl_2 , -10 ^oC to RT , 6 h	75:25	85
6	vanadium	$VO(acac)_2$,TBHP DCM ,0 ^oC to Rt ,16h	10:90	78 [c]

Table 1. [a] Determined by ^1H NMR and GC. [b] Isolated yields as mixture of diastereomers. [c] Isolated yield of pure **62**.

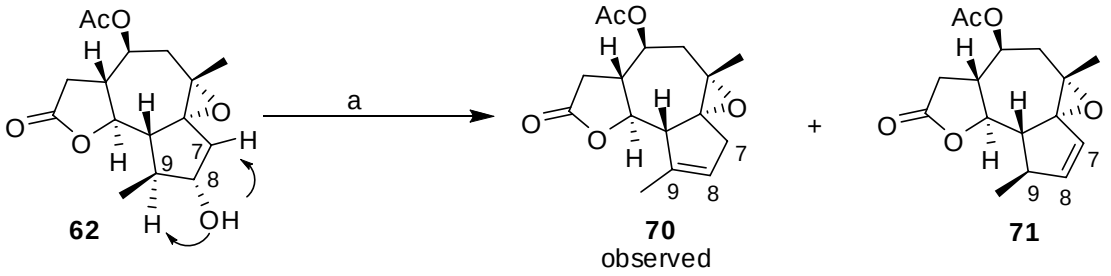


GC chromatograph of epoxides mixture **61** and **62** derived from mCPBA reaction (top image) and β-epoxide **61** exclusively derived from Halohydrin reaction (bottom image)

8. Final steps towards the total synthesis

8.1 Elimination studies

Having solved the major task of setting the epoxide stereochemistry, the next aim was to focus on achieving the full functionalization and complete the total synthesis. For this the C8/C9 double bond has to be incorporated in the intermediate **62** in the right position (Scheme 33). As the elimination can occur in two possible ways leading to the regiomeric mixture of products, the *Zaitsev* product **70** and the *Hofmann* product **71**. Therefore the choice of suitable reaction conditions was essential to carry out this reaction. Out of the various methods known for elimination such as *syn*-elimination using pyrolysis,[104] piperidinium acetates,[105] or *anti*-elimination after inverting the stereochemistry of C8 hydroxyl group by *Mitsunobu* reaction, [106] the *syn*-elimination employing Tf_2O and pyridine was chosen as a choice for this dehydration reaction (Scheme 33).[107] Thus exposure of **62** to pyridine and Tf_2O under Ar atmosphere and low temperature conditions afforded the desired *Zaitsev* product **70** in moderate yield. The reaction temperature plays a decisive role in this reaction. Based on earlier reports from our group on similar substrates, if the reaction was carried out at room temperature the mixture of regiomers are formed.[55]

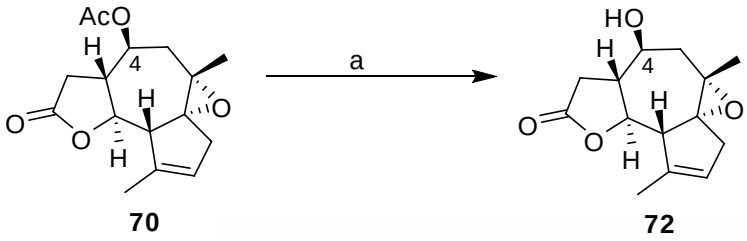


Scheme 33. Conditions: Tf_2O, pyridine, CH_2Cl_2, -10 °C to 0 °C, 18 h, 62%.

8.2 Barton-McCombie desoxygenation

With the incorporation of C8/C9 double bond in the right position as required in the natural product, the next task was to desoxygenate the C4 oxygen functionality which is not required in the target natural product Arglabin (**11**). To perform this well known *Barton-McCombie* desoxygenation[108, 109] protocol for secondary alcohols was implemented. Thus to get the free secondary alcohol at C4 position in **70**, the acetate protection group was first unmasked under mild basic conditions to afford **72** as a crystalline solid in a good yield (Scheme 34). To avoid the relactonization with newly generated C4 hydroxy group the reaction was carried at low

temperature. A single crystal X-ray analysis of **72** confirmed the right stereochemistry of the epoxide group as well as the right placement of C8/C9 double bond (Fig. 15).



Scheme 34. Conditions: a) K_2CO_3, MeOH, 0 °C to RT, 4 h, 70%.

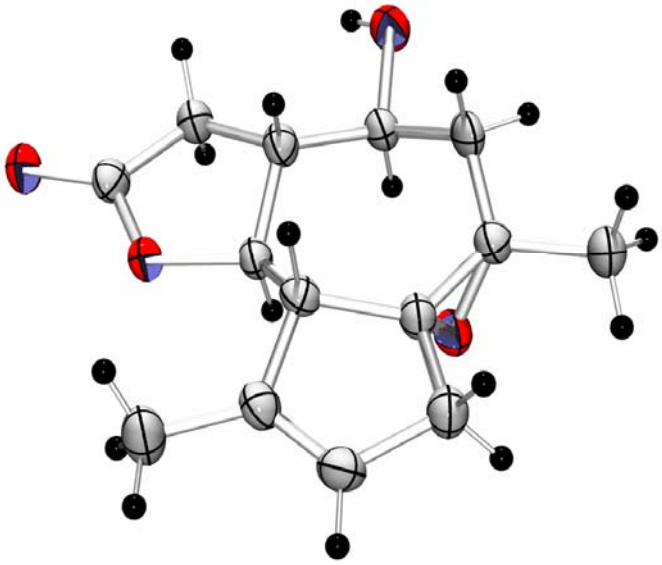
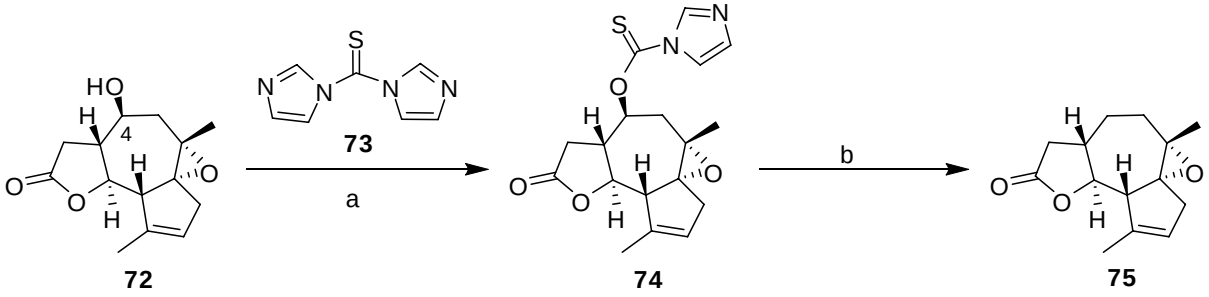


Figure 15. X-ray structure of **72**.

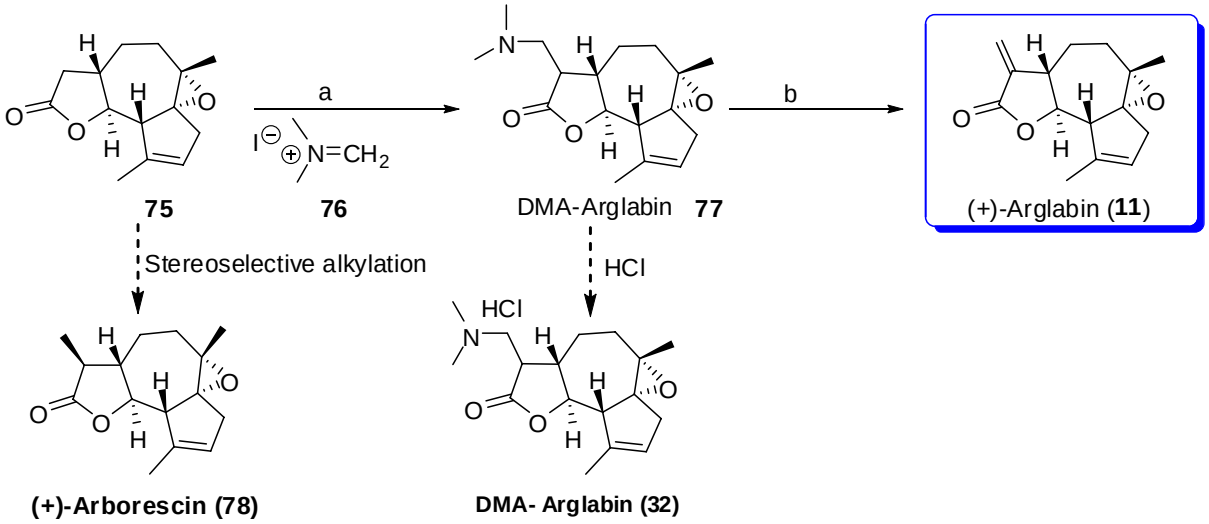
With the creation of free hydroxy group at C4 position in **72**, the stage was set to exploit the two step *Barton-McCombie* desoxygenation protocol. For such transformation, different kinds of xanthates can be introduced first, followed by reduction of radical intermediates using Bu_3SnH/AIBN.[110, 111] Thus treatment of **72** with thiocarbonyldiimidazole **73** led to formation of *O*-imidazolylthiocarbonate **74** which upon subsequent radical reduction with Bu_3SnH/AIBN afforded the desoxygenated product **75** in good yield (Scheme 35).



Scheme 35. *Barton-McCombie* desoxygenation. Conditions: a) 1,1'-thiocarbonyldiimadazole **73,** DMAP, CH_2Cl_2, RT, 4 h, 80%; b) Bu_3SnH, AIBN, toluene, 90 °C, 5 h, 77%.

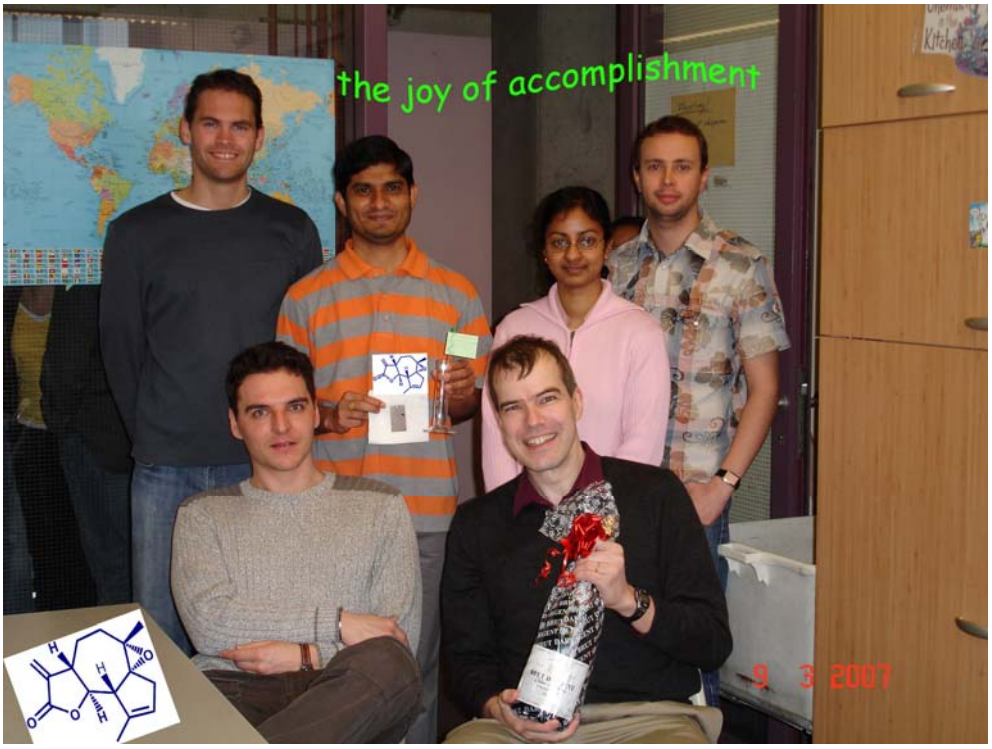
8.3 Eschenmoser reaction and completion of total synthesis

The final task towards the total synthesis of (+)-Arglabin (**11**) was to introduce the C3 *exo* methylene group that is known to be responsible for the biological activity of natural product. A general method for construction of the α-methylene-γ-butyrolactone motif involves the direct conversion of the lactone ring into desired α-methylene lactone via a α-methylenation sequence. A large number of synthetic methods reported in literature are based on this method.[17, 112] A *Mannich* type reaction employing Eschenmoser's salt[113] **76** [*N*, *N* dimethyl(methylene)ammonium Iodide] was attempted to incorporate the *exo* methylene group. Thus alkylation of **75** with Eschenmoser's salt **76** yielded Dimethylamino Arglabin **77** (Scheme 36). Without further purification, the Dimethylamino adduct **77** was subjected to quaternization with methyl iodide leading to the elimination of trimethylamine and afforded the target natural product (+)-Arglabin (**11**) in good yield. The choice of this method has an inherent advantage of synthesizing the Dimethylamino Arglabin **77**, a derivative which can be easily converted to its hydrochloride salt, i.e. DMA-Arglabin-HCl (**32**) that has more bioavailability than the natural product (+)-Arglabin (**11**). Thus the present approach has an advantage of synthesizing both the natural product and its important derivative. Also it's interesting to mention that the intermediate **75** can be subjected to a stereoselective alkylation leading to the total synthesis of (+)-Arborescin (**78**), a guaianolide structurally related to (+)-Arglabin (**11**) and was isolated from *Artemisia arborescens* (Compositae), a plant used for contraceptive purpose by the ancient Greeks and Arabs.[114] The total synthesis of (+)-Arborescin (**78**) was already reported by *Ando et al* starting from naturally occurring α-Santonin.[115]



Scheme 36. Completion of total synthesis of (+)-Arglabin (**11**). Conditions: a) Eschenmoser salt **76**, THF, -78 °C to RT, 4 h, 75%; d) MeI, MeOH, $NaHCO_3$, CH_2Cl_2, 80%.

The synthesized natural product is identical in all spectroscopical data and optical rotation with an authentic sample of natural (+)-Arglabin (**11**) (Synthetic sample $[\alpha]^{23}_{D}$ = + 81.0 (c = 0.3, $CHCl_3$), Authentic sample $[\alpha]^{23}_{D}$ = + 82.1 (c = 0.3, $CHCl_3$)).[116] This led us to accomplish the first enantioselective total synthesis of (+)-Arglabin (**11**).[16]



"The chemist who designs and completes an original and esthetically pleasing multistep synthesis is like the composer, artist or poet who, with great individuality, fashions new forms of beauty from the interplay of mind and spirit."

- E.J. Corey

1990 Nobel Prize for Chemistry

9. Studies towards the total Synthesis of (+)-Moxartenolide

9.1 Isolation and bioactivity

After accomplishing the total synthesis of (+)-Arglabin (**11**) the study was extended towards the total synthesis of (+)-Moxartenolide (**23**) (Fig. 16). (+)-Moxartenolide (**23**), a sesquiterpene γ-lactone was isolated from the aerial parts of *Artemisia argyi* in 1996 as white powder.[117] The leaves of *Artemisia argyi* (Fig. 16) and several related *Artemisia* plants (Compositae) have been used as a Chinese natural medicine, Artemisia Argyi Folium, which is prescribed as a hemostatic and sedative agent in Chinese traditional preparations. The hair and fiber parts of the leaves are called moxa (mogusa in Japanese) and the preparation of moxa from the fresh leave is an important process in obtaining Artemisia Argyi Folium. Moxa has been particularly used for analgesic purposes in Chinese acupuncture-cautery procedures.[117] Relatively little is known about the chemical constituents of the processed leaves "moxa". Extensive chemical studies on the leaves of *Artemisia argyi* led to the isolation of a guaianolide designated as Moxartenolide (**23**) and its structural elucidation was carried out by NMR studies. (+)-Moxartenolide (**23**) displays inhibitory activity on the LPS-induced NF-κB activation with IC_{50} value of 1.20 μM.[118] It is interesting to mention that guaianolide Dehydromatricarin (**79**) isolated from *E. capillifolium*[119] is structurally related to (+)-Moxartenolide (**23**), with only difference being the ester group at C4 position. It was reported that Dehydromatricarin (**79**) exhibits inhibitory activity against growth of HeLa cells, with IC_{50} = 15 μM.

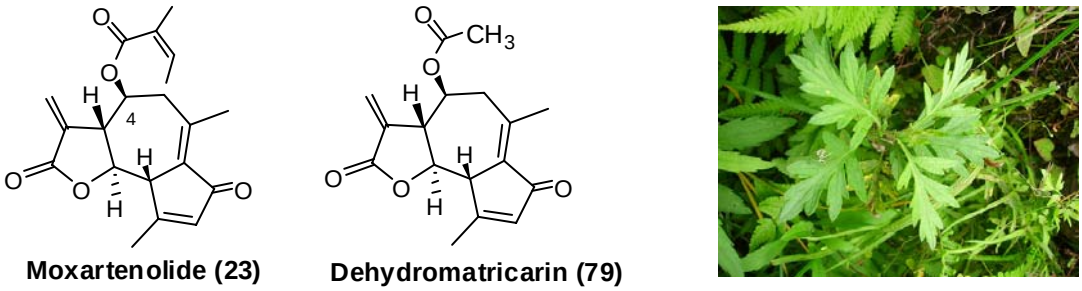


Figure 16. Structures of Moxartenolide (**23**), Dehydromatricarin (**79**) and a picture of *Artemisia argyi*

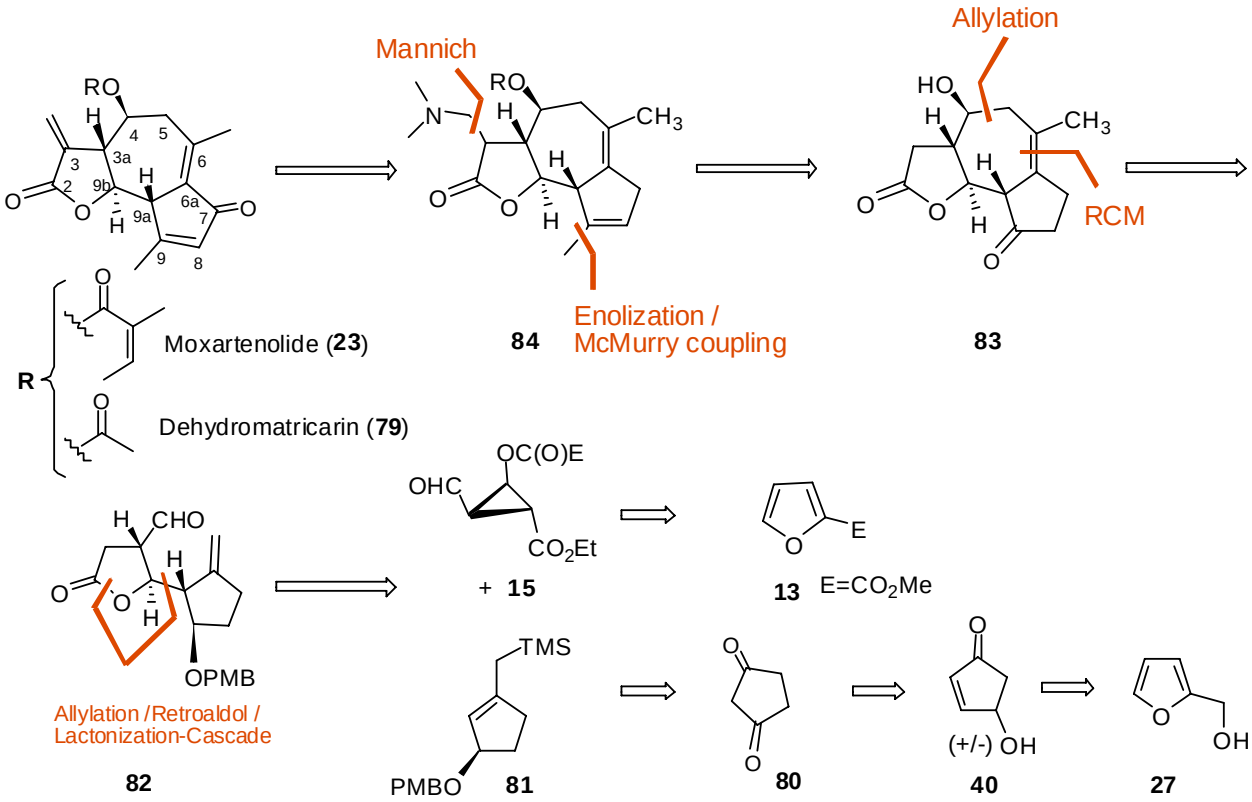
9.2 Importance of NF-κB inhibitors

The recognition of pathogens by innate or adaptive immune receptors leads to activation of cells displaying these receptors, e.g., macrophages, dendritic cells, and lymphocytes. The signal generated by the liganded receptor is communicated to changes in gene expression leading to enhanced expression of effector molecules such as cytokines and adhesion molecules. This process depends on activation of various inducible transcription factors, among which the NF-

κB transcription factors play an evolutionarily conserved and critical role in the triggering coordination of both innate and adaptive immune response.[120] NF-kB represents a group of structurally related and evolutionarily conserved proteins, with five members in mammals: Rel (c-Rel), RelA (p65), RelB, NF-κB1 and NF-κB2. Among the molecules induced by NF-κB are cytokines, chemokines, effector molecules of immunity and pro-survival factors. Mutations that inactivate NF-κB are generally lethal because of the essential role of this protein in cell survival. Partial loss of function causes varying degrees of immunodeficiency. Humans with such mutations have variable levels of immunodeficiency and many show poor inflammatory responses and lack some types of antibodies.[121] NF-κB is central for the overall immune response through its ability to activate genes coding for regulators of apoptosis and cell proliferation.[120] The various functions of NF-κB suggests that modulation of its activity and action represent effective therapeutic strategies for combating diseases such as arthritis, asthma, or autoimmunity that result from hyper- activation of otherwise beneficial immune responses. Thus specific inhibitors of NF-κB might be interesting leads to develop effective therapeutic agents for treatment of inflammation and cancer.

9.3 Retrosynthetic strategy: Initial plans

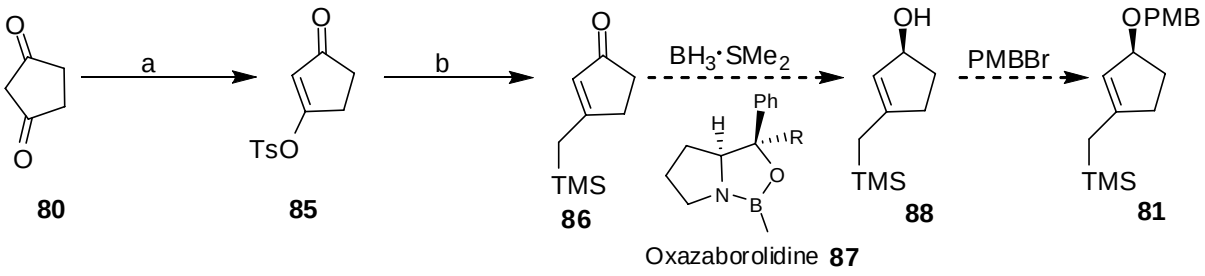
In our initial approach to Moxartenolide (**23**), the main focus was to achieve the functionalization of the lower five membered ring through the chemoselective transformation of the ketone in intermediate **83** to the corresponding enoltriflate, followed by McMurry coupling[122] of it with Methyl Grignard to insert the C9 methyl group (Scheme 37). Such chemoselective transformation of ketone to enoltriflate in the presence of lactone is reported in literature.[123] This transformation makes the C7 position in intermediate **84** doubly allylic which can be easily subjected to allylic oxidation to get the desired enone functionality in the natural product. The *exo* methylene group at C3 can be inserted via the Mannich reaction, as it was performed in the total synthesis of (+)-Arglabin (**11**). Interestingly with the use of appropriate ester group at C4 position both the guaianolides Moxartenolide (**23**) and Dehydromatricarin (**79**) can be achieved from the same intermediate **84**. Thus the synthesis of intermediate **83** is turned out be essential for targeting these natural products. This in turn can be achieved via ring closing metathesis (RCM) of the allylation product derived from **82**, a key building block that was planned to derive from retroaldol / lactonization sequence of **15** and **81**. The synthesis of new chiral allylsilane of type **81** was planned from readily available cyclopenta-1,3-diketone **80**. The synthesis of chiral cyclopropylcarbaldehyde **15** can be achieved starting from furoic ester **13** as described in total synthesis of (+)-Arglabin (**11**).



Scheme 37: Initial retrosynthetic outline for Moxartenolide (**23**) and Dehydromatricarin (**79**).

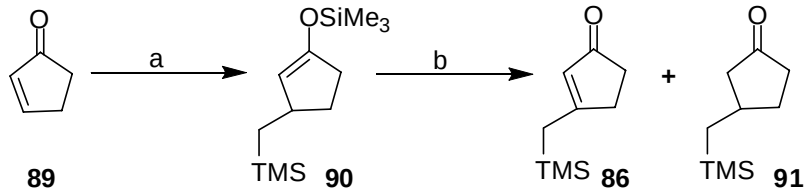
9.4 Synthesis of chiral allylsilane

The synthesis of chiral allylsilane **81** was planned to achieve from **86**, via oxazaborolidine **87** catalyzed enantioselective $BH_3{\cdot}SMe_2$ reduction,[124] followed by the protection of allylic alcohol **88** (Scheme 38). Thus the synthesis started from readily available cyclopenta-1,3-diketone **80** and transforming it to the corresponding enoltosylate **85**. This upon subjection to a Cu(I) mediated Michael addition using appropriate Grignard reagent ($TMSCH_2MgCl$) under goes an addition-elimination mechanism to give the allylsilane **86** in moderate yield.



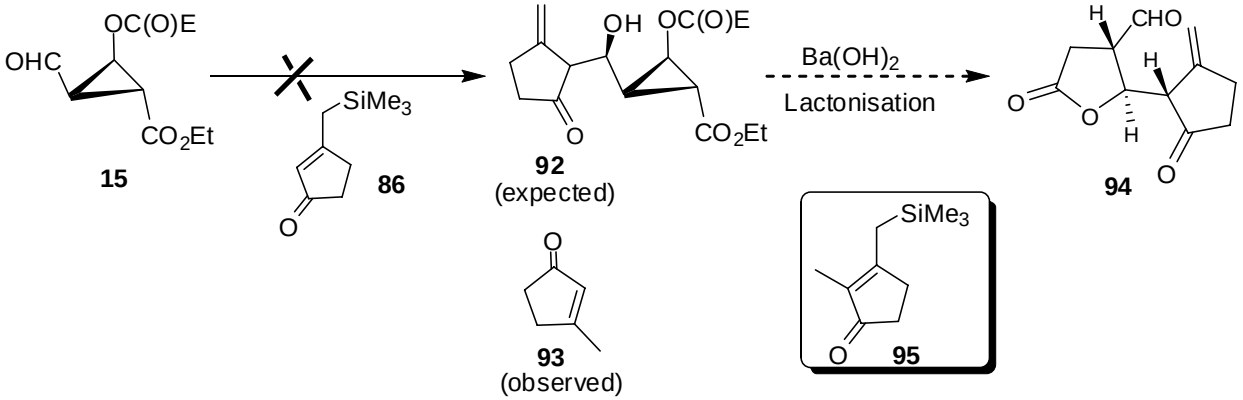
Scheme 38. Synthesis of allylsilane **86**. Conditions: a) Et_3N, THF, RT, *p*Toluenesulfonyl chloride, RT, 2 h, 65 %. b) i) LiCl, CuI , THF, ii) $TMSCH_2MgCl$ -78 °C, 10 h, iii) NH_4Cl, 50 %.

Alternatively, **86** was also obtained starting from readily available cyclopent-2-enone **89** via the Cu(I) mediated 1,4 addition of Grignard reagent ($TMSCH_2MgCl$) followed by trapping the enolate as silylenolether **90** (Scheme 39). Without purification, crude **90** was subjected to a Pd(II) mediated *Saegusa* oxidation[125] to deliver the allylsilane **86** in a moderate yield. The usage of stoichiometric amounts of $Pd(OAc)_2$ in this reaction and also the formation of undesired product **91** in considerable amount (25%) limits the application of this procedure towards the synthesis of **86**. So the synthesis of **86** was carried out using the previous method as described above (Scheme 38).



Scheme 39. Alternative synthesis of allylsilane **86**. Conditions: a) i) LiCl, CuI, THF, ii) TMSCl, -72 °C iii) TMS-CH_2MgCl, 10 h, 72 % (crude) b) $Pd(OAc)_2$ (0.5 eq), *p*Benzoquinone (0.5 eq), CH_3CN, RT, 2h, 55% (**86**), 25% (**91**).

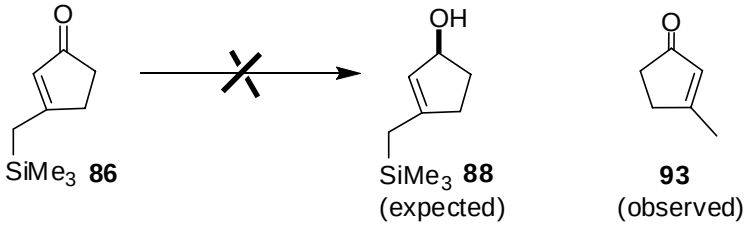
Having the allylsilane **86** in hand, at a first attempt to synthesize the lactone aldehyde **94**, the direct addition of **86** to cyclopropylcarbaldehyde **15** was carried out under Lewis acid conditions (Scheme 40). Under this reaction conditions the addition was unsuccessful leading to decomposition of allylsilane **86** to 3-methylcyclopent-2-enone **93**. The required Felkin-Anh product **92** was never observed. Although allylsilane **95** similar to **86** was reported in literature[126], its application in Sakurai allylation under Lewis acid conditions was not reported so far in the literature.



Scheme 40. Conditions: a) i) $BF_3{\cdot}Et_2O$, CH_2Cl_2 , -78 °C, 15 min, ii) Allylsilane **86**, -78 °C , 6 h, 55% (**93**).

The failure of above reaction indicates that the conjugated allylic double bond in **86** can no longer function as normal allylic bond in addition to electrophilic aldehydes such as **15**. Thus it

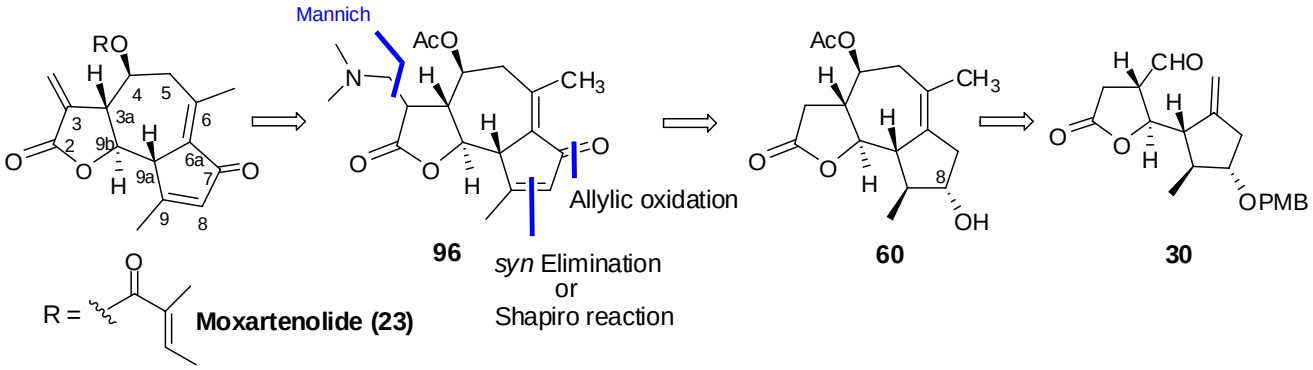
is necessary to prevent the conjugation by reducing the ketone functionality in **86**. To achieve this **86** was subjected to standard Luche reduction conditions using $NaBH_4$ and $CeCl_3$, but unfortunately this resulted only in decomposition of allylsilane **86** to 3-methylcyclopent-2-enone **93** (Scheme 41).



Scheme 41. a) $NaBH_4$, $CeCl_3$, MeOH, -78 °C, 15 min, 55%.

9.5 Modified retrosynthetic strategy

Having experienced the failures in the synthesis of desired allylsilane **88**, recourse was taken to modify the retrosynthesis of the target Moxartenolide (**23**). According to the new retrosynthetic analysis, it was envisioned that intermediate **60** which was utilized in the total synthesis of (+)-Arglabin (**11**), can also be used for the synthesis of (+)-Moxartenolide (**23**) (Scheme 42). Thus the C8/C9 double bond was planned to install either by regioselective *syn* elimination of C8 hydroxy group in **60** or by a *Shapiro* reaction of the C8 oxidized product. The intermediate **60** was synthesized from **30** as described in the total synthesis of (+)-Arglabin (**11**) (see Scheme 23).

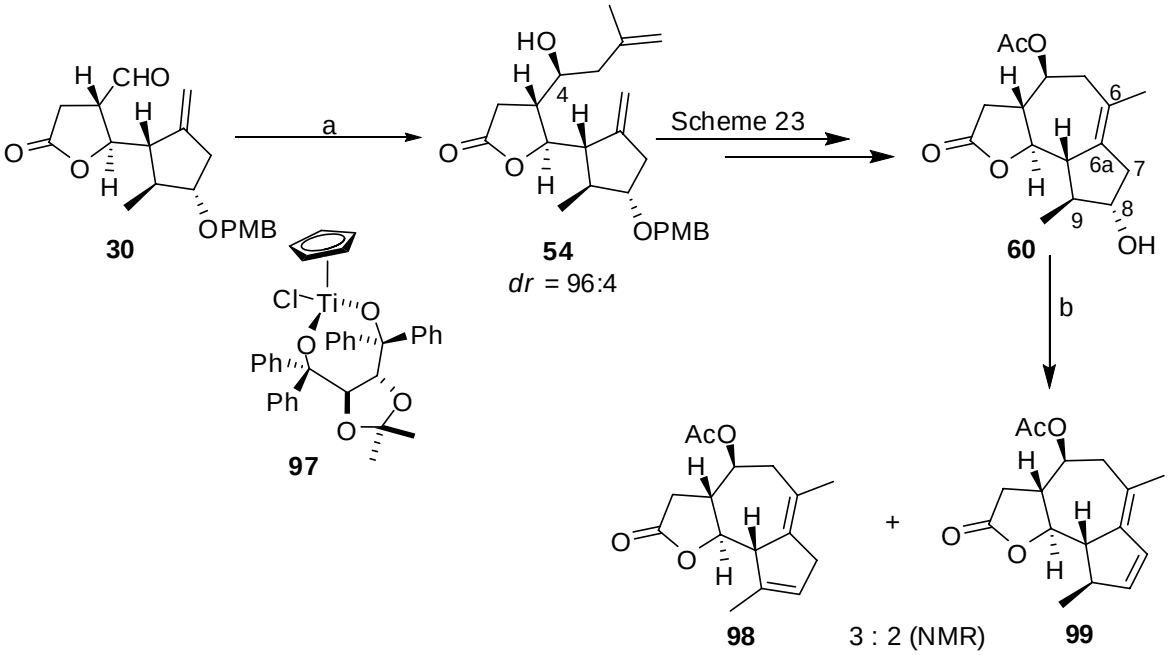


Scheme 42. Modified retrosynthetic plan for Moxartenolide (**23**).

9.6 Syn Elimination studies

According to the above modified retrosynthetic plan, at first *syn* elimination studies was carried out on intermediate **60**. Since the C4 stereogenic centre in the target natural product has to be created stereoselectively, this was done by subjecting lactone aldehyde **30** to an

enantioselective allyltitanation[127] of aldehydes employing chiral auxiliary such as monochlorotitanate **97**, derived from $CpTiCl_3$ and chiral 1,4-diols (Scheme 43). Thus, treatment of **30** with a complex derived from (*R,R)*-**97** and 2-Methyl allylmagnesium chloride gave the desired allylated product **54** with a good diastereoselectivity (96:4) compared to the $BF_3{\cdot}Et_2O$ mediated allylation (80:20, see Scheme 23 in Arglabin total synthesis). With the creation of C4 stereocenter in a diastereoselective fashion, the allylated product **54** was further transformed to the required intermediate **60** following the same strategy described in Arglabin total synthesis (see Scheme 23).



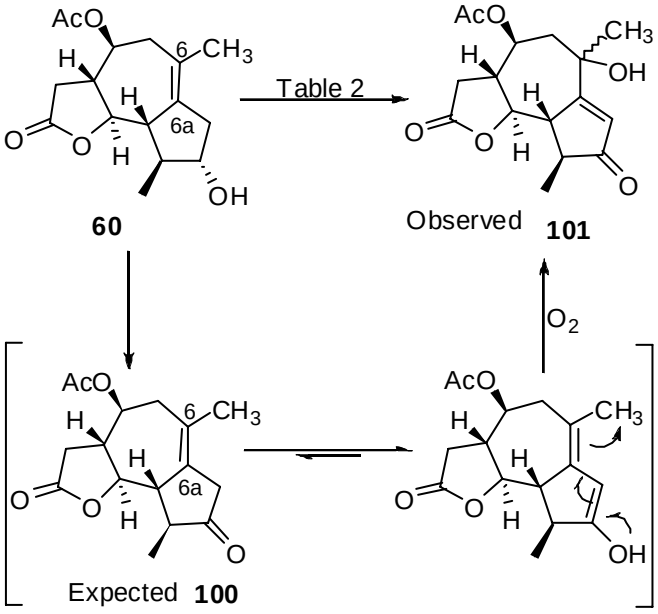
Scheme 43. Conditions. a) (i) *(R,R)*-**97**, 2-Methyl allylmagnesium chloride, THF, -78 °C to 0 °C, 2 h, (ii) **30**, 5 h, 65 % (95:5 epimeric mixture at C4). b) Tf_2O, Pyridine, CH_2Cl_2, -10 °C, 6 h, 68 % (regiomeric mixture of **98** and **99**).

Having the key intermediate **60** in hand, it was subjected syn elimination conditions using Tf_2O and pyridine[107] at low temperature. This led to the isolation of regiomeric mixture of products **98** and **99** in the ratio of 3:2 respectively, determined through ^1H NMR (Scheme 43). Under this reaction conditions the formation of *Zaitsev* product **98** occurred in preference to the *Hofmann* product **99**, which has an extended conjugation system due to the newly formed C7/C8 double bond. But the presence of inseparable mixture of products **98** and **99** made this reaction not to be carried for further studies.

9.7 Oxidation studies

It was envisioned that the oxidation of the secondary alcohol group at C8 position in **60**, followed by a *Shapiro*[128] protocol on the oxidized product should lead us to the same

intermediate **98**. So with this idea the oxidation of **60** was carried out with PCC as oxidant. To our surprise the oxidation took place with good yield, but delivered the undesired product **101** as 1:1 diastereomeric mixture (Table 2, entry 1). The formation of **101** can be readily explained by the enolization of the desired oxidation product **100** followed by keto-enol tautomerization leading to the opening of C6/6a double bond (Scheme 44). The usage of milder oxidizing agents such as Dess-Martin Periodane[11] or TEMPO[138] did not alter the course of the reaction and gave the same undesired product **101** as diastereomeric mixture (Table 2, entries 2, 3).



Entry	Conditions	Yield (%) [a]	**101** Ratio [b]
1.	PCC, CH_2Cl_2, RT, 4 h.	75%	1:1
2.	Dess-Martin - Periodane, $NaHCO_3$, CH_2Cl_2, RT, 2 h.	72%	1:1
3.	TEMPO, NaOCl, KBr, CH_2Cl_2, 0 °C to RT, 4 h.	75%	2:1

Table 2. [a] Isolated yield. [b] Determined by ^{1}H NMR

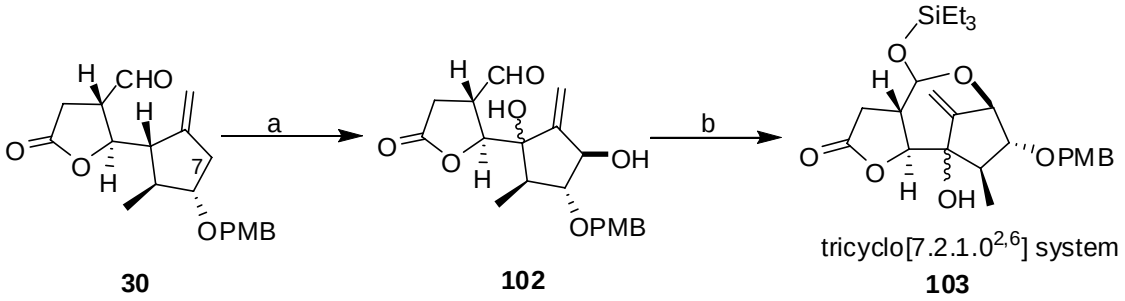
Scheme 44. Oxidation studies on intermediate **60**.

Having observed the above unexpected result due to the *in situ* isomerization of the C6/C6a double bond in the desired oxidation product **100**, the idea of implementing *Shapiro* protocol to synthesize **98** was unsuccessful.

9.8 Allylic oxidations using SeO_2

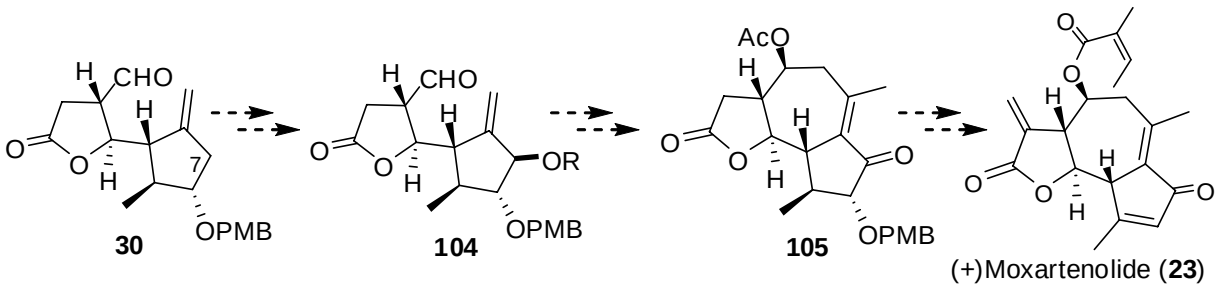
Allylic oxidation of olefinic compounds using SeO_2 is a well known procedure in organic synthesis for the insertion of oxygen into an allylic carbon-hydrogen bond.[129] The recent developments in the asymmetric version[130] of this reaction expands the broad scope of its applicability in complex molecule synthesis. One of the major draw backs involved in a classical SeO_2 reaction is frequent difficulty of removing colloidal selenium from the products and also the formation of organoselenium by-products. These difficulties are overcome by *Sharpless* allylic oxidation conditions[131] which employs catalytic SeO_2 and TBHP as co-oxidant. The use of such mild conditions is quite applicable for complex molecule synthesis. With the above failures in hand, for the total synthesis of Moxartenolide (**23**) it was considered

that the oxidation of C7 position in the target natural product should be carried out before the construction of the tricyclic core, i.e. on the intermediate **30** (see Scheme 42). For this purpose the *Sharpless* allylic oxidation conditions was chosen to implement on intermediate **30**. Thus exposure of **30** to a precomplexed mixture of SeO_2-TBHP gave the oxidation product **102**, the oxidation being not regioselective as it occurred at both the allylic positions in the starting material **30** (Scheme 45). In an attempt to protect the secondary alcohol functionality in **102** using basic conditions, it was observed that **102** undergoes an acetal formation with *in situ* silyl protection taking place to give a tricyclo[7.2.1.$0^{2,6}$] system **103**, which is quite stable to purification on silica gel column chromatography.



Scheme 45. Conditions a) SeO_2 (0.5 eq.), TBHP (2.0 eq), CH_2Cl_2, RT, 20 h, 55 % (4:1 inseparable mix of diastereomers). b) Et_3N, TESCl, DMAP, RT, 4 h, 85% (4:1 inseparable mix of diastereomers).

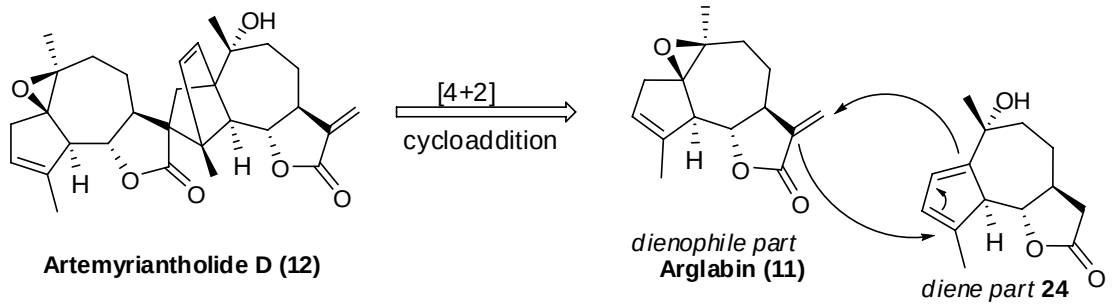
Taking the above observations into consideration, the future perspective for the total synthesis of (+)-Moxartenolide (**23**) would be to oxidize the C7 position in the intermediate **30** regioselectively, by screening various other allylic oxidation systems such as CrO_3-pyridine complexes[132] or by an heterogeneous catalyst Chromium Aluminophosphate-5[133] (CrAPO-5) in combination with TBHP, that are reported for the direct conversion of olefins to α,β-unsaturated ketones (Scheme 46). Even the application of palladium catalysis to generate the π-allylpalladium complex in **30** followed by subsequent attack of nucleophile such as an alkoxide on the π-allylpalladium complex would be of good choice to investigate.[134] These approaches are currently under investigation.



Scheme 46. Future plans towards (+)-Moxartenolide (**23**) starting from **30**.

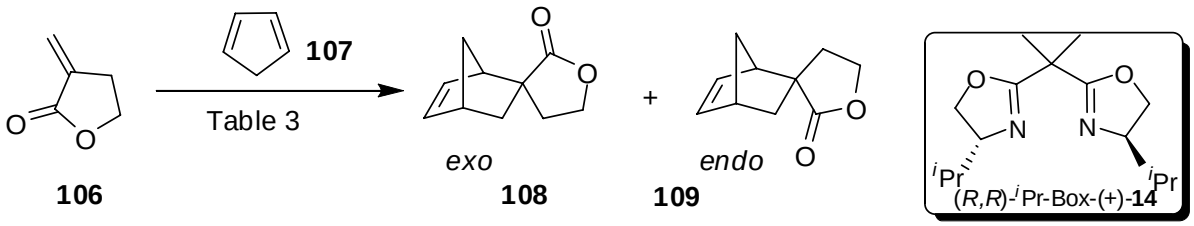
10. Biomimetic approach towards the synthesis of dimeric guaianolides

Dimeric guaianolides isolated from plants belong to a little studied type of sesquiterpenes, although their initial molecules, the mono guaianolides, have been studied in more detail both under chemical and stereo chemical aspects.[46] They are structurally more complex guaianolides and derived through the dimerization of two monomeric guaianolides, presumably *via* a [4+2] cycloaddition. The proposed biosynthesis [53] for Artemyriantholide D (**12**) attracted our attention towards the synthesis of this dimeric guaianolide (see Introduction Scheme 5). Attempts to mimic such process in the laboratory would lead to the biomimetic total synthesis of this natural product. As proposed in the biosynthesis of Artemyriantholide D (**12**), a Diels-Alder reaction is required as key step between Arglabin (**11**) and diene intermediate of type **24** with high exoselectivity to account for the stereochemistry of the dimeric linkage.



Scheme 47. Retrosynthetic strategy for Artemyriantholide D (**12**).

Although such exoselectivity is unusual for Diels-Alder additions taking place in a reaction flask, *Buono et al* [62] has shown that high exoselectivity occurs in the Diels-Alder additions of α-methylene-γ-butyrolactones to cyclopentadiene under kinetically controlled as well as thermal conditions (see Introduction Scheme 10). To validate these results Diels-Alder addition of α-methylene-γ-butyrolactone **106** to cyclopentadiene **107** was carried out using $ZnCl_2$ as Lewis acid according reported procedure (Scheme 48).[62] The result was in accordance with the reported selectivity and gave a ratio of 3:1 for *exo*:*endo* isomers respectively (Table 3, entry 1). The *exo* isomer in this case was partially separated from the mixture by purification on silica gel column chromatography. Crystallization of pure *exo* isomer from pentane-CH_2Cl_2 mixture afforded a crystalline compound which upon single crystal X-ray analysis revealed the stereochemistry of *exo* isomer (Fig. 17). Also the effect of bis (oxazoline) ligand (BOX) in complexation with $Cu(OTf)_2$ as a chiral Lewis acid was studied in this reaction. The use of (*R*,*R*)-^{i}Pr-Box (+)-**14** gave the *endo* isomer in preference to *exo* isomer (*exo*:*endo* = 2:3) (Table 3, entry 2).



Scheme 48. Diels-Alder reaction between α-methylene-γ-butyrolactone **106** and cyclopentadiene **107**.

Entry	Conditions	Yield (%) [a]	Ratio **108** : **109** [b]
1	$ZnCl_2$ (10 mol%), CH_2Cl_2, RT, 6 h	75	3:1
2	(*R*,*R*)-^{i}Pr-Box (+)-**14**, $Cu(OTf)_2$ (10 mol%), CH_2Cl_2, 0 ^{o}C to RT, 6 h	85	2:3

Table 3. [a] Yield of mixture. [b] Determined by GC and ^{1}HNMR

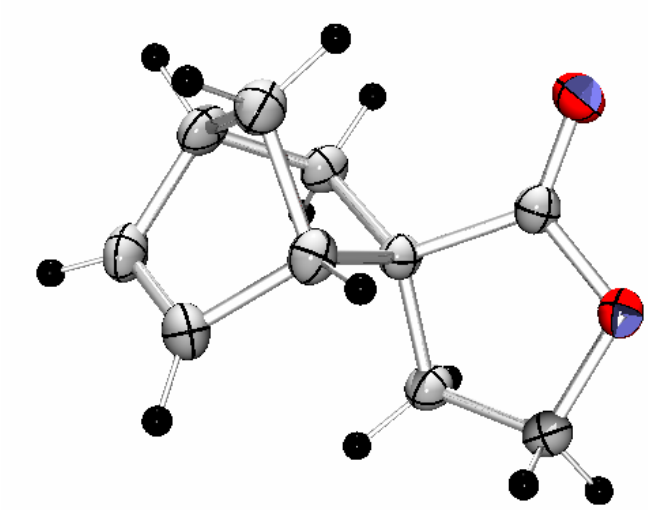
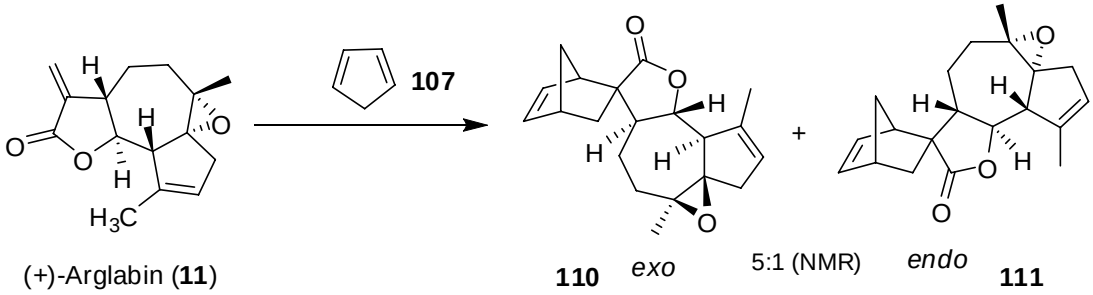


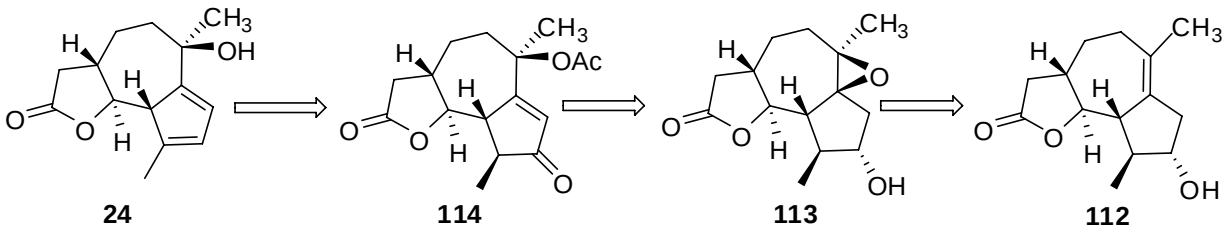
Figure 17. X-ray structure of *exo* isomer **108**

The above high *exo* selectivity prompted us to investigate the Diels-Alder reaction between a stereochemically more complex dienophile such as (+)-Arglabin (**11**) and cyclopentadiene **107** (Scheme 49). Thus the reaction between (+)-Arglabin (**11**) and cyclopentadiene **107** gave a mixture of isomers **110** and **111** with a better ratio (5:1, *exo*:*endo*), again with a preference to *exo* isomer.



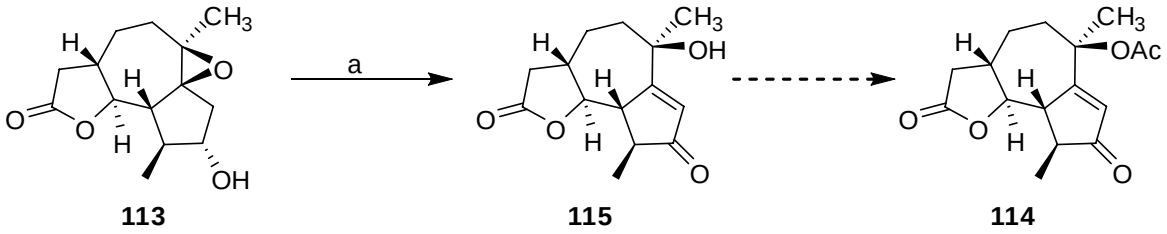
Scheme 49. Diels-Alder reaction between Arglabin (**11**) and cyclopentadiene **107**. Conditions: a) $ZnCl_2$, RT, 12 h, 80% (mixture of **110** and **111**).

The high *exo* selectivities in the above model Diels-Alder reactions promoted us to further extend our studies towards the biomimetic total synthesis of Artemyriantholide D (**12**). To achieve this, as mentioned in the retrosynthetic outline a diene cyclopentadiene intermediate **24** was required to setup the required Diels-Alder reaction (see Scheme 47). To achieve this, it was envisioned that intermediate **114** derived by the opening of epoxide from **113** can serve to get the diene functionality in **24** (Scheme 50). The key intermediate **113** can in turn be synthesized from **112** via halohydrin mediated epoxidation strategy described in the total synthesis of Arglabin (see Scheme 29).



Scheme 50. Retrosynthetic outline for the synthesis of diene intermediate **24**.

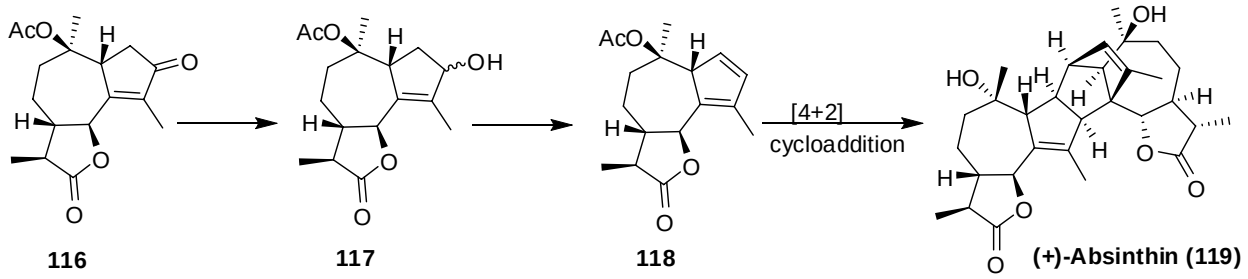
The transformation of **113** to **114** is earlier reported from our group.[135] Thus oxidation of **113** with PCC took place with highly stereoselective opening of the epoxide group delivering **115** in quantitative yield (for a transformation on similar substrate with mechanism see Scheme 44). The protection of the free tertiary alcohol group in **115** leads to the synthesis of the intermediate **114** (Scheme 51).



Scheme 51. Conditions: a) PCC, CH_2Cl_2, RT, 4 h, quantitative.

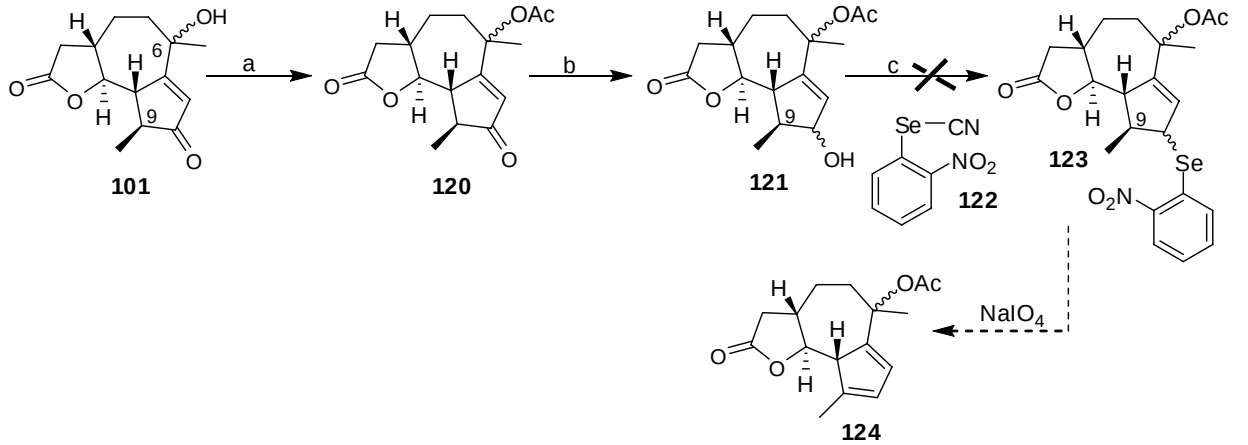
The transformation of **114** to cyclopentadiene intermediate **24** can be achieved in two ways. The first method involves the Luche reduction of the enone function followed by the elimination of allylic alcohol to give the desired intermediate **24**. The second method involves a direct Shapiro reaction on **114** to deliver the desired intermediate **24**. *Zhai* et al had reported a similar transformation in their biomimetic total synthesis of (+)-Absinthin (**119**) (Scheme 52).[136] According to their report the transformation of the intermediate **116** to the diene **118**

was not possible directly by *Shapiro* reaction. So the reduction of enone **116** followed by the subsequent base-promoted elimination of corresponding sulfonates (OMs, OTs, or OTf) of **117** was found to be not successful. But the Mitsunobu arylselenylation[137] of **117** with *o*-nitrophenyl selenocyanate, followed by the oxidative cleavage of the selenides gave the desired cyclopentadiene **118**, which underwent a [4+2] cycloaddition in the reaction flask with out any solvents and reagents to give the dimeric guaianolide (+)-Absinthin (**119**) with all the stereocenters fixed in one pot.



Scheme 52. Key steps in the biomimetic total synthesis of (+)-Absinthin (**119**) from *Zhai* et al. [136]

The preexistence of such biomimetic total synthesis promoted us to further investigate the studies in transforming **114** to cyclopentadiene intermediate **24**. Thus to investigate the Mitsunobu arylselenylation,[137] an intermediate of type **101** was chosen for the model study (for the synthesis of **101** see Scheme 44). Thus the protection of free hydroxy group by acetate followed by the reduction of enone **120** with $NaBH_4$ gave a diastereomeric mixture of allylic alcohols **121**. Treatment of this mixture with *o*-nitrophenyl selenocyanate **122** under Mitsunobu arylselenylation conditions was never successful to give the desired selenides **123**, which on oxidative cleavage with $NaIO_4$ should give the cyclopentadiene intermediate **124**.



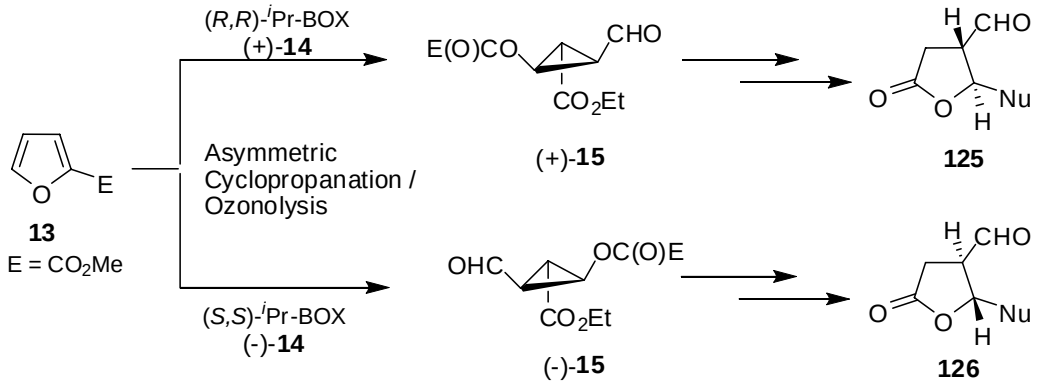
Scheme 53. Conditions: a) Et_3N, Ac_2O, DMAP, CH_2Cl_2, RT, 8 h, 85 % (1:1 inseparable mixture of diastereomers at C6). b) $NaBH_4$, MeOH, RT, 2 h, 78%. c) **122**, $^nBu_3P$, THF, RT, 2 h.

In comparison with the *Zhai* et.al. intermediate **117** (Scheme 52) which underwent Mitsunobu arylselenylation under the same condition, it was rationalized that the C9 stereocenter in the intermediate **121** might be responsible for the breakdown of the reaction with *o*-nitrophenyl selenocyanate **122**. In case of *Zhai* et.al. intermediate **117**, the same C9 position is a sp^2 hybridized planar centre. Thus the failure of Mitsunobu arylselenylation reaction on a model substrate of type **121** led us to modify the approach in synthesizing the cyclopentadiene intermediate **24** required for the biomimetic Diels-Alder reaction. The alternative method involves the transformation of enone functionality in **114** to the cyclopentadiene functionality by *Shapiro* reaction (Scheme 52). These studies are currently under investigation.

11. Summary

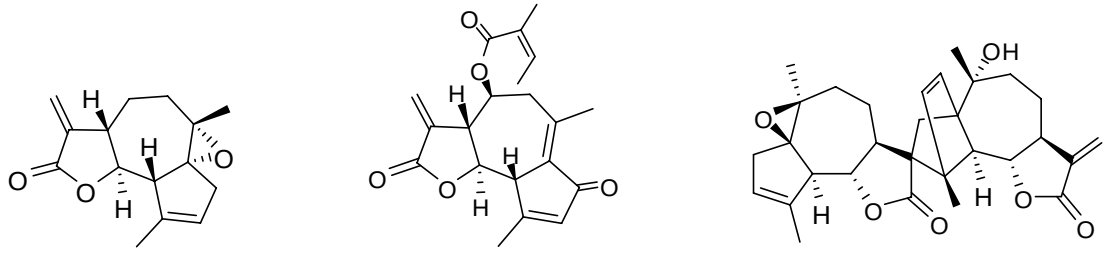
Every natural product type isolated from the seemingly limitless chemical diversity in nature provides a unique set of research opportunities deriving from its distinctive three-dimensional architecture and biological properties. Guaianolides, an interesting class of sesquiterpene lactones exhibit a broad range of biological activity along with the structural diversity and stimulate the development of research in their total synthesis. The essence of total synthesis lies in how readily available starting materials can be converted to complex molecular architectures through controlled, efficient and logically orchestrated carbon - carbon and carbon - heteroatom bond connectivities.

In the present thesis it was shown how simple aromatic starting materials can be converted to chiral building blocks such as *anti*-disubstituted γ-butyro-lactones that are key structural motifs of guaianolides. Starting from furoic ester **13** either of the enantiomers of cyclopropylcarbaldehyde **15** are synthesized followed by transforming them to trans-4,5-disubstituted γ-butyro lactones of type **125** (Scheme 54)



Scheme 54. Transformation of aromatic starting materials to trans-4,5-disubstituted γ-butyro lactones.

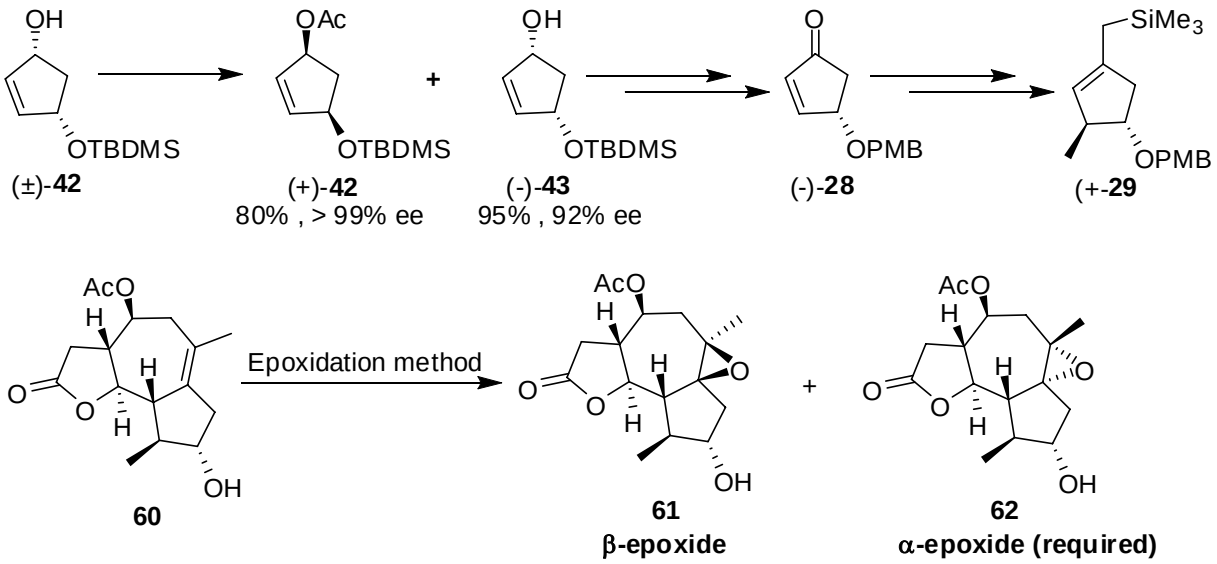
The application of this was shown in the first enantioselective total synthesis of a novel antitumor guaianolide (+)-Arglabin (**11**). The work was further extended towards the enantioselective total synthesis of Moxartenolide (**23**) and dimeric guaianolides such as Artemyriantholide D (**12**) (Fig. 18)



(+) Arglabin (11) **Moxartenolide (23)** **Artemyriantholide D (12)**

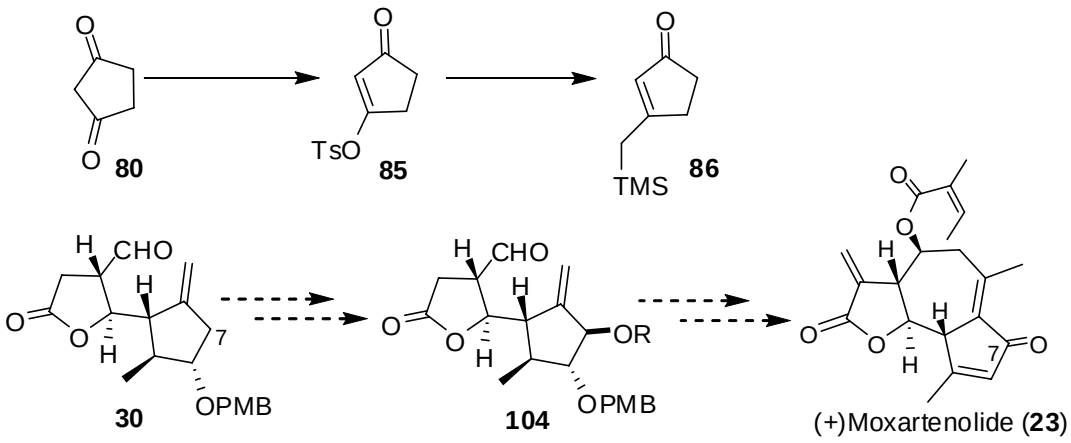
Figure 18. Target guaianolides aimed for total synthesis.

For the total synthesis of (+)-Arglabin (**11**), the synthesis of chiral allylsilane (+)-**29** was carried out starting from kinetically resolved 1,4 diols (+)-**42** and (-)-**43** (Scheme 55). A study of the stereoselective epoxidations was carried out on substrate **60** to get the desired stereochemistry of the epoxide group present in the natural product and completion of total synthesis.



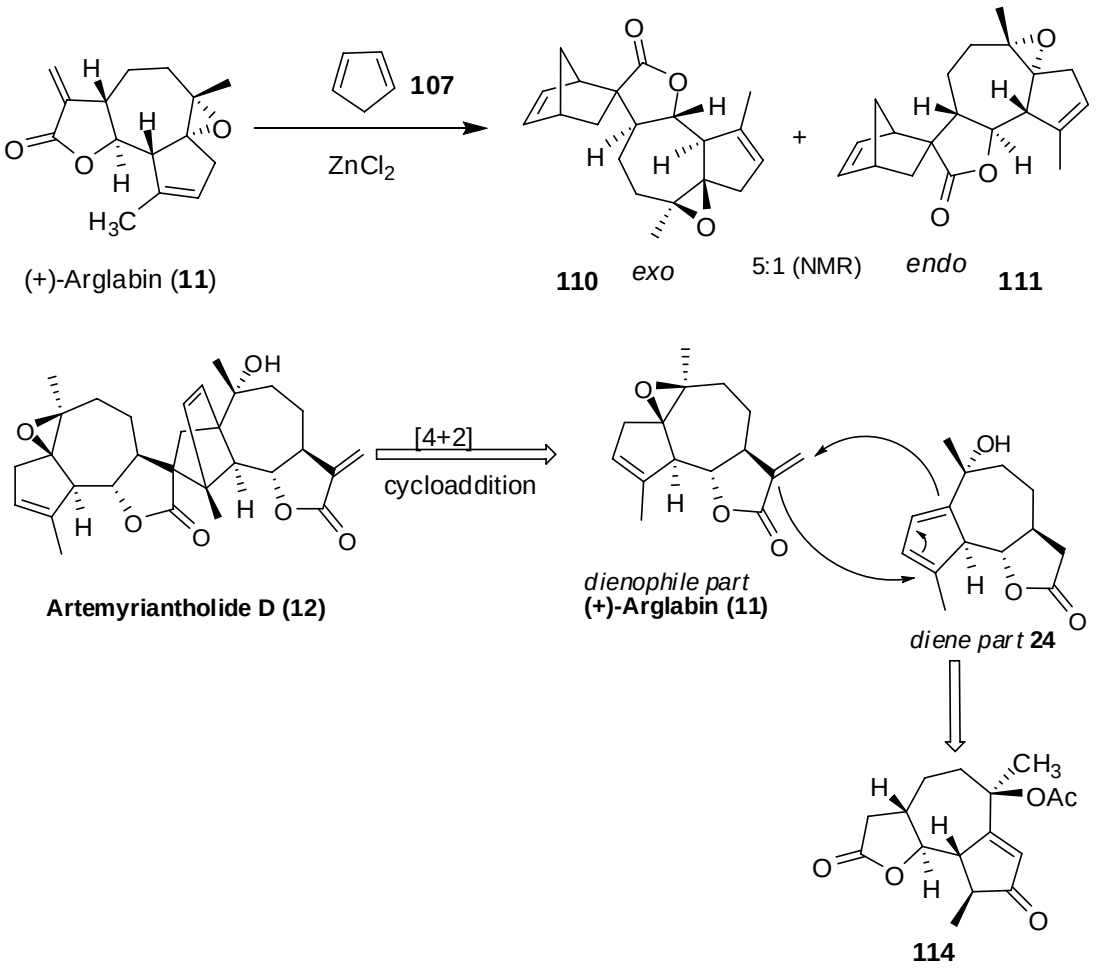
Scheme 55. Synthesis of chiral allyl silane (+)-**29** and epoxidation study on **60**.

In the total synthesis of (+)-Moxartenolide (**23**), the new allylsilane **86** was synthesized starting from cyclopenta-1,3-diketone **80** via addition-elimination mechanism on **85** (Scheme 56). Later oxidative studies were carried out on substrate **30** to regioselectively oxidize the C7 position. The future perspective for the total synthesis of (+)-Moxartenolide (**23**) would be to oxidize the C7 position regioselectively to synthesize intermediate **104**, followed by the construction of tricyclic core to complete the total synthesis



Scheme 56. Synthesis of new allylsilane **86** and future perspective for total synthesis of (+)-Moxartenolide (**23**).

Finally towards the end of thesis, biomimetic studies toward the total synthesis of dimeric guaianolide Artemyriantholide D (**12**) was carried out. Towards this model [4+2] cycloadditions between (+)-Arglabin (**11**) and cyclopentadiene **107** in presence of $ZnCl_2$ showed high *exo* selectivity as required for the biomimetic synthesis of Artemyriantholide D (**12**) (Scheme 57). Also model reactions were carried on substrate similar to **114** for the synthesis of cyclopentadiene intermediate **24** that is required to set up the proposed biosynthetic Diels-Alder reaction with (+)-Arglabin (**11**).



Scheme 57. Diels-Alder between (+)-Arglabin (**11**) and cyclopentadiene **107** showing required exoselectivity.

12. Experimental Part

12.1 General

^{1}H NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova 600, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (7.26 ppm) or tetramethylsilane (0.00 ppm) as internal standard. The spectra were evaluated in 1st order and the coupling constants are given in Hertz [Hz]. The following abbreviations for the spin multiplicity were used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet, sept = septet. The used deuterated solvents are given separately.

^{13}C NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift δ is given in [ppm], calibration was set on chloroform-d_1 (77.16 ppm), or tetramethylsilane (0.00 ppm) as internal standard. The multiplicity of the signals were detected by DEPT 135 and 90 (DEPT = distortionless enhancement by polarization transfer) and are given as: + = primary und tertiary C-atom (positive DEPT 135 signal; tertiary C-atom: DEPT 90 signal), - = secondary C-atom (negative DEPT 135 signal), Cq = quaternary C-atom (DEPT-signal intensity zero).

Melting points were measured on a Büchi SMP 20 in a silicon oil bath. The melting points are uncorrected.

Infrared-Spectra were recorded on a Bio-Rad Excalibur Series or Mattson Genesis Series FT-IR. Solid compounds were measured in KBr, liquid compounds as a neat film between NaCl-plates. The wave numbers are given in [cm^{-1}].

Masspectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. The percentage set in brackets gives the peak intensity related to the basic peak (I = 100%). High resolution mass spectrometry (HRMS): The molecular formula was proven by the calculated precise mass.

Elemental analysis was prepared by the micro analytic section of the University of Regensburg using a Vario EL III or Mikro-Rapid CHN (Heraeus).

Optical rotation was measured at rt on a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm or 0.1 dm cell. The concentration is given in [g/100 ml].

X-ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH) and the crystallography laboratory of the University of Kansas.

Chiral HPLC was performed in the analytic department of the University of Regensburg or on a Kontron Instruments 325 System (HPLC 335 UV detector, λ = 254 nm, Chiracel OD/OD-H column (50x4.6 mm, 10 µm, flow rate: 1 mL/min, 20 °C, *n*-heptane/ethanol 99:1).

Gaschromatography (GC) was measured in the analytic department of the University of Regensburg or on Fisons Instruments GC 8000 series (Data Jet Integrator, CP-chiralsil-DEX-CP column).

Thin layer chromatography (TLC) was prepared on TLC-aluminium sheets (Merck, silica gel 60 F_{254}, 0.2 mm). Detection in UV-light λ = 254 nm, staining with I_2, Mostain, molybdatophosphoric-acid (5% in ethanol), $KMnO_4$ solution or vanillin-sulfuric acid.

Column chromatography was performed in glass columns (G2 or G3). As a stationary phase silica gel Merck-Geduran 60 (0.063-0.200 mm) or flash silica gel Merck 60 (0.040-0.063 mm) was used.

Microwave: Microwave experiments were performed in a Prolabo Synthewave S 402 (2.45 GHz, focused, max. 300 W) or on CEM Discover System.

Ozone-Generator: For ozone generation a Fischer process technology ozone generator OZ 500 MM was used, supplied by an oxygen tank.

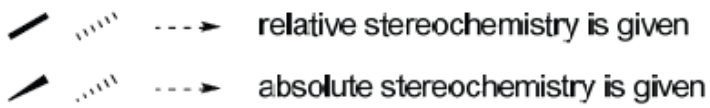
Solvents: Abs. solvents were prepared according to usual lab procedures or taken from the MB-SPS solvent purification system. Ethylacetate, hexanes (40-60 °C) and dichloromethane were purified by distillation before use. Further solvents and reagents were of p.a. quality.

Reactions with oxygen- and moisture sensitive reactants were performed in oven dried and in vacuo heated reaction flasks under a pre-dried inert gas (nitrogen or argon) atmosphere. For cooling to temperatures < -40 °C a cryostat Haake EK 90 or dry ice/*iso*-propanol mixture was used.

12.2 Abbreviations

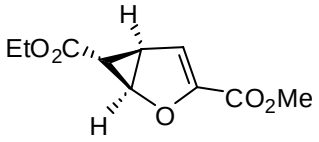
abs	absolute	MeCN	acetonitril
AIBN	azo-isobutyronitrile	Mes	mesyl
Bu	*n-butyl*	min	minute
BuLi	*n-butyl lithium*	MS	molecular sieve
cat	catalytic	NMR	nuclear magnetic resonance
CI	chemical ionization	NMO	*N-methylmorpholin-N-oxid*
dr	diastereomeric ratio	NOE	nuclear Overhauser effect
DBU	1,8-Diazabicyclo[4.4.0] undec-7-ene	Nu	nucleophile
		PCC	pyridinium chlorochromate
DEAD	diethylazodicarboxylate	Pg	protecting group
DMAP	*N,N-dimethylamino pyridine*	Ph	phenyl
DMF	dimethyl formamide	PMB	*p-methoxy-benzyl*
DMS	dimethyl sulfide	PPLE	porcine pancreas lipase enzyme
ee	enantiomeric excess	pyr	pyridine
eq.	equivalents	RCM	ring closing metathesis
EI	electronic ionization	RT	room temperature
Et	ethyl	SAR	structure-activity relationship
Glc	glucose		
h	hour	TBME	*tert-butyl-methyl-ether*
HAT	histone-acetyl-transferase	TBDMS	*tert-butyldimethylsily*
HPLC	high pressure liquid chromatography	TBAF	tetrabutylammonium fluoride
		TPAP	Tetrapropylammonium perruthenate
HRMS	high resolution mass spectrometry		
		^{t}Bu	*tert-butyl*
HWE	Horner-Wadsworth-Emmons	TES	triethylsilyl
^{i}Pr	*iso-propyl*	THF	tetrahydrofuran
IR	infra red	TMS	trimethylsilyl
LAH	lithium aluminium hydride	Tf	trifluormethanesulfonate
M	metal	Ts	tosyl
mCPBA	*m-chloroperbenzoic acid*	quant	quantitative
Me	methyl		

Indication of relative and absolute stereochemistry:



12.3 Enantioselective total synthesis of (+)-Arglabin

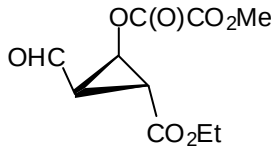
1. (1*R*,2*R*,3*R*)-(+)-2- Oxalic acid 2-ethoxycarbonyl-3-formylcyclopropylester methyl ((+)-35)



A 500 ml flask equipped with a stirring bar and a 500 ml, pressure-equalizing, addition funnel with incorporated Mariotte tube connected to a mineral oil bubbler, was purged with nitrogen and cooled to 0 °C. It was charged with $Cu(OTf)_2$ (0.227 g, 0.628 mmol, 0.66%mol), (*R,R*)-*iso*-propyl-bis(oxazoline) (+)-**14** (0.211 g, 0.799 mmol, 0.84 mol%) and dry CH_2Cl_2 (10 ml) resulting in a deep blue solution. After stirring for 10 min furan-2-carboxylic acid methyl ester **13** (12 g, 95 mmol, 1.0 eq.) was poured in and phenyl hydrazine (3 drops) was added via a syringe leading to a color change to red-brown which indicates the reduction of copper(II) to copper(I). This solution was stirred for 30 min and subsequently ethyldiazoacetate (215 ml solution of 10.14% mass, 0.25 mol, 2.67 eq.) in CH_2Cl_2 was added via the addition funnel during 5 days. On completion of addition the solution was stirred for 1 h until no gas evolution was observed any longer. The reaction mixture was passed through a pad of basic alumina (10x5.5 cm), followed by CH_2Cl_2 (500 ml). The organic layers were combined and concentrated under reduced pressure to afford yellow-brown oil. The residue was purified by fractioned distillation under reduced pressure ($p = 3x10^{-2}$ mbar, b.p. = 38-44 °C) and starting material (4.78 g, 37.9 mmol, 40%) was recovered. The brown residue was purified by column chromatography (silica, 4x36 cm, hexanes: ethylacetate 9:1) to yield the desired product (+)-**35** (10.8 g, 50.90 mol, 85% *ee*, 54% yield, 89% yield based on recovered starting material) as a yellowish oil. To obtain enantiomeric pure product the oil was treated with *n*-pentane (200 ml) followed by CH_2Cl_2 (8 ml) with stirring until the solution changed from cloudy to clear. The solution was kept for 16 h at -27 °C and a small enantiomerically pure crystal was added which gave rise to colorless crystals after 6 d. The supernatant liquid was removed by filtration and the remaining crystals were dried *in vacuo* to afford (+)-**35** (6.90 g, 33.0 mmol, 34%, >99% *ee*) as colorless crystals. After concentration of the mother liquor *in vacuo* the residue was again treated with *n*-pentane (120 ml) and CH_2Cl_2 (2 ml) and set for crystallization at -27 °C for 5 d. Removal of the supernatant liquid and drying *in vacuo* afforded (+)-**35** (0.609 g, 2.87 mmol, 3%, >99% *ee*, total yield: 7.51 g, 35.39 mol, 38% yield, 62% yield based on recovered starting material) as colorless crystals.

R*f* (hexanes: ethylacetate 5:1, Vanilline) = 0.16.- mp. = 42 °C. – $[\alpha]^{20}_D$ = +272 (c = 1.0, CH_2Cl_2). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (dd, *J* = 2.7, 1.1 Hz, 1 H, 6-H), 1.27 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.87 (ddd, *J* = 5.3, 2.9, 2.7 Hz, 1 H, 5-H), 3.81 (s, 3 H, OCH_3), 4.16 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 4.97 (dd, *J* = 5.3, 1.1 Hz, 1 H, 1-H), 6.40 (d, *J* = 2.9 Hz, 1 H, 4-H). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.20 (+, CH_3), 21.43 (+, C-6), 31.97 (+, C-5), 52.26 (+, OCH_3), 61.08 (-, CH_2), 67.54 (+, C-1), 116.19 (+, C-4), 149.15 (Cquart, C-3), 159.54 (Cquart, CO), 171.78 (Cquart, CO). – IR (KBr): $\tilde{\nu}$ = 3118, 2956, 1720, 1617, 1428, 1380, 1297, 1166, 1124, 1041, 954, 831, 725 cm^{-1}.

2. (1*R*,2*R*,3*R*)-(-)-oxalic acid 2-ethoxycarbonyl-3-formyl-cyclopropyl ester methyl ester ((+)-15))

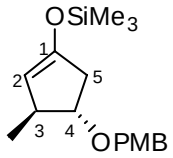


A 100 ml flask was charged with a solution of (+)-**35** (3.022 g, 14.24 mmol, 1.0 eq.) in dry CH_2Cl_2 (50 ml). The flask was equipped with a gas passing tube connected with one side to an ozone generator and with the other side to a drying tube containing KOH coated clay ending up in the hood. The solution was cooled to -78 °C and a constant stream of oxygen containing ozone (O_2 = 150 l/h, O_3 = 7 g/h) was immersed into the solution until a deep blue color appeared (approx. 15 min). Excess of ozone was expelled by passing a constant flow of oxygen for another 10 min into the solution. The gas inlet tube was replaced by a drying tube. DMS (2.28 ml, 57 mol, 4.0 eq.) was added at -78 °C, and the reaction mixture was allowed to warm up slowly to rt and stirred for 22 h. The solution was washed with sat. $NaHCO_3$ (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (10 ml). The combined organic layers were washed with H_2O (5 ml) and the aqueous layer was extracted again with CH_2Cl_2 (5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield the aldehyde (3.199 g, 13.10 mmol, 92%) as a pale yellow oil which can be used without any further purification. To obtain a colorless microcrystalline solid the crude product was crystallized from Et_2O (3 ml) and stored at -35 °C for 2 weeks. The solvent was removed by a pipette and the solid was dried in vacuo to give (+)-**15** (3.124 g, 12.78 mmol) in 94% yield.

m.p. = 52 °C. - $[\alpha]^{20}_D$ = + 37.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* =

7.2 Hz, 3 H), 2.81 (ddd, *J* = 7.2, 6.0, 4.0 Hz, 1 H), 2.93 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.92 (s, 3 H), 4.20 (q, *J* = 7.2 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 1 H), 4.83 (dd, *J* = 7.2, 3.6 Hz, 1 H), 9.47 (d, *J* = 4.0 Hz, 1 H).- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1 (+, CH3), 26.36 (+, C-3), 34.86 (+, C-2), 54.00 (+, CO_2CH_3), 58.87 (+, C-1), 62.03 (-, CH_2), 156.59 (Cquart, CO), 156.86 (Cquart, CO), 168.13 (Cquart, CO_2Et), 192.13 (+, CHO). – IR (KBr): $\tilde{\nu}$ = 2985, 1779, 1751, 1724, 1708, 1445, 1312, 1290, 1208, 1005, 736 cm^{-1}.

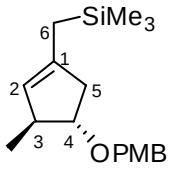
3. ((3*S*,4*S*)-4-(4-methoxybenzyloxy)-3-methylcyclopent-1-enyloxy) trimethylsilane (48)



Under a N_2 atmosphere LiCl (185 mg, 4.38 mmol, 0.3 eq.) and CuI (417mg, 2.19 mmol, 0.15 eq.) were dissolved in abs. THF (15 mL) and stirred for 15 min until a clear solution was obtained. Cyclopentenone (-)-**28** (3.2 g, 14.6 mmol, 1 eq.) (the synthesis of (-)-**28** was reported earlier with full characterization from *Reiser* group, see Ref 75) dissolved in abs. THF (14 mL) was added to the above mixture and stirred for further 20 min. and then cooled down to -78 ^{o}C before TMSCl (9.0 mL, 58.4 mmol, 4 eq.) was added dropwise. After an additional stirring for 20 min was added CH_3MgCl (3M sol. in THF, 22 mL, 66 mmol, 4.5 eq.) drop wise and stirred at -78 ^{o}C for 4 hrs. Et_3N (20.2 mL, 146 mmol, 10 eq.) was injected at once at the same temperature and warmed up to 0 ^{o}C before being poured into a pre-cooled *n*-pentane (150 mL). The yellow emulsion developed was filtered through celite pad under reduced pressure and washed with pre-cooled *n*-pentane. The filtrate was washed with pre-cooled sat. $NaHCO_3$ (4 x 10 mL) to give colorless solution. It was dried over Na_2SO_4, filtered, concentrated in *vacuo* to afford **48** (4.04 g, 90 %) as pale yellow oil and used without further purification.

R_f (hexanes: ethylacetate 75:25, Vanillin) = 0.5. - ^{1}H NMR (300 MHz): δ = 0.2 (s, 9H, $SiMe_3$), 1.03 (d, *J* = 6.92 Hz, 3H, 3-CH_3), 2.31-2.38 (m, 1H, 5-H_A), 2.52-2.60 (m, 1H, 5-H_B), 2.67-2.76 (m, 1H, 3-H), 3.64-3.70 (m, 1H, 4-H), 3.79 (s, 3H, OMe), 4.43 (d, *J* = 6.30 Hz, 2H, -O-CH_2), 4.47-4.49 (m, 1H, 2-H), 6.84-6.89 (m, 2H, PMB), 7.24-7.29 (m, 2H, PMB). - ^{13}C NMR (75 MHz): δ = 0.27 (+, $SiMe_3$), 20.06 (+, 3-Me), 40.40 (-, 5-C), 43.51 (+, 3-C), 55.53 (+, OMe), 71.00 (-, PMB), 84.29 (+, 4-C), 106.66 (+, 2-C), 114.01 (+, 2xPMB), 129.49 (+, 2xPMB), 130.98 (Cq, PMB), 151.04 (Cq, 1-C), 159.34 (Cq, PMB). - IR (neat) $\tilde{\nu}$ = 2956, 2903, 2866,1646, 1613, 1512, 1456, 1249, 1212, 1172, 1087, 1035, 942, 900, 844 cm^{-1}.

4. (((3*S*,4*S*)-4-(4-methoxybenzyloxy)-3-methylcyclopent-1-enyl)methyl)trimethylsilane ((+)-29)



Preparation of the Grignard reagent:

Mg curls (1.154g, 47.2 mmol, 3.6 eq.) and I_2 (catalytic) were stirred in abs. Et_2O (19 mL) under a N_2 atmosphere. At RT $TMSCH_2Cl$ (6.4 mL, 46.2 mmol, 3.6 eq.) was added slowly via a syringe to form the Grignard reagent.

$Ni(acac)_2$ – coupling:

The above freshly prepared $TMSCH_2MgCl$ (11 mL, 26.4 mmol, 2.4 mmol/mL, 2 eq.) was added to $Ni(acac)_2$ (542 mg, 2.11 mmol, 0.15 eq.) taken in a three neck schlenk flask under a N_2 atmosphere at room temperature to give a dark brown solution. The solution was set to reflux at 35 ^oC and to this was added crude **48** (4.04 g, 13.2 mmol, 1 eq.) drop wise over 15 min via a syringe. The mixture was refluxed for 16 h at 35 ^oC. When the starting material was disappeared completely, H_2O (5 mL) was added slowly to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with Et_2O (2x50 mL). The combined org. phase was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and subjected to silica gel column chromatography (PE: EA = 98:2). The desired allylsilane **29** (2.89 g, 62 %) was obtained as clear pale yellow oil.

R_f(hexanes: ethylacetate 80:20, Vanillin) = 0.8. $[\alpha]_D^{23}$ = + 23.6 (c = 0.55, $CHCl_3$).

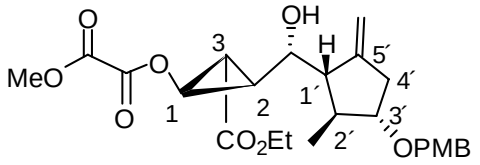
^{1}H NMR (300 MHz): δ = 0.01 (s, 9H, $SiMe_3$), 1.01 (d, *J* = 7.00 Hz, 3H, 3-CH_3), 1.51 (bs, 2H, CH_2-TMS), 2.23-2.30 (m, 1H, 5-H_A), 2.47-2.55 (m, 1H, 5-H_B), 2.7-2.8 (m, 1H, 3-H), 3.68-3.74 (m, 1H, 4-H), 3.80 (s, 3H, OMe), 4.45 (d, *J* = 3.62 Hz, 2H, -O-CH_2), 5.01 (bs, 1H, 2-H), 6.85-6.88 (m, 2H, PMB), 7.26-7.28 (m, 2H, PMB).

^{13}C NMR (75 MHz): δ = -0.9 (+, $SiMe_3$), 19.97 (+, 3-C), 22.01 (-, 6-C), 43.78 (-, 5-C), 46.60 (+, 3-C), 55.67 (+, O-Me), 71.06 (-, PMB), 87.17 (+, 4-C), 114.15 (+, 2xPMB), 126.24 (+, 2-C), 129.59 (+, 2xPMB), 131.38 (Cq, PMB), 138.43 (Cq, 1-C), 159.41 (Cq, PMB).

IR (neat) $\tilde{\nu}$ = 2953, 1612, 1512, 1455, 1346, 1298, 1172, 1083, 1037, 843, 447 cm^{-1}.

MS (EI, 70 eV): *m/z* (%): 121.1 (100), 73.1 (53), 183.1 (15), 209.1 (9), 304.2 (9) [M^+]. - HRMS: (EI, 70 eV): 304.1854 ($C_{18}H_{28}O_2Si$: cal. 304.1859 [M^+]).

5. (1R,2S,3R)-2-((R)-((1´S,2´S,3´S)-2´-methyl-3´-(p-methoxybenzyloxy)-5´ methylenecyclopentyl)(hydroxy)methyl)-3-(ethoxycarbonyl)cyclopropylmethyl oxalate (50)



A solution of (+)-**15** (1.45 g, 5.94 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was cooled down to -78 ^oC under N_2 atmosphere. BF_3·Et_2O (0.72 mL, 6.5 mmol) was added via syringe and stirred for 20 min. Allylsilane (+)-**29** (1.9 g, 6.25 mmol) in CH_2Cl_2 (10 mL) was added subsequently via syringe drop wise for 15 min. The resulting brown solution was stirred for 16 h at -78 ^oC, and then it was quenched with sat. $NaHCO_3$ (2 mL), allowed to warm up to room temperature. The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (5 X2 mL). The combined org. layers were washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to yield **50** (4.4 g, 80%). The yellowish oil thus obtained (as a single stereoisomer) was used without further purification.

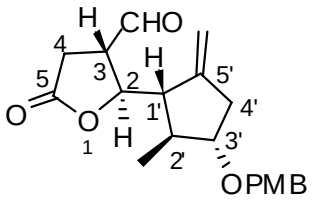
R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.42.

^{1}H NMR (300 MHz): δ = 1.26 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.87-1.94 (m, 1H, 2-H), 2.21 (dd, *J* = 6.03, 2.58 Hz, 1H, 3-H), 2.28-2.37 (m, 1H, 1`-H), 2.41-2.48 (m, 1H, 2`-H), 2.55-2.63 (m, 2H, 4`-H), 3.57-3.61 (m, 1H, 3`-H), 3.77-3.80 (m, 1H, CHOH), 3.79 (s, 3H, PMB), 3.88 (s, 3H, CO_2Me), 4.09-4.21 (m, 2H, CH_2PMB), 4.39-4.49 (q, *J* = 7.1 Hz, CH_2CH_3), 4.7 (dd, *J* = 7.2, 2.6 Hz, 1H, 1-H), 5.02-5.03 (m, 1H, C=CH_2), 5.10-5.11 (m, 1H, C=CH_2), 6.84-6.87 (m, 1H, PMB), 7.21-7.24 (m, 1H, PMB) .

^{13}C NMR (75 MHz): δ = 14.16 (+, CH_2CH_3), 19.97 (+, 2`-$CH_3$), 25.52 (+, 3-C), 30.80 (+, 2-C), 38.25 (-, 4`-C), 39.54 (+, 2`-C), 53.7 (+, PMB), 55.28 (+, OMe), 55.50 (+, 1-C), 58.86 (+, 1`-C), 61.25 (-, CH_2CH_3), 70.20 (-, PMB), 70.86 (+, C-OH), 84.01 (+, 3`-C), 108.89 (-, C=CH_2), 113.90 (+, 2xPMB), 129. 19 (Cq, PMB), 129.43 (+, 2xPMB), 149.74 (Cq, C=CH_2), 157.12 (Cq, CO), 157.36 (Cq, CO), 159.30 (Cq, PMB), 170.90 (Cq, CO_2Et).

IR (neat) $\tilde{\nu}$ = 3499, 3427, 2956, 1778, 1754, 1726, 1612, 1513, 1455, 1372, 1309, 1248, 1159, 1093, 1034, 828, 448 cm^{-1}.

6. (2*R*,3*S*)-2-((1′*S*,2′*S*,3′*S*)-3′-(4-methoxybenzyloxy)-2′-methyl-5′-methylenecyclopentyl) Oxotetrahydrofuran-3-carbaldehyde (30)



The crude cyclopropylalcohol **50** (4.4 g, 9.23 mmol, 1 eq.) was dissolved in MeOH (15 mL) and cooled down to 0 °C. $Ba(OH)_2$ x 8 H_2O (1.863 g, 5.9 mmol, 0.65 eq.) was added portion wise over a period of 2 h and the mixture was stirred for additional 1 h at 0 °C. After removal of approximately 80 % volume of MeOH under reduced pressure at rt, CH_2Cl_2 (50 mL) and H_2O are added and the org. phase was separated. The aqueous phase was again extracted with CH_2Cl_2 (25 X2 mL). The combined org. layers were dried over Na_2SO_4, filtered, concentrated in *vacuo.* This was then purified by silica gel column chromatography (PE: EA= 3:1) to afford **30** (2.1 g, 62 %, over two steps) as a single diastereomer, as colorless oil.

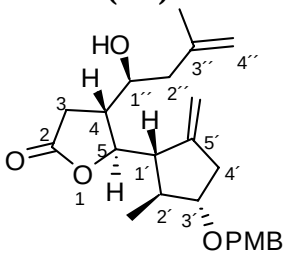
R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.35. $[\alpha]_D^{23}$ = +74.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.05 (d, *J* = 6.9 Hz, 3H, 2′-Me), 2.10 - 2.20 (m, 1H, 2′-H), 2.33 - 2.41 (m, 1H, 4`-H), 2.45 - 2.50 (m, 1H, 1′-H), 2.64 – 2.78 (m, 2H, 4′-H & 4-H), 2.90 (dd, *J* = 7.0, 7.1 Hz, 1H, 4-H), 3.31 – 3.39 (m, 1H, 3-H), 3.51 – 3.57 (m, 1H, 3′-H), 3.79 (s, 3H, OMe), 4.42 (s, 2H, PMB), 4.91 (dd, *J* = 6.1 Hz, 2H), 5.03 – 5.11 (m, 2H, C=CH_2), 6.85 – 6.88 (m, 2H, PMB), 7.21 - 7.24 (m, 2H, PMB), 9.61 (d, *J* = 0.9 Hz, 1H, CHO).

^{13}C NMR (75 MHz): δ = 18.24 (+, 2′- CH_3), 29.43 (-, 4-C), 39.73 (-, 4`-C), 41.55 (+, 2′-C), 49.54 (+, 3-C), 54.01 (+, 1`-C), 55.30 (+, O-Me), 71.17 (-, PMB), 80.49 (+, 2-C), 84.19 (+,3′-C), 112.48 (-, =CH_2), 113.87 (+, 2xPMB), 129.32 (+, 2xPMB), 130.19 (Cq, PMB), 146.78 (Cq, 5′-C), 159.27 (Cq, PMB), 174.30 (Cq, 5-C), 197.41 (+, CHO).

IR (neat) $\tilde{\nu}$ = 3000, 2860, 2840, 1778, 1727, 1610, 1512, 1458, 1354, 1248, 1175, 1089, 1032, 821 cm^{-1}. - MS (EI, 70 eV): *m/z* (%):121.1 (100), 137.0 (34.9), 138 (3.6) 344.2 (1.2) [M^+]. - HRMS: (EI, 70 eV): 344.1631 ($C_{20}H_{24}O_5$: cal. 344.1624 [M^+]).

7. (4*R*,5*R*)-4-((S)-1´´-hydroxy-3´´-methylbut-3´´-enyl)-5-((1´*S*,2´*S*,3´*S*)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl)dihydrofuran-2(3H)-one (1´´ S: 1´´ R=80:20) (54)



A solution of γ-butyrolactone carbaldehyde **30** (608 mg, 1.76 mmol, 1 eq.) in CH_2Cl_2 (4 mL) was cooled down to -78 °C. Under a N_2 atmosphere 2-Methylallyltrimethyl silane (460 μL, 2.64 mmol, 1.5 eq.) was injected at once and the resulting solution was stirred for 15 min. BF_3 ˙Et_2O (210 μL, 1.9 mmol, 1.07 eq.) was added to this mixture *via* syringe over 5 min and the mixture was stirred at -78 °C for 16 h. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the reaction mixture was quenched with $NaHCO_3$ (2 mL) and was slowly warmed up to ambient temperature. The org. phase was separated, the aqueous phase was again extracted with CH_2Cl_2 (2X5 mL). The combined org. phases were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by silica gel column chromatography (PE: EA= 3:1) afforded **54** (494 mg, 70%) as a 4:1 diastereomeric mixture, as colorless oil.

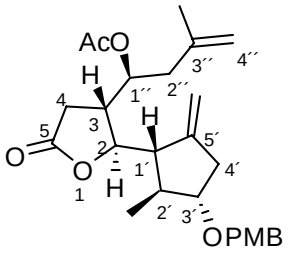
R_f (hexanes: ethylacetate 60:40, Vanillin) = 0.61.

^{1}H NMR (300 MHz): δ = 1.02 (d, *J* = 6.8 Hz, 3H, 2`-Me), 1.69 (s, 3H, 3``-Me), 1.81-1.83 (bs, 1H, OH), 2.01-2.04 (m, 2H, 2``-H), 2.08-2.16 (m, 1H, 1`-H), 2.27-2.45 (m, 4H, 2`-H, 3-H, 4`-H, 4-H), 2.57 (dd, *J* = 20.0, 5.1 Hz, 1H, 3-H), 2.67-2.69 (m, 1H, 4`-H), 3.45-3.51 (m, 1H, 3`-H), 3.69-3.75 (m, 1H, 1``-H), 3.78 (s, 3H, OMe), 4.44 (bs, 2H, PMB, diast: 4.45), 4.66 (dd, *J* = 4.5, 1.2 Hz, 1H, 5-H), 4.77 (bs, 1H, =CH_2), 4.90 (m, 1H, =CH_2), 4.95 (bs, 1H, =CH_2), 5.03 (bs, 1H, =CH_2), 6.83-6.86 (m, 2H, PMB), 7.22-7.25 (m, 2H, PMB).

^{13}C NMR (75 MHz): δ = 18.25 (+, 2`-CH_3), 22.23 (+, 3``-$CH_3$), 29.21 (-, 4`-C), 40.13 (-, 3-C), 41.04 (+, 4-C), 42.27 (+, 2`-C), 43.86 (-, 2``-C), 53.53 (+, 1`-C), 55.30 (+, O-CH_3), 68.22 (+, 1``-C), 71.33 (-, PMB*C*$H_2$), 83.79 (+, 5-C), 84.26(+, 3`-C), 111.44 (-, =$CH_2$), 113.84 (+, 2xPMB), 114.62 (-, =$CH_2$), 129.35 (+, 2xPMB), 130.41 (Cq, PMB), 141.41 (Cq, 3``-C), 147.08 (Cq, PMB), 159.23 (Cq, 5`-C), 176.94 (Cq, 2-C).

IR (neat) $\tilde{\nu}$ = 3461, 2994, 2886, 1770, 1651, 1613, 1514, 1455, 1355, 1300, 1249, 1179, 1092, 1034, 896, 821, 759, 456 cm^{-1}. - MS (CI, NH_3): *m/z* (%) = 121.1 (14.80), 138.1 (6.12), 154.1 (6.46), 418.2 (100) [M + NH_4^+]. - HRMS: (EI, 70 eV): 400.2247 ($C_{24}H_{32}O_5$: cal. 400.2250 [M^+]).

8. (S)-1´´-((2R,3R)-2-((1´*S*,2´*S*,3´S)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylene-cyclopentyl)-5-oxotetrahydrofuran-3-yl)-3´´-methylbut-3´´-enyl acetate (1´´ S: 1´´ R=80:20) (55)



To a solution of **54** (550 mg, 1.37 mmol, 1 eq.) in CH_2Cl_2 (5 mL) was added DMAP (16.7 mg, 0.137 mmol), Et_3N (0.482 mL, 3.43 mmol), Ac_2O (0.259 mL, 2.74 mmol) and stirred at room temperature for 24 h. The reaction mixture was quenched with H_2O (1mL) and the layers were separated. The org. phase was washed with $NaHCO_3$ (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column chromatography (PE: EA= 4:1) to afford **55** (516 mg, 85%) as colorless oil (*dr* = 4:1).

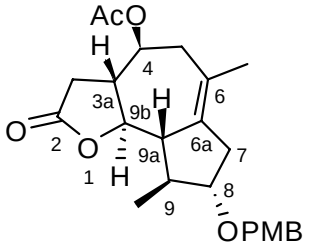
R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.76.

^{1}H NMR (300 MHz): δ = 1.02 (d, *J* = 6.8 Hz, 3H, 2`-Me), 1.70 (s, 3H, 3``-Me), 1.94 (s, 3H, OAc, diast: 1.98), 2.17-2.23 (m, 1H, 4`-H), 2.25-2.31 (m, 3H, 2``-H & 1`-H), 2.59 (bs, 2H, 4-H), 2.66-2.73 (m, 1H, 4`-H), 3.46-3.52 (m, 1H, 3`-H), 3.77 (s, 3H, OMe), 4.42 (d, *J* = 2.2 Hz, 2H, PMB-CH_2), 4.45-4.46 (m, 1H, 2-H), 4.70 (bs, 1H, =CH_2), 4.79 (m, 1H, =CH_2), 4.93 (bs, 1H, =CH_2), 5.04 (bs, 1H, =CH_2), 5.13-5.18 (m, 1H, 1``-H), 6.83-6.86 (m, 2H, PMB), 7.21-7.24 (m, 2H, PMB).

^{13}C NMR (75 MHz): δ = 18.32 (+, 2`-CH_3), 20.77 (+, 3``-$CH_3$), 22.19 (+, OAc), 29.30 (-, 4`-C), 39.59 (-, 4-C), 40.44 (+, 3-C), 40.98 (-, 2``-C), 41.14 (+, 2`-C), 54.16 (+, 1`-C), 55.23 (+, O-CH_3), 71.06 (-, PMB), 71.15 (+, 1``-C), 83.42 (+, 2-C), 84.35 (+, 3`-C), 111.49 (-, =$CH_2$), 113.74 (+, 2xPMB), 114.28 (-, =$CH_2$), 129.16 (+, 2xPMB), 130.51 (Cq, PMB), 140.48 (Cq, 3``-C), 147.26 (Cq, PMB), 159.12 (Cq, 5`-C), 170.30 (Cq, 5-C), 176.05 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 2959, 2934, 1776, 1738, 1610, 1514, 1455, 1373, 1298, 1242, 1174, 1091, 1033, 948, 897, 824, 736 cm^{-1}. - MS (EI, 70 eV): *m/z* (%):121.1 (100), 137.1 (29.41), 151.1 (6.97), 191.1 (2.93), 246.2 (6.17), 442.2 (1.17) [M^+]. - HRMS: (EI, 70 eV): 442.2360 ($C_{26}H_{34}O_6$: cal. 442.2655 [M^+]).

9. (3aR,4S,8S,9S,9aS,9bR)-8-(4-methoxybenzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (56)



In a 25-mL schlenk flask equipped with a condenser, **55** (250 mg, 0.565 mmol, 1 eq.) was dissolved in abs. Toluene (5 mL). A gentle stream of argon was introduced into the solution throughout the reaction and the reaction set up was put down into a preheated 90 ^{o}C oil bath. Grubbs' II catalyst (24 mg, 0.028 mmol, 5 mol %) dissolved in abs. Toluene (1 mL) was added followed by two additional 5 mol% batches every 2 h (total catalyst loading 15 mol%, reaction time 6 h). After cooling the solution to room temperature the solvent was removed under reduced pressure and chromatography on flash silica gel (PE : EA=2:1) afforded **56** (202 mg, 86 %) as pure single diastereomer and *epi*-**56** (36 mg) as pure single diastereomer.

Major Isomer:

R_f(hexanes: ethylacetate 70:30, Vanillin) = 0.61. $[\alpha]_D^{23}$ = + 28.8 (c = 0.645, $CHCl_3$).

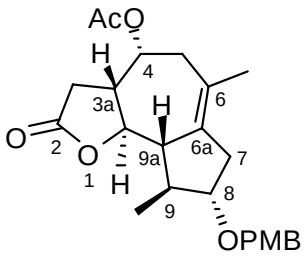
^{1}H NMR (300 MHz): δ = 1.04 (d, *J* = 6.8 Hz, 3H, 9-Me), 1.72 (s, 3H, 6-Me), 2.00 (s, 3H, OAc), 2.15 (dd, *J* = 11.42, 2.38 Hz, 1H, 3-H_A), 2.28-2.48 (m, 7H, 3-H_B, 3a-H, 5-H_B, 7-H, 9-H , 9a-H) 2.54 (d, *J* = 9.49 Hz, 1H, 5-H_A), 3.44-3.51 (m, 1H, 8-H), 3.75 (s, 3H, OMe), 3.89 (t, *J* = 9.94 Hz, 1H, 9b-H), 4.42 (bs, 2H, PMB-*CH_2*), 4.59-4.66 (m, 1H, 4-H), 6.83 (d, *J* = 8.67 Hz, 2H, PMB), 7.21 (d, *J* = 8.64 Hz, 2H, PMB).

^{13}C NMR (75 MHz): δ = 18.83 (+, 9-CH_3), 21.06 (+, 6-CH_3), 23.57 (+, OAc), 35.14 (-, 7-C), 36.99 (-, 3-C), 41.22 (-, 5-C), 42.11 (+, 9-C), 52.37 (+, 3a-C), 53.33 (+, 9a-C), 55.23 (+, O-CH_3), 70.63 (-, PMB), 70.82 (+, 8-C), 83.73 (+, 9b-C), 83.91 (+, 4-C), 113.78 (+, 2xPMB), 126.22 (Cq, C-6), 129.27 (+, 2xPMB), 130.56 (Cq, PMB), 136.27 (Cq, C-6a), 159.13 (Cq, PMB), 169.97 (Cq, 2-C), 174.63 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 2362, 1783, 1738, 1514, 1242, 1030, 946 cm^{-1}.- MS (EI, 70 eV): *m/z* (%): 77 (33.54), 121.1 (100), 146.0 (36.53), 253.9 (40.70), 287.0 (21.70), 414.2 (3.23) [M^+]. - HRMS: (EI, 70 eV): 414.2046 ($C_{24}H_{30}O_6$: cal. 414.2042 [M^+]).

Minor Isomer:

(3aR,4R,8S,9S,9aS,9bR)-8-(4-methoxybenzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5, 7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (56*epi*)



R_f(hexanes: ethylacetate 70:30, Vanillin) = 0.55. $[\alpha]_D^{23}$ = - 29.4 (c = 0.486, $CHCl_3$).

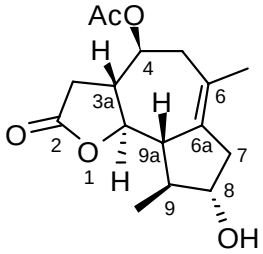
^{1}H NMR (300 MHz): δ = 1.11 (d, *J* = 6.5 Hz, 3H, 9-Me), 1.65 (s, 3H, 6-Me), 2.06 (s, 3H, OAc), 2.30-2.41 (m, 7H, 3-H_B, 3a-H, 5-H_B, 7-H, 9-H, 9a-H), 2.55 (dd, *J* = 9.24, 6.0 Hz, 1H, 3-H_A), 2.69 (dd, *J* = 10.16, 6.13 Hz, 1H, 5-H_A), 3.44-3.51 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 4.13-4.20 (m, 1H, 9b-H), 4.48 (bs, 2H, PMB-*CH_2*), 5.11 (d, *J* = 5.9, 1H, 4-H), 6.87 (d, *J* = 8.63 Hz, 2H, PMB), 7.26 (d, *J* = 8.57 Hz, 2H, PMB).

^{13}C NMR (75 MHz): δ = 18.84 (+, 9-CH_3), 20.98 (+, 6-CH_3), 24.60 (+, OAc), 33.10 (-, 7-C), 37.04 (-, 3-C), 37.90 (-, 5-C), 42.87 (+, 9-C), 51.26 (+, 3a-C), 53.22 (+, 9a-C), 55.30 (+, O-CH_3), 67.85 (-, PMB), 70.91 (+, 8-C), 81.46 (+, 9b-C), 83.99 (+, 4-C), 113.78 (+, 2xPMB), 126.35 (Cq, C-6), 129.22 (+, 2xPMB), 130.72 (Cq, PMB), 134.91 (Cq, C-6a), 159.13 (Cq, PMB), 170.57 (Cq, 2-C), 174.93 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 2362, 1783, 1738, 1514, 1242, 1030, 946 cm^{-1}.

MS (EI, 70 eV): *m/z* (%): 77 (33.54), 121.1 (100), 146.0 (36.53), 253.9 (40.70), 287.0 (21.70), 414.2 (3.23) [M^+]. - HRMS: (EI, 70 eV): 414.2046 ($C_{24}H_{30}O_6$: cal. 414.2042 [M^+]).

10. (3aR,4S,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydro-azuleno[4,5-b]furan-4-yl acetate (60)



To a solution of **55** (220 mg, 0.531 mmol, 1eq.) in CH_2Cl_2 (5 mL) were added pH 7.2 buffer (1 mL), DDQ (156 mg, 0.690mmol) and stirred at room temperature for 4 h. After the completion of reaction as indicated by TLC (PE: EA =1:1), the mixture was diluted to (8 mL) and quenched with H_2O (2 mL). The layers were separated and the aqueous phase was gain extracted with CH_2Cl_2 (3 X 2mL). The combined org. phases were dried over Na_2SO_4 and concentrated in *vacuo.* Purification on silica gel (PE: EA=3:2) afforded **60** (141 mg, 90%) as a white solid, which was recrystallized from *n*-pentane-CH_2Cl_2 mixture, which on single crystal X-ray analysis gave the crystal structure of **60**.

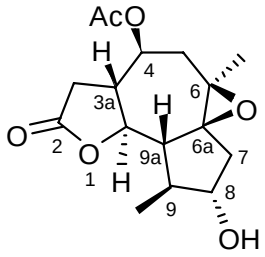
R_f (hexanes: ethylacetate 60:40, Vanillin) = 0.34. mp = 106–107 ^oC. $[\alpha]_D^{23}$ = + 3.0 (c = 1.3, $CHCl_3$).

^1H NMR (300 MHz): δ = 1.05 (d, *J* = 6.8 Hz, 3H), 1.70 (s, 3H), 1.98 (s, 3H), 2.04-2.17 (m, 3H), 2.25-2.41 (m, 5H), 2.50-2.64 (m, 2H), 3.68-3.64 (m, 1H), 3.85-3.91 (m, 1H), 4.58-4.66 (m, 1H).

^{13}C NMR (75 MHz): δ = 17.37 (+, 9-CH_3), 20.08 (+, 6-CH_3), 22.58 (+, OAc), 34.07 (-, 7-C), 38.50 (-, 3-C), 40.16 (-, 5-C), 44.96 (+, 9-C), 51.28 (+, 3a-C), 52.21 (+, 9a-C), 69.85 (+, 8-C), 76.64 (+, 9b-C), 83.07 (+, 4-C), 125.33 (Cq, C-6), 134.61 (Cq, C-6a), 169.09 (Cq, 2-C), 173.74 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 3441, 2960, 2845, 1769, 1735, 1440, 1373, 1240, 1146, 1068, 1029, 992, 964, 799, 460 cm^{-1}.- MS (EI, 70 eV): *m/z* (%): 43.0 (100), 55.0 (12.92), 79.1 (10.02), 91.0 (14.34), 105.0 (12.17) 145.0 (16.25), 159.2 (11.05), 234.2 (13.24). - PI- LSIMS (MeOH / Glycerin): 217.2 (100), 235.3 (90.0), 295.3 (86) [M+H^+], 387.4 (42) [M+H^++gly]. - HRMS: (EI, 70 eV): 295.1547 ($C_{16}H_{23}O_5$: cal. 295.1545 [M+H^+]).

11. (3aR,4S,6S,6aR,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (61)



Halohydrin method

To a solution of **60** (22 mg, 0.074 mmol, 1 eq.) and $NaBrO_3$ (22 mg, 0.14 mmol) in CH_3CN (1 mL) and H_2O (2 mL) was added 1 M solution of $NaHSO_3$ (30 mg, 0.29 mmol) drop wise and the reaction mixture was stirred at room temperature for more than 48 h. After the reaction, the resulting solution was extracted with diethyl ether (2 x 2 mL). Then the combined organic layers were washed with aqueous Na_2SO_3, brine and dried over Na_2SO_4. After filtration, the solvent was evaporated in *vacuo* to give crude material which was purified by silica gel column chromatography (PE: EA= 3:2) to afford **61** (18.4 mg, 80%) as pure single diastereomer, as colorless oil. Crystallization from pentane-CH_2Cl_2 mixture at 0 ^oC afforded crystalline product which on single crystal X-ray analysis gave the crystal structure of **61**.

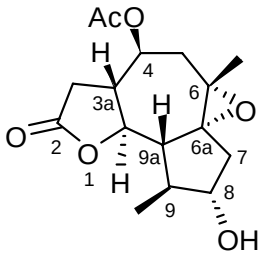
R_f (hexanes: ethylacetate 65:35, Vanillin) = 0.37. mp = 171-172 ^oC $[\alpha]_D^{23}$ = + 30.7 (c = 1.32, $CHCl_3$).

^1H NMR (300 MHz): δ = 1.14 (d, *J* = 7.2 Hz, 3H), 1.43 (s, 3H), 1.75-1.81 (m, 2H), 1.90-1.92 (m, 1H), 2.05 (d, *J* = 6.20 Hz, 1H), 2.07 (s, 3H), 2.12-2.15 (m, 1H), 2.32-2.46 (m, 4H), 2.62-2.66 (m, 1H), 4.14-4.16 (m, 1H), 4.35 (t, *J* = 10.66 Hz, 1H), 4.84-4.88 (m, 1H).

^{13}C NMR (75 MHz): δ = 18.11 (+, 9-CH_3), 20.96 (+, 6-CH_3), 21.44 (+, OAc), 35.20 (-, 7-C), 39.37 (-, 3-C), 44.85 (-, 5-C), 45.57 (+, 9-C), 52.27 (+, 3a-C), 54.55 (+, 9a-C), 57.93 (+, 8-C), 70.08 (+, 9b-C), 70.76 (Cq, 6a-C), 77.29 (Cq, 6-C), 81.50 (+, 4-C), 169.96 (Cq, 2-C), 174.06 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 3480, 2590, 2586, 1780, 1732, 1350, 1237, 1010, 992, 964, 799, 460 cm^{-1}. - MS [PI- LSIMS (CH_2Cl_2/MeOH / Glycerin)]: *m/z* (%): 277.3 (100), 311.3 (11.0) [$M+H^+$], 369.4 (43.2), 403.3 (14) [$M+H^+$+gly]. - HRMS: (EI, 70 eV): 311.1502 ($C_{16}H_{23}O_6$: cal. 311.1495 [$M+H^+$]).

12. (3aR,4S,6R,6aS,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (62)



VO(acac)$_2$ mediated epoxidation

To a solution of **60** (120 mg, 0.406 mmol, 1eq.) in CH_2Cl_2 (4 mL) under a N_2 atmosphere at 0 ^{0} C was added *tert*-butyl Hydroperoxide (3M sol in Toluene, 0.20 mL, 0.60 mmol) and $VO(acac)_2$ (2.1 mg, 2 mol%) and stirred for 16 h at room temperature. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the reaction mixture was quenched with sat. $NaHSO_3$ sol. (1 mL). The layers were separated and the aqueous phase was once again extracted with CH_2Cl_2 (2 x 3 mL). The combined org. phases were washed with H_2O, brine, dried over Na_2SO_4, and concentrated in *vacuo.* Purification on silica gel column chromatography (PE: EA= 3:2) afforded **62** (98 mg, 78%) as pure single diastereomer, as colorless oil.

R_f(hexanes: ethylacetate 70:30, Vanillin) = 0.41. $[\alpha]_D^{23}$ = + 42.4 (c = 0.896, $CHCl_3$).
^{1}H NMR (300 MHz): δ = 1.22 (d, *J* = 6.74 Hz, 3H), 1.33 (s, 3H), 1.63-1.70 (m, 1H), 1.86-1.92 (m, 1H), 2.03 (s, 3H), 2.05-2.12 (m, 3H), 2.30-2.36 (m, 2H), 2.40-2.54 (m, 3H), 3.74-3.80 (m, 1H), 4.07-4.21 (m, 1H), 4.87-4.96 (m, 1H).

^{13}C NMR (75 MHz): δ = 18.78 (+, 9-CH_3), 21.02 (+, 6-CH_3), 23.24 (+, OAc), 34.28 (-, 7-C), 39.60 (-, 3-C), 40.26 (-, 5-C), 47.43 (+, 9-C), 50.73 (+, 3a-C), 50.95 (+, 9a-C), 59.96 (+, 8-C), 69.83 (+, 9b-C), 70.84 (Cq, 6a-C), 77.27 (Cq, 6-C), 81.90 (+, 4-C), 169.77 (Cq, 2-C), 174.79 (Cq, OAc).

IR (neat) $\tilde{\nu}$ = 3438, 2910, 1782, 1739, 1595, 1373, 1237, 1035 cm^{-1}. - MS (EI, 70 eV): *m/z* (%): 43.1 (100), 59.1 (21.8), 72.1 (12.54), 126.1 (5.01), 250.1 (23.59), 292.1 (2.0) [M^+-H_2O]. - HRMS: (EI, 70 eV): 292.1312 ($C_{16}H_{20}O_5$: cal. 292.1311 [M^+-H_2O]).

***m*CPBA method:** To a solution of **60** (50 mg, 0.169 mmol, 1 eq.) in CH_2Cl_2 (5 mL) under a N_2 atmosphere at -10 ^{o}C was added *m*CPBA (70% w/w, 2 eq., 82.5mg, 0.338 mmol) at once at this

temperature and the solution was stirred for 6 hours, while the reaction mixture was slowly warmed up to room temperature. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the reaction mixture was quenched with sat. $NaHCO_3$ sol. (1 mL). The layers were separated and the aqueous phase was once again extracted with CH_2Cl_2 (2 x 2 mL). The combined org. phases were washed with H_2O, brine, dried over Na_2SO_4, and concentrated in *vacuo.* Purification on silica gel column chromatography (PE: EA= 4:1) afforded mixture of diastereomeric epoxides **61** and **62** (45 mg, 85%, 3:1 ratio respectively) as colorless oil.

Dioxirane method:

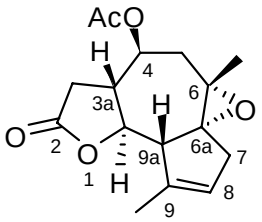
a) Biphasic method:

A cold solution of potassium peroxomonosulfate ($KHSO_5$) (49 mg, 0.0813 mmol, 1.5 eq.) in water (0.5 mL), was added dropwise slowly to a stirred biphasic mixture of CH_2C1_2 (2 mL) and buffered (pH 7.2) water (0.5 mL) kept at 0 ^oC and containing **60** (16 mg, 0.0542 mmol, 1 eq.), acetone (40 μL, 0.1 mol), and 18-crown-6 (2.86 mg, 0.0108 mmol). After the completion of addition the reaction was stirred for 6 hours at the same temperature and finally after the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the acetone was removed at rotavapour followed by the extraction of the mixture with CH_2C1_2. The layers were separated and the aqueous phase was once again extracted with CH_2Cl_2 (2 x 2 mL). The combined org. phases were washed with H_2O, brine, dried over Na_2SO_4, and concentrated in *vacuo* to afford a mixture of product and 18-crown-6. Purification on silica gel column chromatography (PE: EA= 4:1) separated 18-crown-6 and afforded mixture of diastereomeric epoxides **61** and **62** (11 mg, 65%, 88:12 ratio respectively) as colorless oil.

b) Monophasic method:

A cold solution of potassium peroxomonosulfate ($KHSO_5$) (49 mg, 0.0813 mmol, 1.5 eq.) in water (0.5 mL), was added dropwise slowly to a stirred 1M solution of acetone and water (4:1) containing **60** (16 mg, 0.0542 mmol, 1 eq.), acetone (40 μL, 0.1 mol), and $NaHCO_3$ (0.0813 mmol 1.5 eq.) stirred for 6 hours while the reaction mixture was slowly warmed up to room temperature. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the acetone was removed at rotavapour followed by the extraction of the mixture with CH_2C1_2. The organic phase was washed with sat. Na_2SO_3 sol. (1 mL), followed by washing with H_2O, brine, dried over Na_2SO_4, and concentrated in *vacuo.* Purification on silica gel column chromatography (PE: EA= 4:1) afforded mixture of diastereomeric epoxides **61** and **62** (12 mg, 70%, 84:16 ratio respectively) as colorless oil.

13. (3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (70)



A solution of **62** (91 mg, 0.293 mmol, 1 eq.) in CH_2Cl_2 (5 mL) under a N_2 atmosphere was cooled to -10 ^oC and added pyridine (0.118 mL, 1.46 mmol). To this mixture Tf_2O (0.074 mL, 0.44 mmol) was added drop wise and the reaction mixture was stirred for 18 h while the temperature was increased slowly to 0 ^oC. The reaction mixture was quenched with $NaHCO_3$ (1 mL), diluted with CH_2Cl_2 (2 mL) and the layers were separated. The aqueous layer was extracted once again with CH_2Cl_2 (2 x 2 mL), the combined org. phases were dried, filtered and concentrated in *vacuo*. Purification on silica gel column chromatography (PE: EA= 4:1) afforded **70** (53 mg, 62%) as a colorless solid.

R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.7. $[\alpha]_D^{23}$ = + 67.9 (c = 0.53, $CHCl_3$).

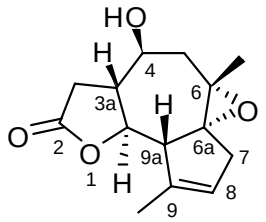
^{1}H NMR (300 MHz):δ = 1.34 (s, 3H), 1.91 (bs, 3H), 2.03 (s, 3H), 2.06-2.10 (m, 1H), 2.13-2.20 (m, 2H), 2.29-2.39 (m, 2H), 2.45-2.53 (m, 1H), 2.72-2.79 (m, 1H), 2.86-2.92 (m, 1H), 4.16-4.22 (m, 1H), 4.91-4.99 (m, 1H), 5.55 (s, 1H).

$^{-13}$C NMR (75 MHz): δ = 18.17 (+, 9-CH_3), 21.04 (+, 6-CH_3), 22.55 (+, OAc), 33.95 (-, 7-C), 39.35 (-, 3-C), 39.54 (-, 5-C), 51.64 (+, 3a-C), 60.57 (Cq, 6-C), 69.83 (+, 9a-C), 72.15 (Cq, 6a-C), 80.91 (+, 9b-C), 124.92 (+, 8-C), 140.24 (Cq, 9-C), 169.75 (Cq, 2-C), 174.91 (Cq, OAc).-

IR (neat) $\tilde{\nu}$ = 2923, 1788, 1739, 1595, 1425, 1237, 1033. cm^{-1}.

MS (CI, NH_3): *m/z* (%) = 103.2 (3.26), 310.2 (100) [M + NH_4^+], 311.2 (15.99), 327.2 (4.25) [M+ NH_4^++ NH_3^+] HRMS: (EI, 70 eV): 292.1316 ($C_{16}H_{20}O_5$: cal. 292.1311 [M^+]).

14. (3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl hydroxide (72)



To a solution of **70** (40 mg, 0.136 mmol, 1.0 eq.) in MeOH (4 ml) was cooled to 0 °C. K_2CO_3 (10 mg, 0.230 mmol, 0.55 eq.) was added and the mixture was stirred for 4 h at 0 °C while the reaction mixture was warmed up to RT slowly. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), the solvent MeOH was evaporated at rotavapour at RT by applying vacuum. The residue was dissolved in Et_2O (5 ml) and the mixture was extracted, washed with $NaHCO_3$ (1 ml), H_2O (1 ml) and brine (2 ml). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes: ethylacetate 70:30) to give **72** (24 mg, 70%) product as a colorless solid, which up on crystallization from pentane-CH_2Cl_2 mixture at 0 ^oC afforded crystalline product which on single crystal X-ray analysis gave the crystal structure of **72**.

R_f (hexanes: ethylacetate 1:1, Vanillin) = 0.3. mp = 124-125 ^oC, $[\alpha]_D^{23}$ = + 101.7. (c = 0.93, $CHCl_3$).

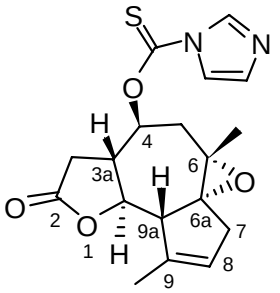
^1H NMR (300 MHz): δ = 1.30 (s, 3H), 1.60-1.68 (m, 1H), 1.87 (bs, 3H), 1.90-1.99 (m, 1H), 2.01-2.06 (m, 1H), 2.09-2.14 (m, 1H), 2.25-2.32 (m, 1H), 2.34-2.39 (m, 1H), 2.59-2.69 (m, 1H), 2.74-2.75 (m, 1H), 2.851 (d, *J* = 10.624 Hz, 1H), 3.63-3.73 (m, 1H), 4.02-4.12 (m, 1H), 5.50 (s, 1H).

^{13}C NMR (75 MHz): δ = 18.20 (+, 9-CH_3), 22.75 (+, 6-CH_3), 34.32 (-, 7-C), 39.41 (-, 3-C), 43.55 (-, 5-C), 51.66 (+, 3a-C), 53.85 (+, 9a), 60.85 (Cq, 6-C), 67.88 (+, 4-C), 72.52 (Cq, 6-Ca), 81.22 (+, 9b-C), 124.74 (+, 8-C), 140.46 (Cq, 9-C), 175.82 (Cq, 2-C).

IR (neat) $\tilde{\nu}$ = 3434, 2923, 1781, 1176, 1099, 1045, 842 cm^{-1}.

MS (CI, NH_3): *m/z* (%) = 180.1 (3.75), 251.1 (1.42) [$M+H^+$], 268.2 (100) [$M + NH_4^+$], 285.2 (6.32) [$M + NH_4^+ + NH_3^+$]. - HRMS: (EI, 70 eV): 250.1211 ($C_{14}H_{18}O_4$: cal. 250.1205 [M^+])

15. (3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl-1´H-imidazole-1´-carbothioate (74)



To a solution of **72** (18 mg, 0.072 mmol, 1 eq.) in CH_2Cl_2 under N_2 atmosphere, was added thiocarbonyldiimidazole (38 mg, 0.216 mmol) and DMAP (4 mg, 0.03 mmol) and the resulting solution was stirred at room temperature for 4 h. After the completion of reaction, solvent was removed under reduced pressure and the resulting crude material was purified by column chromatography on silica gel (PE: EA =1:1) to afford **74** (20.7 mg, 80%) as pure pale yellow colored oil.

R_f(hexanes: ethylacetate 1:1, Vanillin) = 0.39. $[\alpha]_D^{23}$ = + 86.4. (c = 0.39, $CHCl_3$)

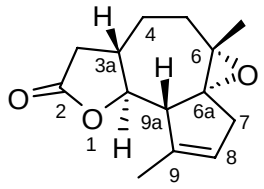
^{1}H NMR (300 MHz): δ = 1.39 (s, 3H), 1.94 (bs, 3H), 2.0 (s, 1H), 2.14-2.20 (m, 1H), 2.26-2.34 (m, 1H), 2.43-2.45 (m, 1H), 2.48-2.52 (m, 1H), 2.53-2.59 (m, 1H), 2.62-2.68 (m, 1H), 2.77-2.84 (m, 1H), 2.96-3.0 (m, 1H), 4.0-4.1 (m, 1H), 4.2-4.3 (m, 1H), 5.5 (s, 1H), 5.70-5.77 (m, 1H), 7.05 (s, 1H).

^{13}C NMR (75 MHz): δ = 18.15 (+, 9-CH_3), 22.42 (+, 6-CH_3), 33.81 (-, 7-C), 38.53 (-, 3-C), 39.30 (-, 5-C), 51.37 (+, 3a-C), 51.51 (+, 9a), 60.36 (Cq, 6-C), 72.25 (Cq, 6-Ca), 79.38 (+, 4-C), 80.53 (+, 9b-C), 117.79 (+, 8-C), 125.13 (+, 2XC-Imadazole), 131.24 (+, Imidazole), 140.00 (Cq, 9-C), 173.98 (Cq, 2-C), 182.34 (Cq, C=S).

IR (neat) $\tilde{\nu}$ = 2927, 1784, 1385, 1335, 1285, 1230, 1099, 972, 731, 464 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 43.1 (100), 69.1 (45.21), 81.1 (41.36), 107.1 (33.75), 145.1 (31.29), 189.1 (18.95), 233.2 (19.41), 360.1 (6.0) [M^+]. - HRMS: (EI, 70 eV): 360.1146 ($C_{18}H_{20}N_2O_4S$): cal. 360.1144 [M^+]).

16. (3[1]R,4aS,6aS,9aS,9bR)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3H-chromeno[5,6-b]furan-8(4aH)-one (75)



To **72** (20 mg, 0.05 mmol, 1eq.) taken in a three neck round bottom flask under N_2 atmosphere was dissolved in abs. Toluene (4 mL) and AIBN (4.5 mg, 0.027 mmol) was added to it at 40 ^{o} C. The reaction mixture was heated to 90 ^{o}C and Bu_3SnH (44.7 μL, 0.166 mmol) was added dropwise injected *via* syringe. The resulting mixture was refluxed at 90 ^{o}C for 5 h. After the completion of reaction the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography on silica gel (PE: EA = 4:1) to afford **75** (10 mg, 77 %) as a colorless oil.

R_f(hexanes: ethylacetate 1:1, Vanillin) = 0.6. $[\alpha]_D^{23}$ = + 87.0 (c = 0.90, $CHCl_3$).

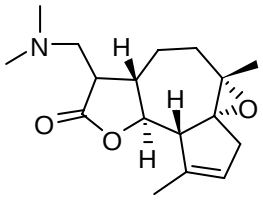
^{1}H NMR (300 MHz): δ = 0.88-0.93 (m, 1H), 1.32 (s, 3H), 1.46-1.54 (m, 1H), 1.56-1.67 (m, 2H), 1.79-1.84 (m, 1H), 1.92 (bs, 3H), 1.95-2.0 (m, 1H), 2.06-2.10 (m, 1H), 2.16-2.28 (m, 1H), 2.43-2.51 (m, 1H), 2.73-2.87 (m, 1H), 4.02-4.09 (m, 1H), 5.55 (s, 1H).

^{13}C NMR (75 MHz): δ = 18.22 (+, 9-CH_3), 22.74 (+, 6-CH_3), 23.71 (-, 4-C), 33.53 (-, 5-C), 36.17 (-, 7-C), 39.61 (-, 3-C), 47.50 (+, 3a-C), 52.44 (+, 9a), 62.61 (Cq, 6-C), 72.47 (Cq, 6-Ca), 84.66 (+, 9b-C), 124.73 (+, 8-C), 140.62 (Cq, 9-C), 176.33 (Cq, 2-C).

IR (neat) $\tilde{\nu}$ = 2900, 2320, 1776, 1440, 1215, 454 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 43.1 (100), 55.1 (63.96), 96.1 (78.44) 107.1 (57.49), 176.0 (47.67), 201.1 (20.60), 234.1 (33.70) [M^+]. - HRMS: (EI, 70 eV): 234.1259 ($C_{14}H_{18}O_3$): cal. 234.1256 [M^+]).

17. (3[1]R,4aS,6aS,9aS,9bR)-7-((dimethylamino)methyl)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3H-chromeno[5,6-b]furan-8(4aH)-one (77)



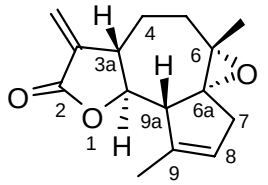
To a solution of LHMDS prepared as usual from Hexamethyldisilazane (45 μL, 0.212 mmol) and *n*BuLi (1.6 M hexane, 106 μL, 0.17 mmol) in THF (0.5 mL) was added a solution of **75** (20 mg, 0.085 mmol) in THF (0.5 mL) at -78 ^{o}C. After 1 h stirring, the resulting lithium enolate was added to a solution of Eschenmoser's salt (31 mg, 0.17 mmol) in THF (1 mL) at -78 ^{o}C *via* cannula. The resulting mixture was stirred at -78 ^{o}C for 1 h and then it was stirred for overnight while the temperature was raised slowly up to room temperature. After the completion of reaction as indicated by TLC (PE: EA= 1:9), the reaction mixture was quenched with sat. NH_4Cl (0.5 mL) solution and extracted with diethyl ether (2 mL). The phases were separated and the aqueous phase was once again extracted with diethyl ether (2 x 1 mL). The combined org. phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude material. This crude **77** (18 mg, 75%) as a diastereomeric mixture, was used for the final step of the synthesis without further purification.

R_f (hexanes: ethylacetate 40:60, Vanillin) = 0.1

^{1}H NMR (300 MHz): δ = 0.91–0.96 (m, 2H), 1.36 (bs, 3H), 1.98 (bs, 3H), 2.13 (bs, 3H), 2.23 (bs, 6H), 2.31-2.49 (m, 2H), 2.75-2.87 (m, 4H), 4.54-4.61 (m, 1H), 5.57 (s, 1H).

18. (+)-Arglabin (11)

[(3[1]R,4aS,6aS,9aS,9bR)-1,4a-dimethyl-7-methylene-5,6,6a,7,9a,9b-hexahydro-3H-chromeno[5,6-b]furan-8(4aH)-one]



The Dimethylamino Arglabin **77** (10 mg, 0.034 mmol) was dissolved in MeOH (0.5 mL) and treated with excess of MeI (0.5 mL) and stirred at room temperature for 24 h. After 24 h solvent MeOH was removed under reduced pressure and the remaining solid was taken in a separatory funnel containing a mixture of 10 % aqueous $NaHCO_3$ (1 mL) and CH_2Cl_2 (1 mL). The mixture was then shaken until all the solid had dissolved and the org. phase was separated, the aqueous phase was extracted once again with CH_2Cl_2 (2 x 1 mL). The combined org. phases were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give crude material. This was then purified by column chromatography on silica gel (PE: EA = 4:1) to afford the final product (+) Arglabin (**11)** (6.7 mg, 80%) as a white crystalline solid.

Synthetic sample

R_f(hexanes: ethylacetate 40: 60, Vanillin) = 0.87. $[\alpha]_D^{23}$ = + 81.0 (c = 0.30, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.35 (s, 3H, 6-*CH*$_3$), 1.45-1.52 (m, 1H), 1.81-1.87 (m, 1H), 1.97 (bs, 3H, 9-*CH*$_3$), 2.02-2.06 (m, 1H), 2.13-2.28 (m, 3H), 2.75-2.81 (m, 1H), 2.92-2.95 (m, 1H), 3.98-4.0 (m, 1H), 5.41 (d, *J* = 3.14 Hz, 1H, =*CH*$_2$), 5.57-5.58 (m, 1H, 9b-H), 6.15 (d, *J* = 3.38 Hz, 1H, =*CH*$_2$).

^{13}C NMR (75 MHz): δ = 18.24 (+, 9-CH_3), 21.42(-, 4-C), 22.77 (+, 6-CH_3), 33.45 (-, 5-C), 39.69 (-, 7-C), 51.02 (+, 3a-C), 52.82 (+, 9a-C), 62.66 (Cq, 6-C), 72.49 (Cq, 6-Ca), 82.86 (+, 9b-C), 118.26 (-, =*CH*$_2$), 124.88 (+, 8-C), 139.10 (Cq, =*CH*$_2$), 140.54 (Cq, 9-C), 170.41 (Cq, 2-C).

IR (neat) $\tilde{\nu}$ = 2926, 2853, 1767, 1440, 1307, 1255, 1156, 1064, 995, 958, 429 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 43.1 (78.30), 96.1 (100), 108.9 (50.90), 188.80 (23.96), 203.1 (16.27), 228.1 (7.70), 246.1 (9.47) [M^+]. - HRMS: (EI, 70 eV): 246.1263 ($C_{15}H_{18}O_3$): cal. 246.1256 [M^+]).

Authentic sample [116]

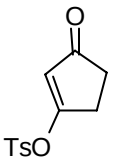
R_f(hexanes: ethylacetate 40: 60, Vanillin) = 0.87. $[\alpha]_D^{23}$ = + 82.1 (c = 0.30, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 1.34 (s, 3H, 6-*CH*$_3$), 1.46-1.50 (m, 1H), 1.81-1.88 (m, 1H), 1.96 (bs, 3H, 9-*CH*$_3$), 2.02-2.07 (m, 1H), 2.11-2.27 (m, 3H), 2.74-2.80 (m, 1H), 2.91-2.95 (m, 1H), 3.96-4.0 (m, 1H), 5.41 (d, *J* = 3.11 Hz, 1H, =*CH*$_2$), 5.56-5.57 (m, 1H, 9b-H), 6.13 (d, *J* = 3.39 Hz, 1H, =*CH*$_2$).

^{13}C NMR (75 MHz): δ = 18.29 (+, 9-CH_3), 21.42(-, 4-C), 22.80 (+, 6-CH_3), 33.42 (-, 5-C), 39.70 (-, 7-C), 51.99 (+, 3a-C), 52.79 (+, 9a-C), 62.69 (Cq, 6-C), 72.50 (Cq, 6-Ca), 82.89 (+, 9b-C), 118.35 (-, =*CH*$_2$), 124.92 (+, 8-C), 139.0 (Cq, =*CH*$_2$), 140.51 (Cq, 9-C), 170.49 (Cq, 2-C).

12.4 Studies towards total synthesis of (+)-Moxartenolide

19. 3-oxocyclopent-1-enyl 4-methylbenzenesulfonate (85)



To a solution of **80** (200 mg, 2.04 mmol, 1 eq.) in THF (4 mL) was added Et_3N (0.84 ml, 6.12 mmol) dropwise at 0 ^oC and stirred for 10 min at the same temperature. This was followed by the addition of ToSCl (972 mg, 5.102 mmol) portion wise for every 10 min in three batches and the reaction mixture was stirred for 2 hours while it was warmed up slowly to RT. After the completion of reaction as indicated by TLC (PE: EtOAc = 1:1) the reaction mixture was quenched by slow addition of saturated solution of $NaHCO_3$. It was extracted with Et_2O and the org. phase was washed with $NaHCO_3$ (1 mL), H_2O (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column chromatography (PE: EA= 4:1) to afford **85** (330 mg, 65%) as a brown colored crystalline solid.

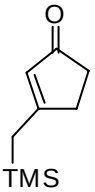
R_f(hexanes: ethylacetate 1:1, Vanillin) = 0.75. mp = 75 – 77 ^oC

^1H NMR (300 MHz, $CDCl_3$) δ = 2.42-2.45 (m, 2H), 2.48 (bs, 3H), 2.65-2.69 (m, 2H), 5.92 (t, *J* = 1.57Hz, 1H), 7.40 (d, *J* = 8.06Hz, 2H), 7.86 (d, *J* = 8.41Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.83 (+, CH_3), 28.69 (-, CH_2), 34.07 (-, CH_2), 115.03 (+, CH), 128.48 (+, CH), 130.31 (+, CH), 146.75 (Cq), 178.95 (Cq), 204.81 (Cq).

Elemental analysis: Observed C: 56.62%, H: 5.02%. Calculated C: 57.13%, H: 4.79%.

20. 3-((trimethylsilyl)methyl)cyclopent-2-enone (86)



Preparation of the Grignard reagent:

Mg curls (162 mg, 6.66 mmol, 4.2 eq.) and I_2 (catalytic) were stirred in abs. Et_2O (4 mL) under a N_2 atmosphere. At room temperature $TMSCH_2Cl$ (0.88 mL, 6.34 mmol, 4 eq.) was added slowly via a syringe to form the Grignard reagent.

1,4 Addition:

Under a N_2 atmosphere LiCl (20.1 mg, 0.475 mmol, 0.3 eq.) and CuI (45 mg, 0.237 mmol, 0.15 eq.) were dissolved in abs. THF (2 mL) and stirred for 15 min until a clear solution was obtained. Enoltosylate **85** (0.4 g, 1.586 mmol, 1 eq.) dissolved in abs. THF (2 mL) was added to the above mixture and stirred for further 20 min. and then cooled down to -78 ^oC. After an additional stirring for 20 min was added above prepared $TMSCH_2MgCl$ (1 mL, 6.3 mmol, 4.0 eq.) drop wise and stirred at -78 ^oC for 10 hrs. The reaction mixture was quenched by slow addition of saturated solution of NH_4Cl. It was extracted with Et_2O and the org. phase was washed with $NaHCO_3$ (1 mL), H_2O (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column chromatography (PE: EA= 9:1) to afford **86** (133 mg, 50%) as pale yellow oil. This decomposes on long standing at RT and has to be stored in refrigerator as solution in CH_2Cl_2. Also **86** decompose rapidly in $CDCl_3$ solution on long standing.

R_f (hexanes: ethylacetate 60:40, Vanillin) = 0.47.

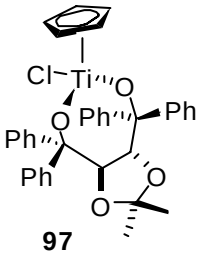
^1H NMR (300 MHz, C_6D_6) δ = 0.215 (s, 9H, TMS), 1.45 (s, 2H), 1.87-1.89 (m, 2H), 2.05-2.08 (m, 2H), 5.72(s, 1H), 6.91(s, 1H), 7.15(s, 1H).

^{13}C NMR (75 MHz, C_6D_6) δ = -1.66 (+, CH_3, TMS), 26.06 (-, CH_2), 33.51 (-, CH_2), 35.59 (-, CH_2), 116.57 (+, CH), 128.10 (Cq), 207.70 (Cq).

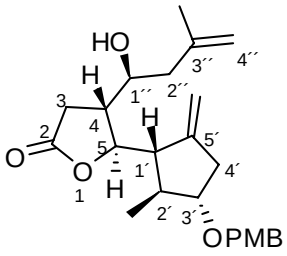
IR (neat) $\tilde{\nu}$ = 2957, 2927, 2856, 1731, 1669, 1593, 1461, 1250, 1202, 1126, 1073, 841, 744 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 57 (30), 149 (100), 168 (40) [M^+], 279 (20). - HRMS: (EI, 70 eV): 168.3080 ($C_9H_{16}OSi$): cal. 168.3082 [M^+].

21. (4*R*,5*R*)-4-((S)-1´´-hydroxy-3´´-methylbut-3´´-enyl)-5-((1´*S*,2´*S*,3´*S*)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl)dihydrofuran-2(3H)-one (1´´ *S*: 1´´ *R* = 96:4) (54)



97



Enantioselective allyltitanation of aldehyde **30** employing chiral auxiliary monochlorotitanate **97** [127]

The titanium complex **97** (0.408 g, 0.666 mmol, 1.7 eq.) was dissolved in absolute ether (7 mL) and kept at 0 ^{o}C. A freshly prepared Grignard reagent 2-Methyl allylmagnesium chloride [1 ml, 0.8 M) from 2-Methyl allylchloride (58 μL, 1.5 eq.), Mg curls (16 mg, 1.7 eq.), was added drop wise and stirred for 2 h, which resulted in a orange suspension. The reaction mixture was then cooled to -78 ^{o}C and the aldehyde **30** (135 mg, 0.392 mmol, 1 eq.) dissolved in dry THF (1 mL) was added to the above orange suspension in ether. The resultant solution was allowed to stir at -78 ^{o}C for 4 h. After the disappearance of starting material as indicated by TLC (PE: EA= 1:1), to this was added 45 % solution of ammonium fluoride and kept at room temperature for over night., passed through celite and washed with ether. The collected organic solution was washed with brine and the compound was extracted using ether. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by silica gel column chromatography (hexane: ethyl acetate 2:1) aforded the allylated product **54** as 96:4 diastereomeric mixture, as colorless viscous liquid (107 mg, 68 %).

R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.61. $[\alpha]_D^{23}$ = +62.0 (c 0.5, $CHCl_3$).

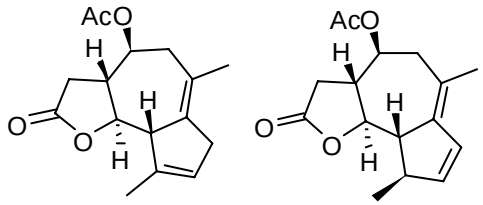
^{1}H NMR (300MHz): = 1.07(d, *J* = 6.9 Hz, 3H), 1.71(s, 3H), 1.96 (br s, 1H), 2.04-2.07(m, 2H), 2.10-2.18 (m, 1H), 2.30-2.47(m, 3H), 2.53-2.65 (m, 1H), 2.69-2.77(m, 1H), 3.47-3.54 (m, 1H), 3.72-3.77 (m, 1H), 3.80(s, 3H), 4.46 (s, 2H), 4.66-4.70 (m, 1H), 4.80 (br s, 1H), 4.91 (br s, 1H), 5.00 (br s, 1H), 5.05 (br s, 1H), 6.85-6.89 (m, 2H), 7.26-7.27 (m, 2H).

^{13}C NMR (300MHz): δ = 17.2, 21.2, 28.2, 28.7, 39.1, 40.0, 41.2, 42.8, 52.5, 54.3, 67.2, 70.3, 82.8, 83.3, 110.4, 112.8, 113.5, 128.3, 129.4, 140.4, 146.1, 158.2, 180.0

IR (Neat) $\tilde{\nu}$ = 3458, 2932, 2871, 1769, 1652, 1612, 1586, 1513, 1456, 1376, 1354, 1302, 1200, 1174, 1089, 894, 819, 524 cm^{-1}

HRMS: (EI, 70 eV): Calcd. for $C_{24}H_{32}O_5$ [M^+]: 400.2250, Found: 400.2240.

22. (3aR,4S,9aS,9bR,Z)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (98) and (3aR,4S,9R,9aS,9bR,Z)-6,9-dimethyl-2-oxo-2,3,3a,4,5,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (99)



98 3:2 **99**

A solution of **60** (20 mg, 0.068 mmol, 1 eq.) in CH_2Cl_2 (2 mL) under a N_2 atmosphere was cooled to -10 ^oC and added pyridine (30 μL, 0.34 mmol). To this mixture Tf_2O (18 μL, 0.101 mmol) was added drop wise and the reaction mixture was stirred for 6 h. The reaction mixture was quenched with $NaHCO_3$ (1 mL), diluted with CH_2Cl_2 (2 mL) and the layers were separated. The aqueous layer was extracted once again with CH_2Cl_2 (2 x 2 mL), the combined org. phases were dried, filtered and concentrated in *vacuo.* Purification on silica gel column chromatography (PE: EA= 9:1) afforded regiomeric mixture of **98** and **99** (3:2 ratio, 12.5 mg, 68%) as a colorless oil.

R_f(hexanes: ethylacetate 60:40, Vanillin) = 0.5

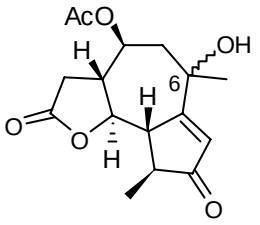
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.13 (d, *J* = 7.06Hz, 2H), 1.74 (bs, 3H), 1.87-1.90 (m, 5H), 2.06 (s, 6H), 2.06-2.66 (m, 11H), 2.96-2.98 (m, 2H), 3.07-3.09 (m, 1H), 3.27-3.30 (m, 1H), 3.75-3.84 (m, 2H), 4.66-4.73 (m, 2H), 5.52 (s, 1H), 5.86-5.92 (m, 1H), 6.20-6.23 (m, 1H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 10.94, 14.03, 17.63, 21.07, 21.48, 22.85, 22.93, 22.96, 23.72, 28.90, 30.34, 34.44, 35.40, 37.70, 38.71, 40.98, 41.58, 43.78, 53.09, 53.16, 53.52, 55.07, 68.14, 70.80, 70.82, 83.30, 84.11, 125.13, 126.24, 128.85, 130.86, 137.89, 140.34, 141.13, 143.03, 170.04, 174.60, 174.72.

IR (neat) $\tilde{\nu}$ = 2955, 1784, 1738, 1441, 1372, 1234, 1166, 1084, 1028, 994, 959, 915 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 71.1 (20), 145 (50), 159 (30), 183 (25), 207 (60), 216 (100), 276 (10) [M^+].

23. 3aR,4S,6R,9S,9aS,9bR)-6-hydroxy-6,9-dimethyl-2,8-dioxo-2,3,3a,4,5,6,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (6 *R*: 6 *S*=1:1) (101)



Using PCC

The compound **60** (80 mg, 0.275 mmol, 1 eq.) was dissolved in dry dichloromethane (2 mL). To this Molecular sieves (MS 4A^{o}) were added and stirred for few minutes. PCC (75 mg, 0.344 mmol) was added to the above solution and stirred for 4 h. After the disappearance of starting material as indicated by TLC (PE: EA= 3:2), the crude reaction mixture was passed through celite and concentrated under reduced pressure. Product was purified by silica gel column chromatography using (PE: EA= 4:1) as the eluent to afford **101** (63 mg, 75%) as 1:1 diastereomeric mixture, as colorless oil.

R_f (hexanes: ethylacetate 60:40, Vanillin) = 0.16

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24 (d, *J* = 3.56Hz, 3H), 1.27 (d, *J* = 2.52Hz, 3H), 1.59 (bs, 6H), 2.02 (s, 2H), 2.07-2.09 (m, 8H), 2.13-2.18 (m, 4H), 2.40-2.50 (m, 3H), 2.69-2.77 (m, 5H), 3.06-3.09 (m, 1H), 3.45-3.59 (m, 1H), 3.86-3.93 (m, 1H), 4.06-4.13 (m, 3H), 4.99-5.06 (m, 1H), 5.16-5.22 (m, 1H), 6.04 (s, 1H), 6.33 (s, 1H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 14.18 (+), 15.69 (+), 16.05 (+), 21.07 (+), 21.13(+), 21.20 (+), 29.88 (+), 30.83 (+), 35.59 (-), 35.69 (-), 44.44 (+), 45.09 (-), 45.57 (-), 46.78 (+), 49.12 (+), 54.37 (+), 55.00 (+), 60.46 (-), 70.29 (+), 71.77 (Cq), 71.90 (Cq), 72.55 (+), 81.88 (+), 83.15 (+), 129.46 (+), 130.51 (+), 170.06 (Cq), 170.24 (Cq), 171.31 (Cq), 174.02 (Cq), 174.57 (Cq), 178.54 (Cq), 179.74 (Cq), 209.04 (Cq), 210.05 (Cq).

IR (neat) $\tilde{\nu}$ = 3466, 3442, 2976, 2934, 1779, 1730, 1699, 1604, 1372, 1237, 1170, 1100, 1027, 1003, 974, 918, 882, 734, 657, 590, 544, 518 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 43.1 (100), 55.1 (15), 111.1 (10), 139.1 (20), 205.1 (20), 248.2 (10, -OAc), 308.1 (5) [M^{+}]. - HRMS: (EI, 70 eV): 308.1255 ($C_{16}H_{20}O_6$): cal. 308.1260[M^{+}].

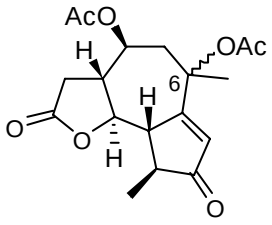
Using Dess-Martin Periodinane[11]

To a solution of **60** (8 mg, 0.023 mmol, 1 eq.) in CH_2Cl_2 (1 mL) at RT was added solid $NaHCO_3$ (7 mg, 0.083 mmol, 3.5 eq.) followed by Dess–Martin periodinane (16.5 mg, 0.039 mmol, 1.7 eq.). Stirring was continued for 2 hours before the addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous sodium thiosulfate solution (1 mL) and CH_2Cl_2 (1 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 mL), the combined organics washed with the before mentioned 1:1 saturated aqueous $NaHCO_3$ solution and saturated aqueous sodium thiosulfate solution (1 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (PE: EA= 4:1) to afford **101** (6 mg, 72%) as 1:1 diastereomeric mixture, as colorless oil.

Using TEMPO[138]

To a solution of **60** (8 mg, 0.023 mmol, 1 eq.) in CH_2Cl_2(1 mL) at 0 ^oC was added solid TEMPO (3 mg, 0.015 mmol, 0.5 eq.) followed by KBr (1 mg, 0.08 mmol, 0.2 eq.) and NaOCl solution (10-13% in H_2O, 30 µL, 0.8 mL/1mmol of substrate). The reaction mixture was stirred for 4 hours while the temperature was warmed up to RT slowly. After the disappearance of starting material as indicated by TLC (PE: EA= 3:2), the reaction mixture was extracted with CH_2Cl_2, followed by washing with H_2O, brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (PE: EA= 4:1) to afford **101** (6.5 mg, 75%) as 1:1 diastereomeric mixture, as colorless oil.

24. (3aR,4S,6R,9S,9aS,9bR)-6,9-dimethyl-2,8-dioxo-2,3,3a,4,5,6,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4,6-diyl diacetate (6 *R*: 6 *S*=1:1) (120)



To a solution of **101** (25 mg, 0.081 mmol, 1 eq.) in CH_2Cl_2 (1 mL) was added DMAP (5 mg, 0.04 mmol, 0.5 eq.), Et_3N (0.034 mL, 0.243 mmol, 3 eq.), Ac_2O (0.015 mL, 0.162 mmol) and stirred at room temperature for 24 h. The reaction mixture was quenched with H_2O and the layers were separated. The org. phase was washed with $NaHCO_3$ (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column

chromatography (PE: EA= 3:1) to afford **120** (24 mg, 85%) as 1:1 diastereomeric mixture, as colorless oil.

R_f(hexanes: ethylacetate 1:1, Vanillin) = 0.26.

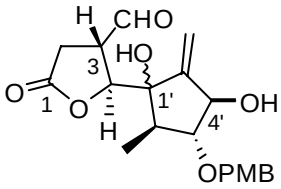
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24-1.25 (m, 3H), 1.27-1.28 (m, 3H), 1.68 (s, 4H), 1.74 (s, 3H), 2.03-2.11 (m, 12H), 2.17-2.36 (m, 2H), 2.40-2.79 (m, 10H), 2.87-2.90 (m, 1H), 3.83-3.90 (m, 1H), 4.27-4.34 (m, 1H), 4.92-4.99 (m, 1H), 5.19-5.29 (m, 1H), 6.12-6.13 (m, 1H, diastereomeric), 6.17-6.18 (m, 1H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 16.02 (+), 16.08 (+), 21.02 (+), 21.84 (+), 27.44 (+), 30.44 (+), 35.27 (-), 35.41 (-), 43.32 (-), 44.99 (-), 46.06 (+), 46.27 (+), 47.28 (+), 50.58 (+), 54.42 (+), 54.79 (+), 70.07 (+), 70.94 (+), 78.96 (Cq), 79.67 (Cq), 82.19 (+), 82.34 (+), 130.51 (+), 131.53 (+), 169.45 (Cq), 169.96 (Cq), 170.09 (Cq), 173.83 (Cq), 176.01 (Cq), 176.35 (Cq), 208.19 (Cq), 208.81 (Cq).

IR (neat) v = 2979, 2934, 2199, 1786, 1732, 1704, 1607, 1431, 1370, 1235, 1176, 1095, 1021, 1005, 970, 879, 811, 734, 650, 609, 516 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 91.1 (25), 248.1 (100), 290.2 (20), 308.1 (15), 350.2 [M^+]. - HRMS: (EI, 70 eV): 350.1366 ($C_{18}H_{22}O_7$): cal. 350.1366 [M^+].

25. (2*R*,3*S*)-2-((1´*S*,2´*S*,3´*S*)- 1`,5`,-dihydroxy 3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl) Oxotetrahydrofuran-3-carbaldehyde (102)



Sharpless allylic oxidation using SeO_2[131]

To a solution of 14 mg (0.126 mmol, 0.5 eq.) of Se02 in CH_2C1_2 (1 mL) was added 65 μL (0.505 mmol, 4 eq.) of 70% tert-butyl hydroperoxide. After the mixture had been stirred for 0.5 h at 25 ^{o}C (water bath), 87 mg (0.252 mmol, 1 eq.) of lactone carbaldehyde **30** dissolved

in CH_2C1_2 (1 mL) was added drop wise several minutes. The mixture was stirred at 25 ^oC for 48 h. After the disappearance of starting material as indicated by TLC (PE: EA= 1:4), the reaction mixture was poured into water (1 mL) contained in a separatory funnel, and washed with a NaI solution (0.5 M) to destroy the excess of t-butyl hydroperoxide. Then the organic phase was washed with a 10% sodium thiosulphate solution, brine, dried over Na_2SO_4 and evaporated. Purification of the crude reaction mixture by silica gel column chromatography (PE: EA= 3:1) to afford **102** (52 mg, 55%) as 4:1 diastereomeric mixture, as colorless oil.

R_f(hexanes: ethylacetate 20:80, Vanillin) = 0.28

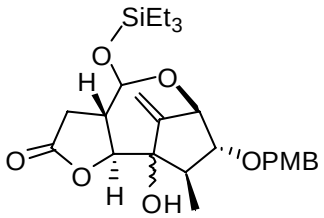
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.07 (d, *J* = 7.18Hz, 3H), 1.23-1.26 (m, 1H), 2.29-2.34 (m, 1H), 2.80-2.87 (m, 1H), 3.34-3.39 (m, 1H), 3.46-3.53 (m, 1H), 3.80 (s, 4H), 4.34-4.39 (m, 1H), 4.64-4.66 (m, 2H), 4.68-4.70 (m, 1H), 5.43-5.44 (m, 2H), 6.87-6.90 (m, 2H), 7.27-7.30 (m, 2H), 9.63 (s, 1H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 13.43 (+), 29.06 (-), 41.97 (+), 46.83 (+), 55.32 (+), 72.39 (-), 77.24 (Cq, 1`-C), 78.13 (+, 4`-C), 83.24 (+), 89.22 (+), 111.84 (-, $=CH_2$), 113.99 (+, PMB), 129.50 (+, PMB), 130.18 (Cq, PMB), 152.68 (Cq, =C), 159.40 (Cq, PMB), 174.38 (Cq, C=O), 197.62 (+, CHO).

IR (neat) $\tilde{\nu}$ = 2963, 2874, 2836, 2199, 1768, 1727, 1612, 1585, 1513, 1464, 1419, 1363, 1303, 1247, 1181, 1076, 1030, 910, 822, 731, 457, 428 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 44.1 (30), 121 (100, PMB), 205.1 (15), 237.2 (15), 263.1 (50), 376.2 (10) [M^+]. - HRMS: (EI, 70 eV): 376.1516 ($C_{20}H_{24}O_7$): cal. 376.1511 [M^+].

26. Compound (103).



tricyclo[7.2.1.$0^{2,6}$] system

To a solution of **102** (40 mg, 0.111 mmol, 1 eq.) in CH_2Cl_2 (2 mL) was added DMAP (7 mg, 0.055 mmol, 0.5 eq.), Et_3N (0.031 mL, 0.222 mmol, 2 eq.), followed by the dropwise addition of TESCl (0.057 mL, 0.333 mmol, 3 eq.) and stirred at room temperature for 4 h. The reaction mixture was quenched with H_2O and the layers were separated. The org. phase was washed with $NaHCO_3$ (1 mL), brine and dried over Na_2SO_4. The filtrate was concentrated in *vacuo* and purified by silica gel column chromatography (PE: EA= 4:1) to afford **103** (45 mg, 85%) as 1:1 diastereomeric mixture, as colorless oil.

R_f(hexanes: ethylacetate 1:1, Vanillin) = 0.47.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.61-0.64 (m, 6H, diastereomeric), 0.66-0.69 (m, 6H), 0.94-0.99 (m, 18H), 1.61 (s, 2H), 2.51-2.60 (m, 2H), 2.65-2.69 (m, 1H), 2.76-2.85 (m, 2H), 2.90-2.91 (m, 1H), 3.05-3.17 (m, 2H), 3.31-3.35 (m, 2H), 3.77-3.80 (m, 6H), 4.34-4.35 (m, 2H), 4.50-4.63 (m, 5H), 4.71-4.73 (m, 1H), 5.07-5.08 (m, 1H), 5.25-5.26 (m, 1H), 5.37-5.40 (m, 1H), 5.68-5.72 (m, 2H), 6.85-6.88 (m, 4H), 7.28-7.31 (m, 4H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 4.89 (-), 4.93 (-, diastereomeric), 6.81 (+), 6.83 (+), 13.13 (+), 13.98 (+), 30.48 (-), 32.82 (-,diastereomeric), 38.80 (+), 39.25 (+), 43.64 (+), 46.59 (+), 55.25 (+), 72.28 (-), 72.36 (-,diastereomeric), 77.31 (+), 77.70 (+), 88.52 (+), 88.61 (+), 88.98 (+), 88.92 (+), 97.85 (+), 104.60 (+), 109.85 (-), 113.70 (+),113.71 (+), 129.73 (+), 129.81 (+), 130.40 (+), 152.54 (+), 153.82 (+), 159.18 (+), 174.82 (+), 175.65 (+).

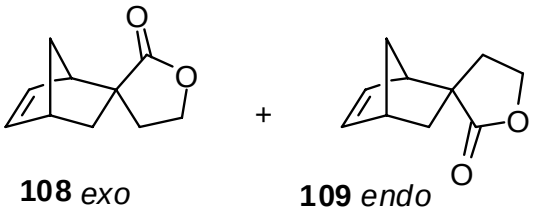
IR (neat) $\tilde{\nu}$ = 2955, 2908, 2875, 2837, 2364, 2199, 2063, 1783, 1612, 1513, 1458, 1413, 1345, 1301, 1248, 1174, 1144, 1102, 1031, 1007, 963, 915, 834, 742, 677, 544, 480, 455, 427 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 44.1 (20), 87.0 (10), 121.0 (100, PMB), 191 (10), 219 (10), 299 (5), 369 (10), 490.1 [M^+]. - HRMS: (EI, 70 eV): 490.2379 ($C_{26}H_{38}SiO_7$): cal. 490.2387 [M^+].

12.5 Biomimetic studies towards synthesis of Dimeric guaianolides

27. 4',5'-dihydro-2'H-spiro[bicyclo[2.2.1]hept[5]ene-2,3'-furan]-2'-one

(108, *exo*) and (109, *endo*)



108 *exo* + **109** *endo*

Using $ZnCl_2$

To a solution of 2-methylenecyclopentanone **106** (300 mg, 3.06 mmol, 1 eq.) in CH_2Cl_2 (2 mL), was added $ZnCl_2$ (41.6 mg, 0.305 mmol, 10 mol %) weighed under N_2 atmosphere, and the mixture was stirred for 15 minutes at RT under N_2 atmosphere. This was followed by the dropwise addition of cyclopentadiene **107** (1 mL, 12.2 mmol, 4 eq.) at the same RT and the resulting mixture was stirred for 6 hours. After the disappearance of 2-methylenecyclopentanone **106** as indicated by TLC (R_f = 0.4, PE: EA = 1.1, UV active, I_2 active), the reaction was stopped and the solvent CH_2Cl_2 was removed under reduced pressure at RT, followed by the purification of the resulting crude material by silica gel column chromatography (PE: EA= 4:1) to afford **108** and **109** as 3:1 diastereomeric mixture (376 mg, 75%), as colorless oil. Upon careful separation on silica gel column chromatography using (PE: EA= 9:1) the *exo* isomer was separable to some extent (90 mg) and the rest a mixture of **108** (*exo*) and **109** (*endo*) isomers (285 mg). Crystallization of pure **108** (*exo*) isomer from pentane-CH_2Cl_2 mixture at low temperature afforded crystalline **108** which on single crystal X-ray analysis revealed its structure.

R_f (**108**, hexanes: ethylacetate 40:60, I_2 active) = 0.76.

^{1}H NMR (**108,** 300 MHz, $CDCl_3$) δ = 1.02-1.07 (m, 1H), 1.34-1.38 (m, 1H), 1.81-1.90 (m, 1H), 1.98-2.0 (m, 2H), 2.14-2.19 (m, 1H), 2.85-2.91 (m, 2H), 4.09-4.22 (m, 2H), 6.09-6.11 (m, 1H), 6.24-6.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 35.30 (+), 39.26 (+), 42.75 (-), 46.95 (Cq), 47.68 8 (+), 49.12 (-), 65.03 (+), 134.09 (-), 134.87 (-), 182.34 (Cq).

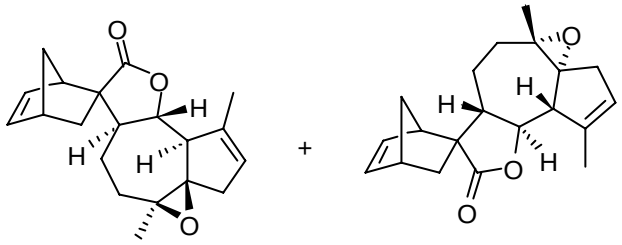
IR (neat) $\tilde{\nu}$ = 3062, 2971, 2873, 1755, 1454, 1369, 1334, 1280, 1209, 1149, 1023, 929, 859, 821, 780, 726 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 66.1 (100), 99.0 (85), 164.1 (10) [M^+]. - HRMS: (EI, 70 eV): 164.0833 ($C_{10}H_{12}O_2$): cal. 164.0837 [M^+].

Using (*R*,*R*)-^{i}Pr-Box (+)-**14** and $Cu(OTf)_2$

To a solution of (*R*,*R*)-^{i}Pr-Box (+)-**14** (13.5 mg, 0.0509 mmol, 10 mol%) in CH_2Cl_2 (0.5 mL), was added $Cu(OTf)_2$ (20.2 mg, 0.055 mmol, 1.1 eq. with respect to ligand (+)-**14**) weighed under N_2 atmosphere, and the resulting blue colored complex was stirred for 10 minutes at 0 ^{o}C under N_2 atmosphere. This was followed by the dropwise addition of 2-methylenecyclopentanone **106** (50 mg, 0.509 mmol, 1 eq.) and stirred for another 15 minutes at 0 ^{o}C. The reaction mixture was further treated with cyclopentadiene **107** (0.207 mL, 2.54 mmol, 5 eq.) and the resulting mixture was stirred for 6 hours while the temperature was raised up to RT. After the disappearance of 2-methylenecyclopentanone **106** as indicated by TLC (R_f = 0.4, PE: EA = 1.1, UV active, I_2 active), the reaction was stopped and the solvent CH_2Cl_2 was removed under reduced pressure at RT, followed by the purification of resulting crude material by silica gel column chromatography (PE: EA= 4:1) to afford **108** and **109** as 2:3 diastereomeric mixture (71 mg, 85%), as colorless oil.

28. Compounds 110 (*exo*) and 111 (*endo*)



110 *exo* **111** *endo*

To a solution of (+)-Arglabin (**11**) (5 mg, 0.0203 mmol, 1 eq.) in CH_2Cl_2 (0.5 mL), was added $ZnCl_2$ (0.5 mg, 0.002 mmol, 10 mol %) weighed under N_2 atmosphere, and the mixture was stirred for 15 minutes at 0 ^{o}C under N_2 atmosphere. This was followed by the dropwise addition of cyclopentadiene **107** (9 µL, 0.101 mmol, 5 eq.) at the same 0 ^{o}C and the resulting

mixture was stirred for 6 hours while the temperature was raised up to RT.. After the disappearance of (+)-Arglabin (**11**) as indicated by TLC (R_f = 0.56, PE: EA = 1.1, UV active, Vanillin), the reaction was stopped and the solvent CH_2Cl_2 was removed under reduced pressure at RT, followed by the purification of the resulting crude material by silica gel column chromatography (PE: EA= 9:1) to afford **110** and **111** as 5:1 diastereomeric mixture (376 mg, 75%), as colorless oil.

R_f(hexanes: ethylacetate 40:60, I_2 active) = 0.73.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.30 (s, 4H), 1.55 (s, 8H), 1.96-1.97 (m, 5H), 2.98 (s, 1H), 4.16-4.23 (m, 1H), 5.56 (s, 2H), 5.98-6.01 (m, 1H), 6.20-6.23 (m, 1H).

^{13}C NMR (75 MHz , $CDCl_3$) δ = 18.53, 23.06, 23.58, 22.97, 23.73, 28.91, 29.69, 30.35, 34.04, 34.96, 38.72, 39.32, 41.31, 47.64, 47.84, 52.58, 52.76, 55.81, 62.13, 72.16, 81.35, 124.78, 134.74, 137.94, 141.05, 181.80.

IR (neat) $\tilde{\nu}$ = 3726, 3547, 2929, 2856, 2390, 2324, 2319, 2000, 1766, 1442, 1379, 1315, 1238, 1164, 1085, 1029, 961, 921, 867, 731 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 43.1 (70), 66.1 (100, CPD), 109.0 (45), 187.1 (90), 213.0 (25), 228 (15), 247.1 (40, (+)-Arglabin), 312.1 (40) [M^+]. - HRMS: (EI, 70 eV): 312.1720 ($C_{20}H_{24}O_3$): cal. 312.1275 [M^+].

13. Appendix

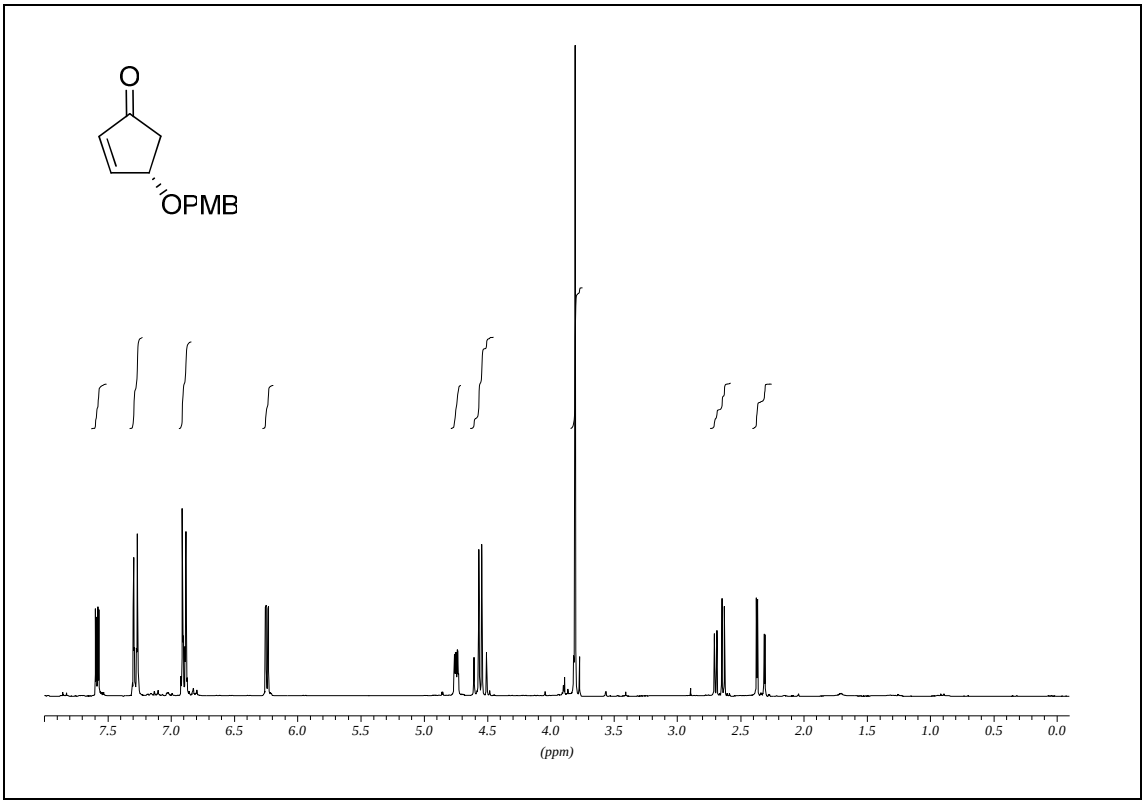
13.1 NMR - spectra

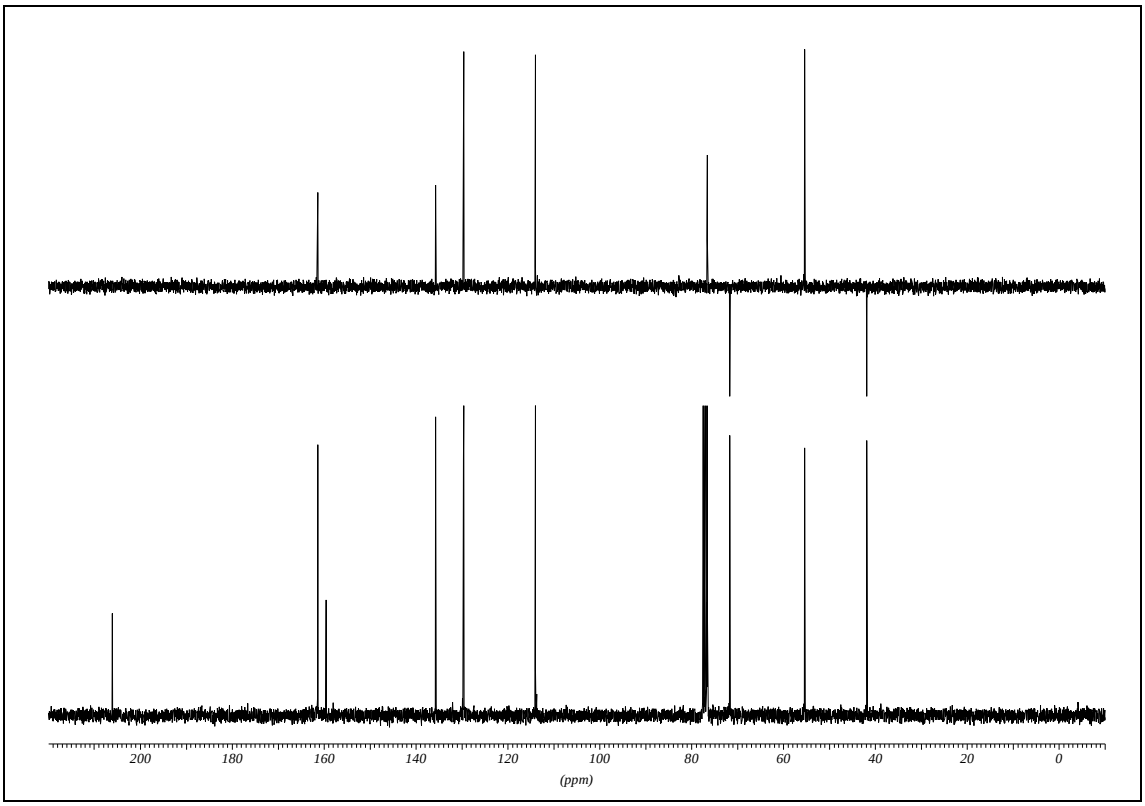
^{1}H-NMR spectra - upper image

^{13}C-NMR spectra (DEPT 135 integrated) - lower image

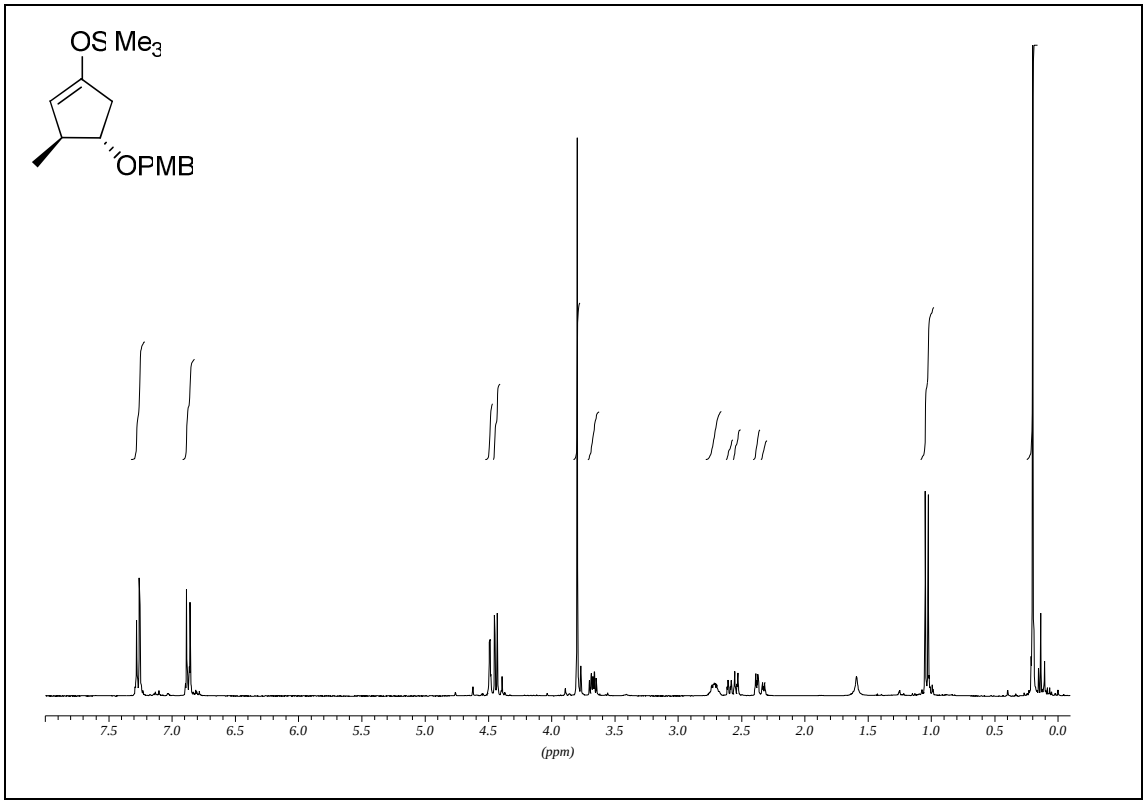
Solvents, if not stated otherwise: $CDCl_3$

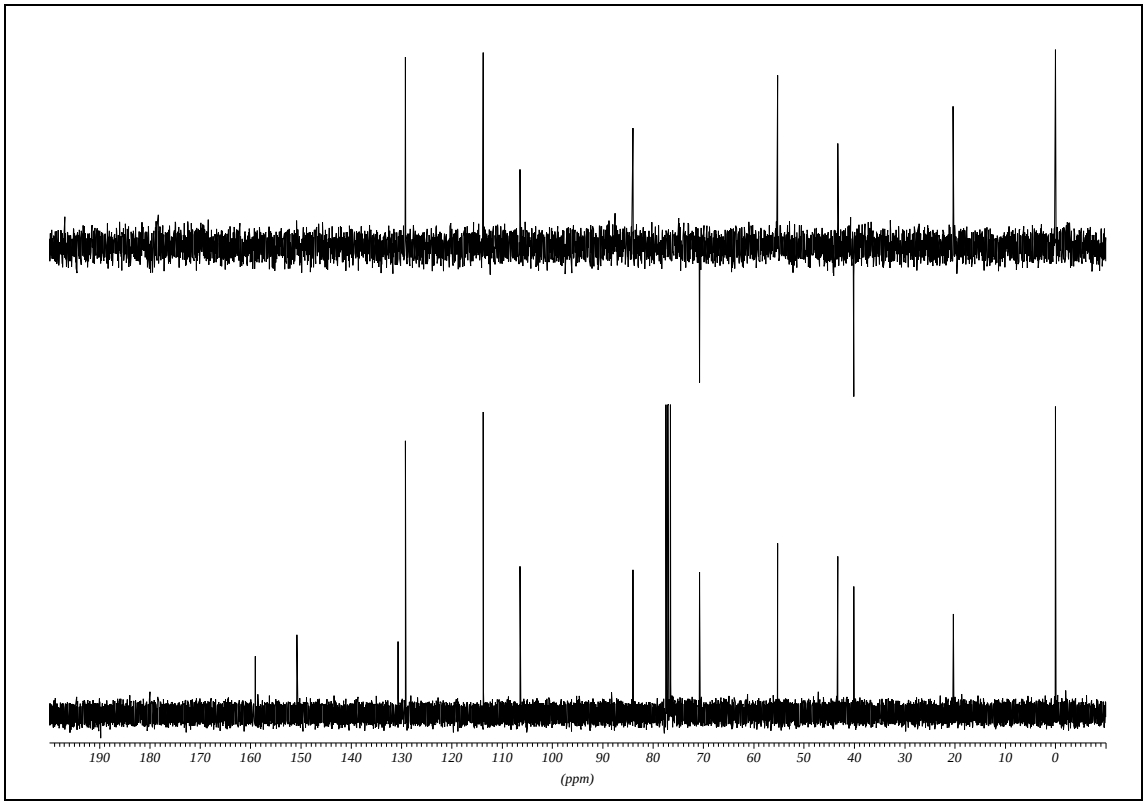
(*S*)-4-(4-methoxybenzyloxy)cyclopent-2-enone (28)



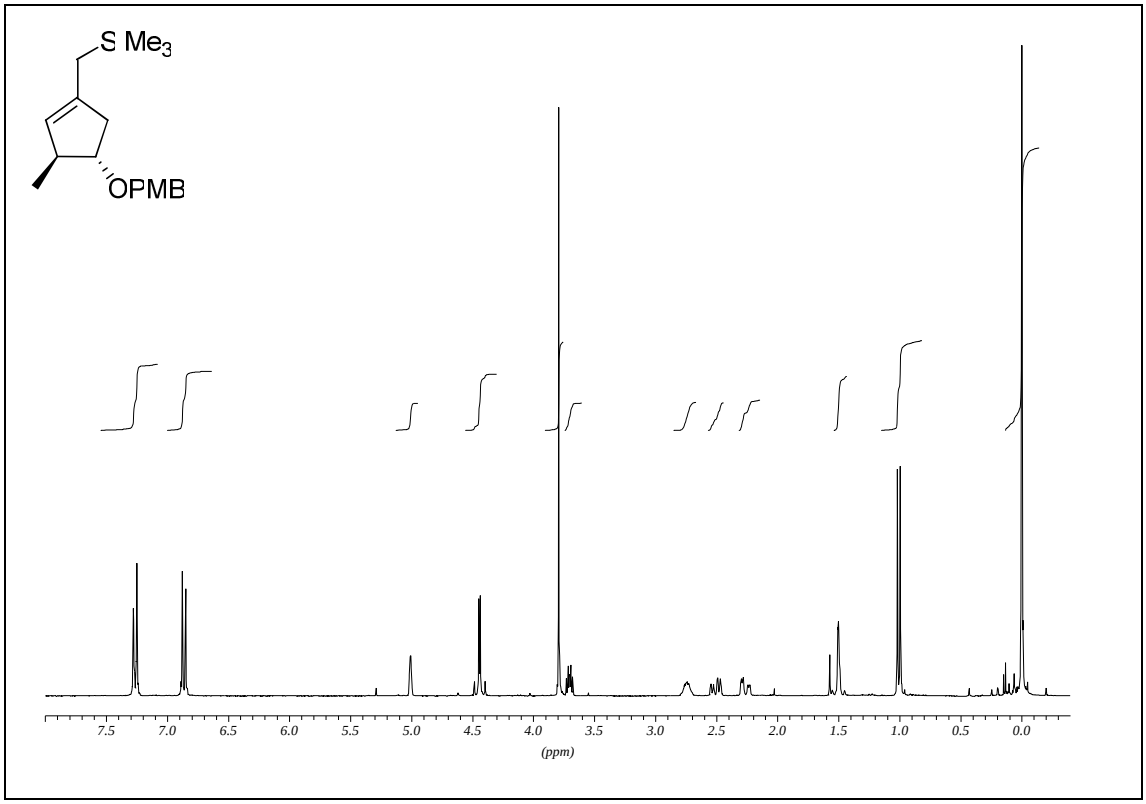


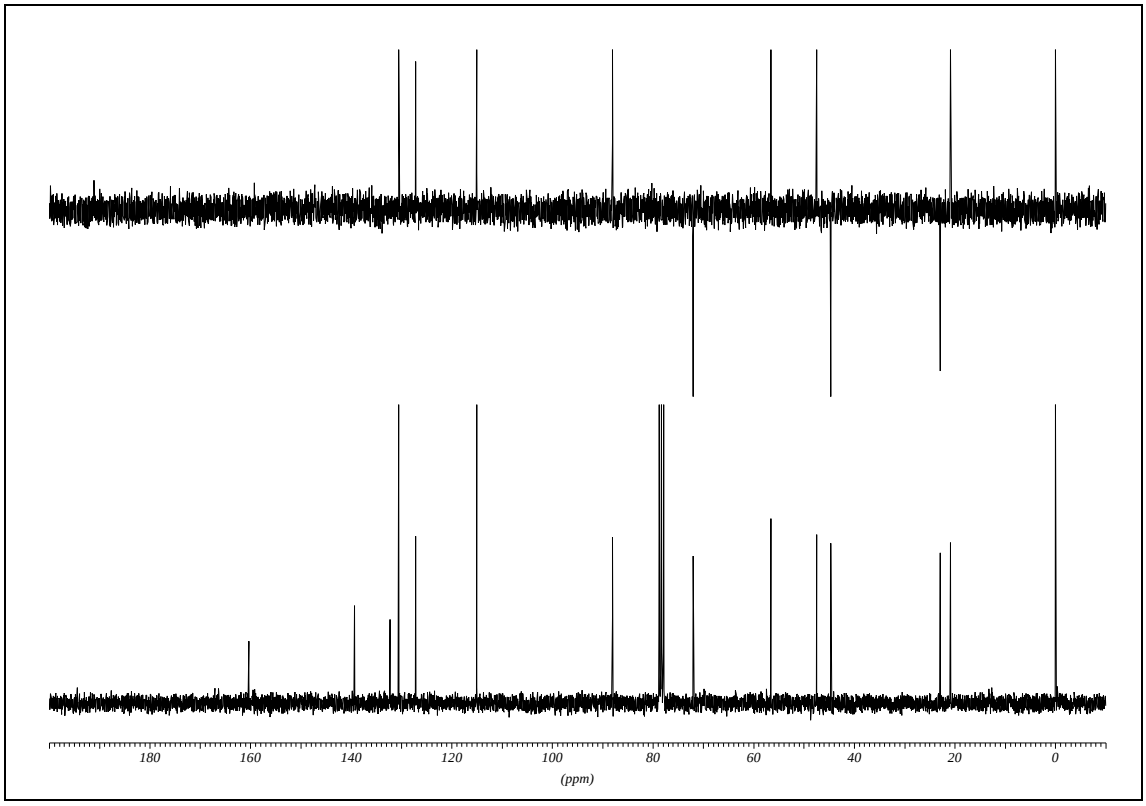
((3*S*,4*S*)-4-(4-methoxybenzyloxy)-3-methylcyclopent-1-enyloxy)trimethylsilane (48)



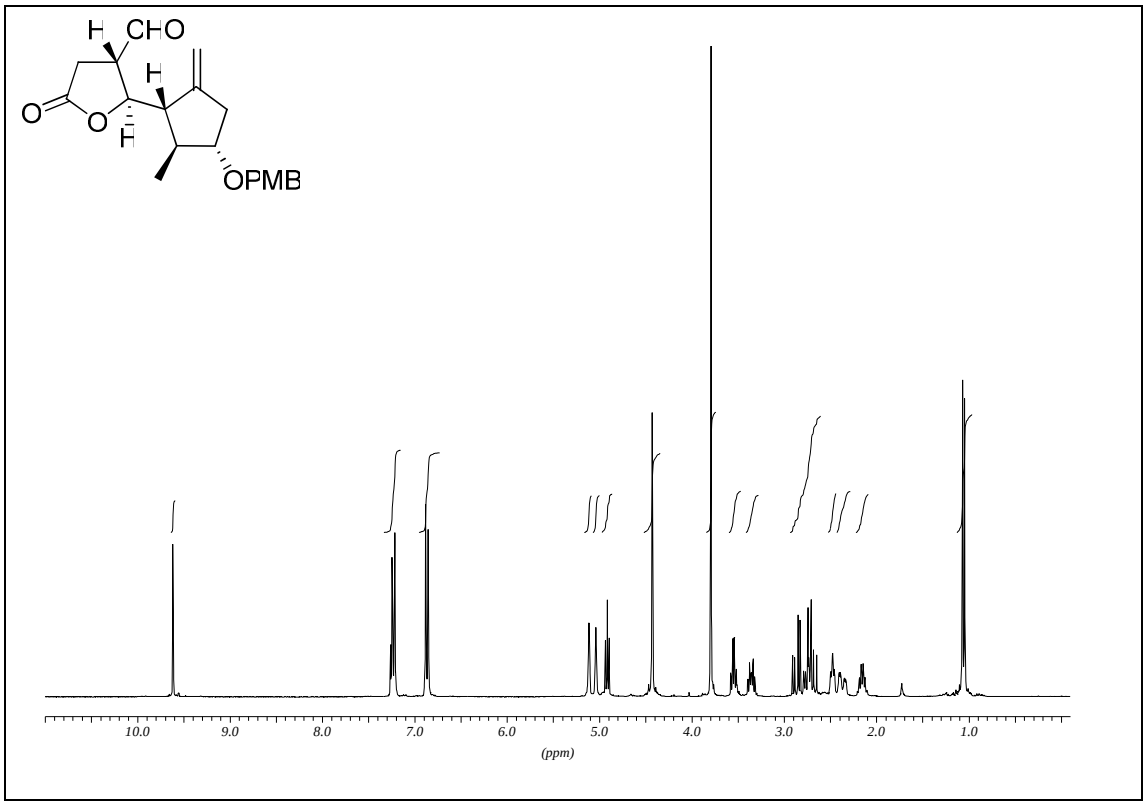


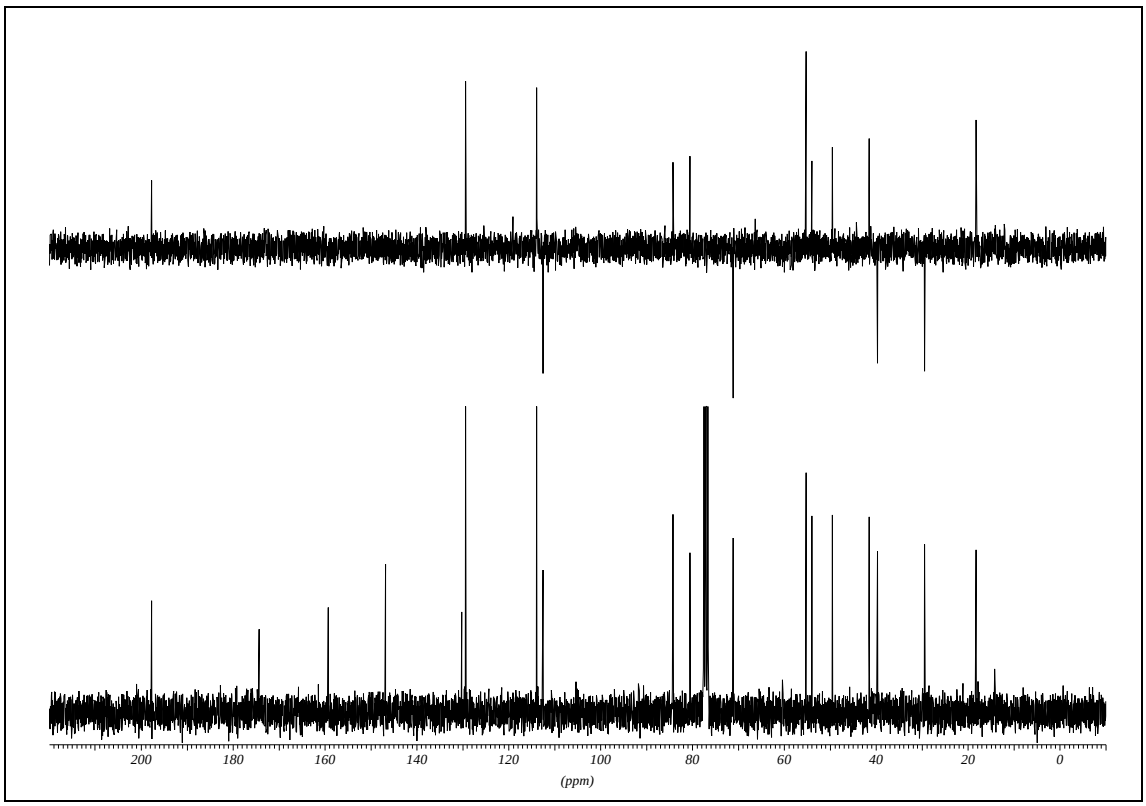
(((3*S*,4*S*)-4-(4-methoxybenzyloxy)-3-methylcyclopent-1-enyl)methyl)trimethylsilane (29)



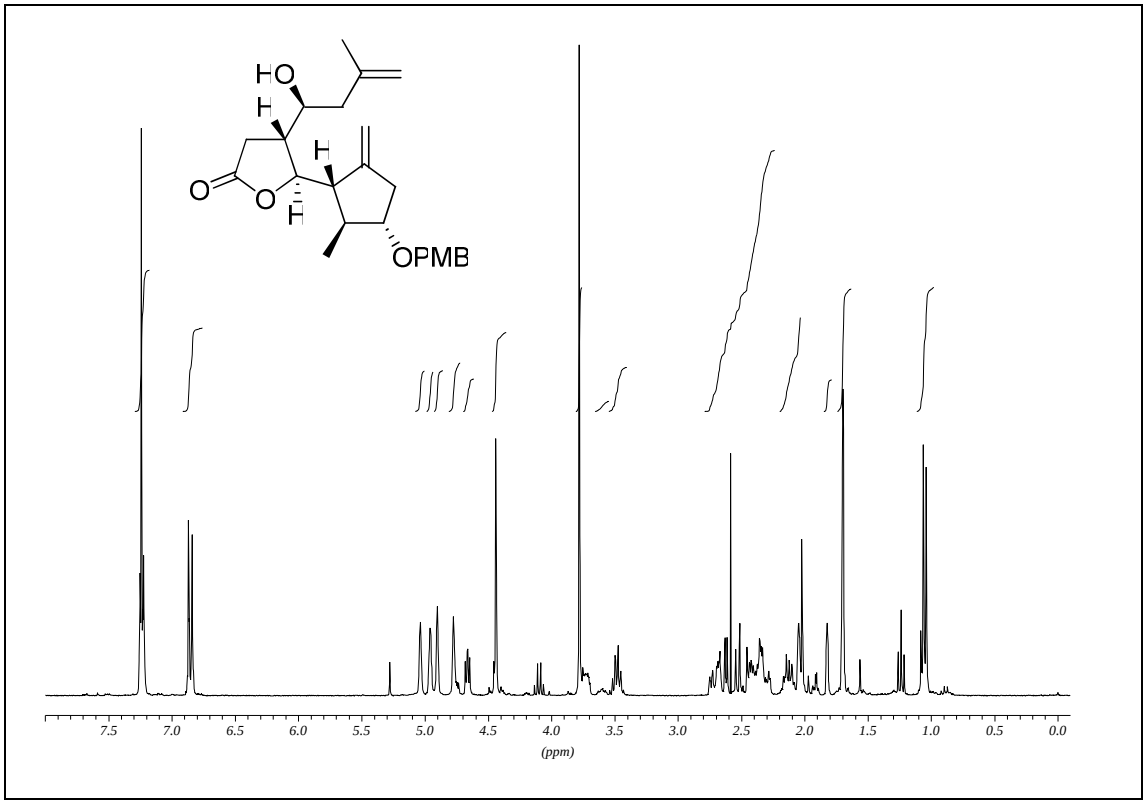


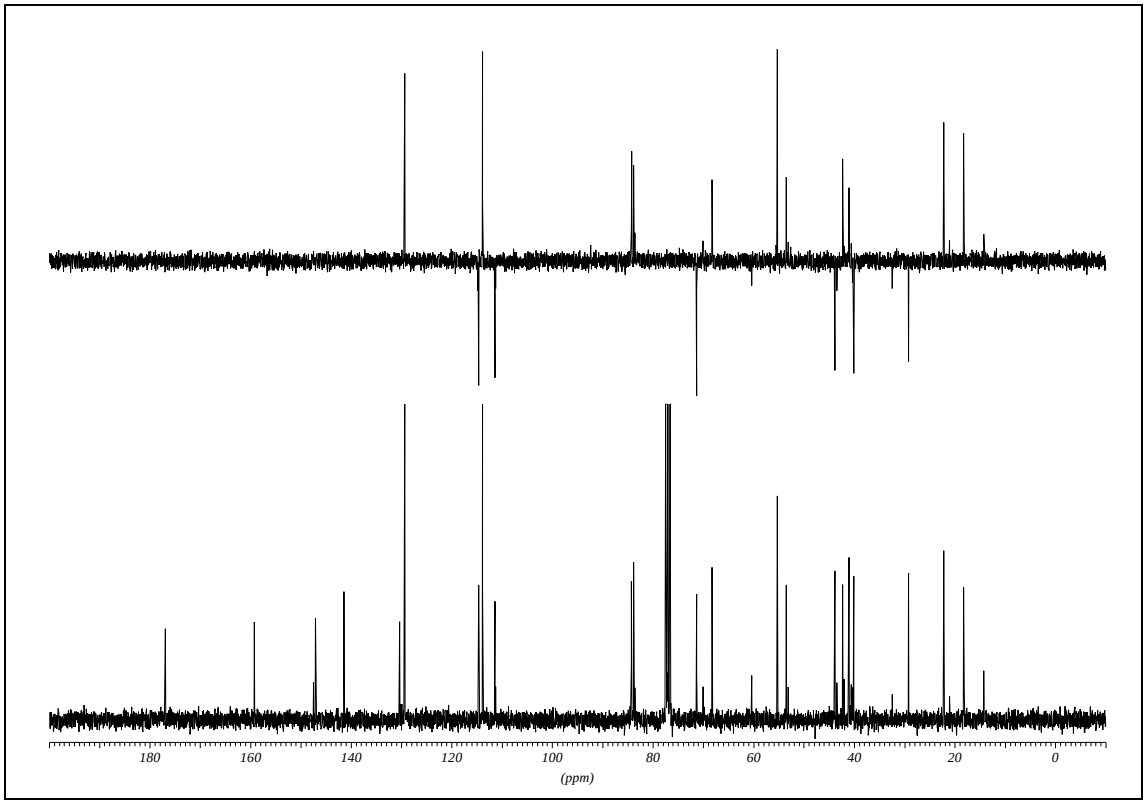
(2*R*,3*S*)-2-((1´*S*,2´*S*,3´*S*)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl)-5-oxotetrahydrofuran-3-carbaldehyde (30)



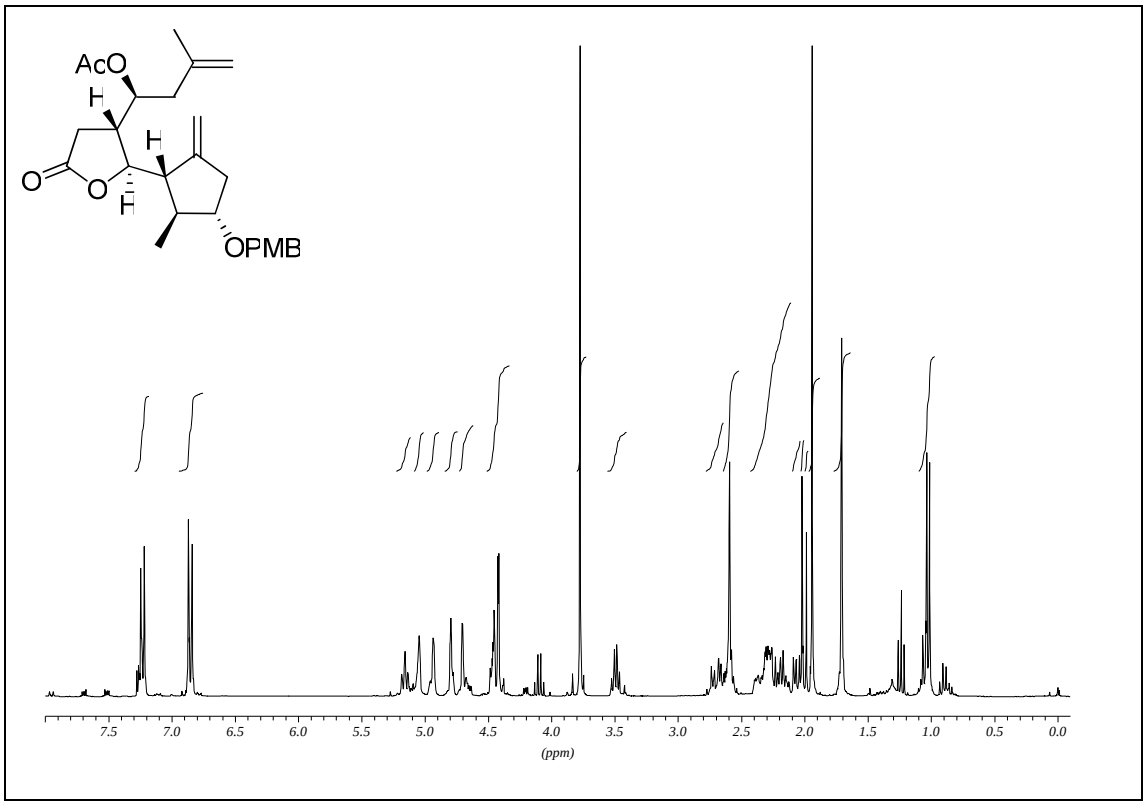


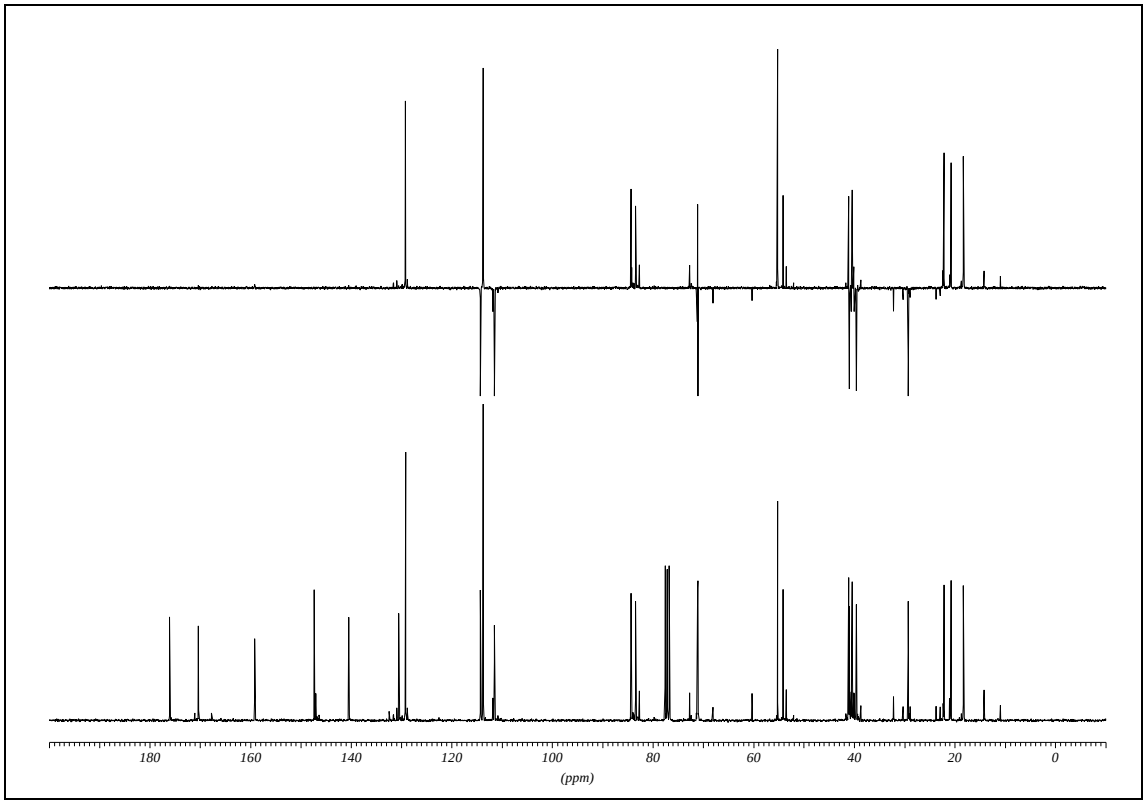
(4*R*,5*R*)-4-((S)-1´´-hydroxy-3´´-methylbut-3´´-enyl)-5-((1´*S*,2´*S*,3´*S*)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl)dihydrofuran-2(3H)-one (54) (1´´ S: 1´´ R=80:20)



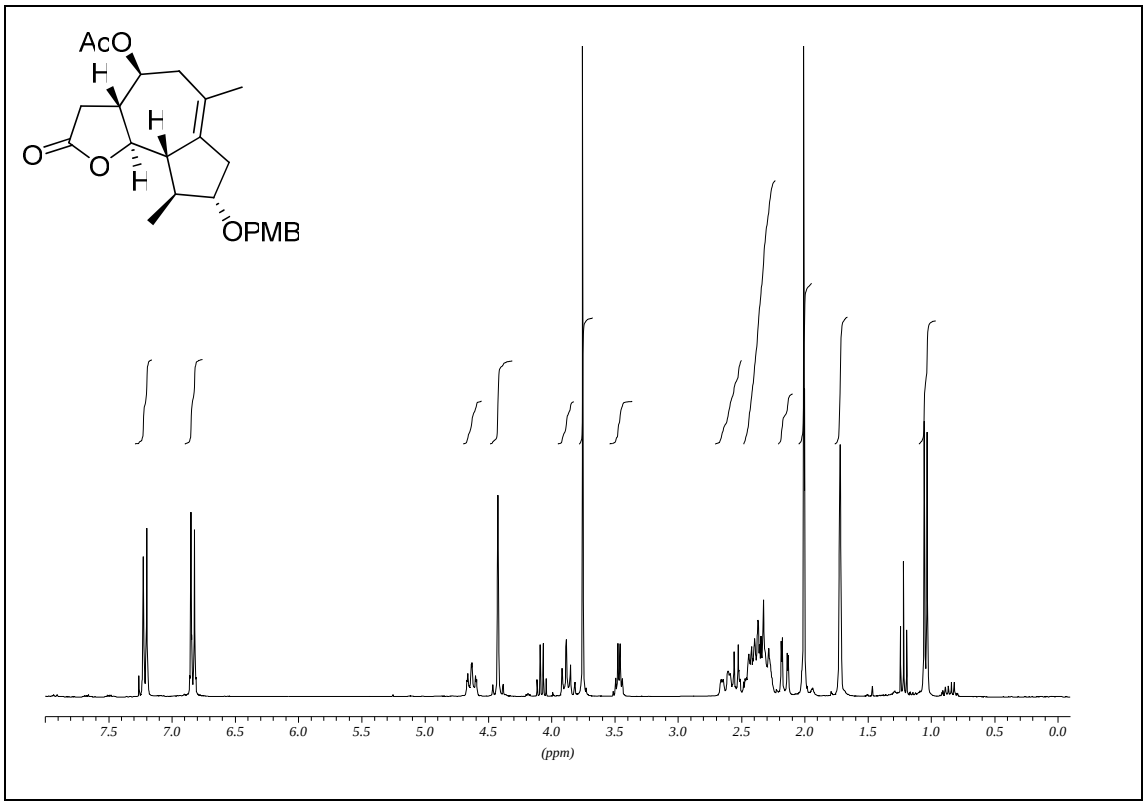


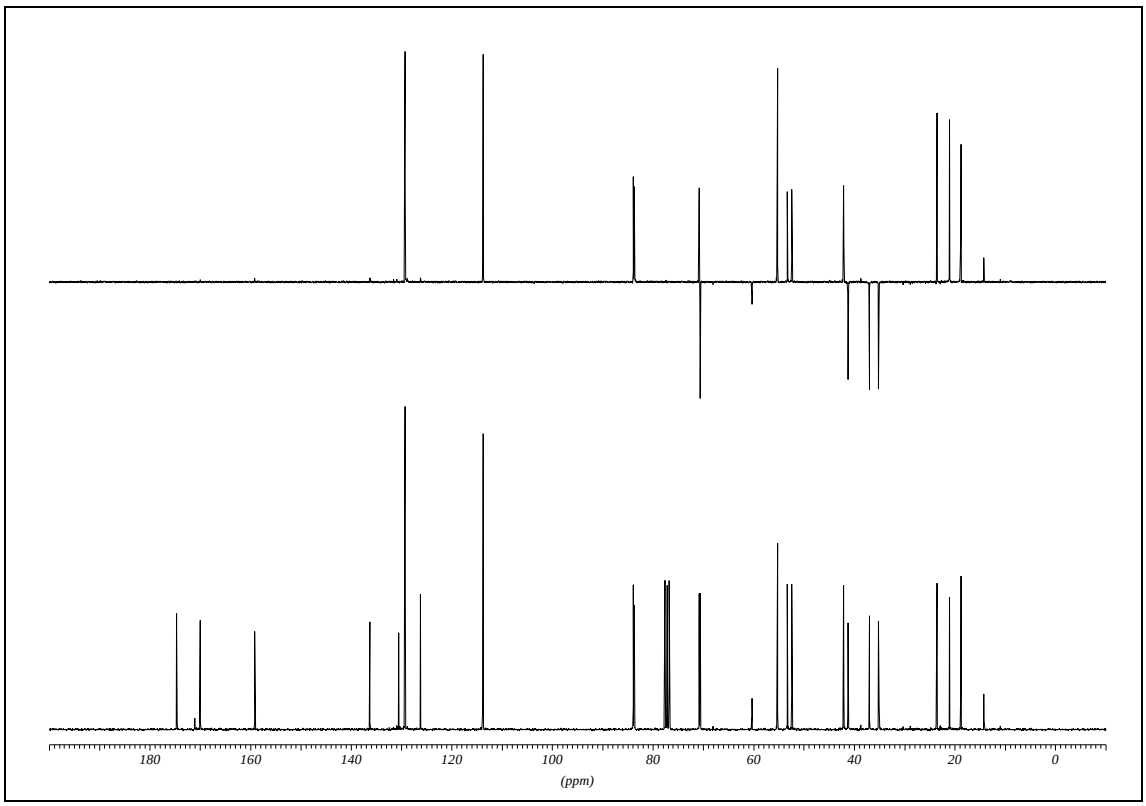
(S)-1´´-((2R,3R)-2-((1´*S*,2´*S*,3´S)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylene-cyclopentyl)-5-oxotetrahydrofuran-3-yl)-3´´-methylbut-3´´-enyl acetate (55)
(1´´ S: 1´´ R=80:20)



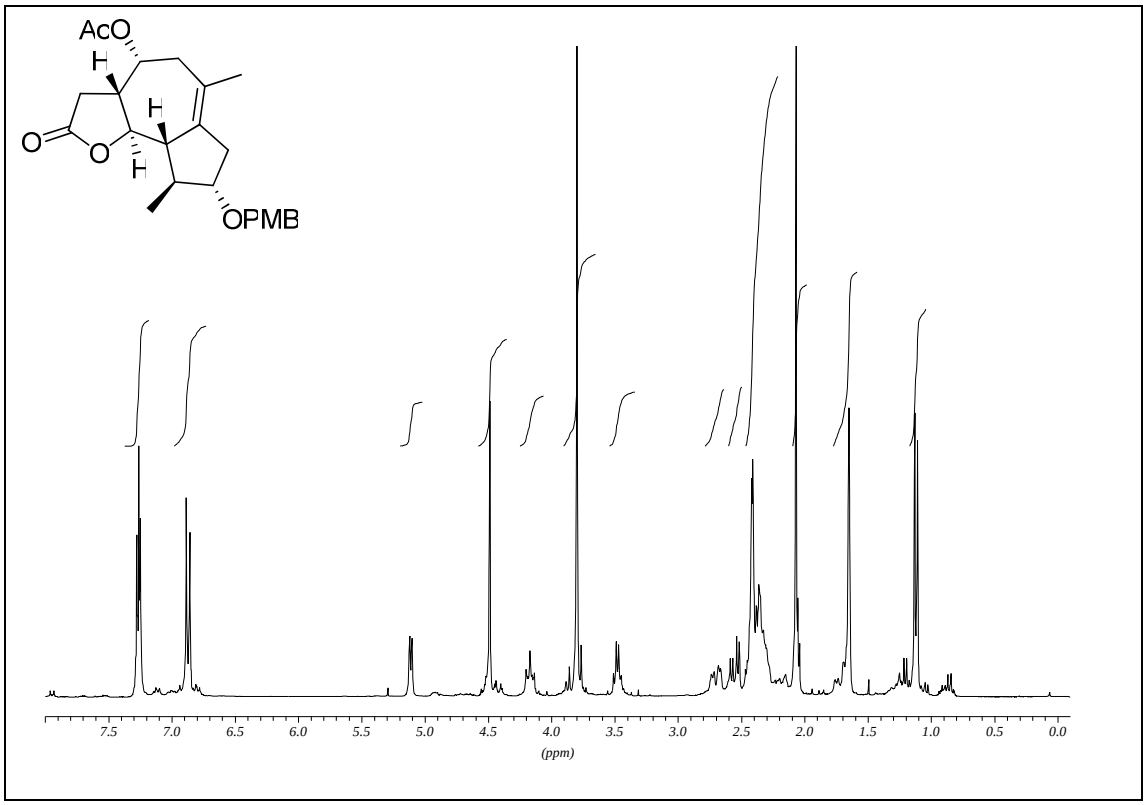


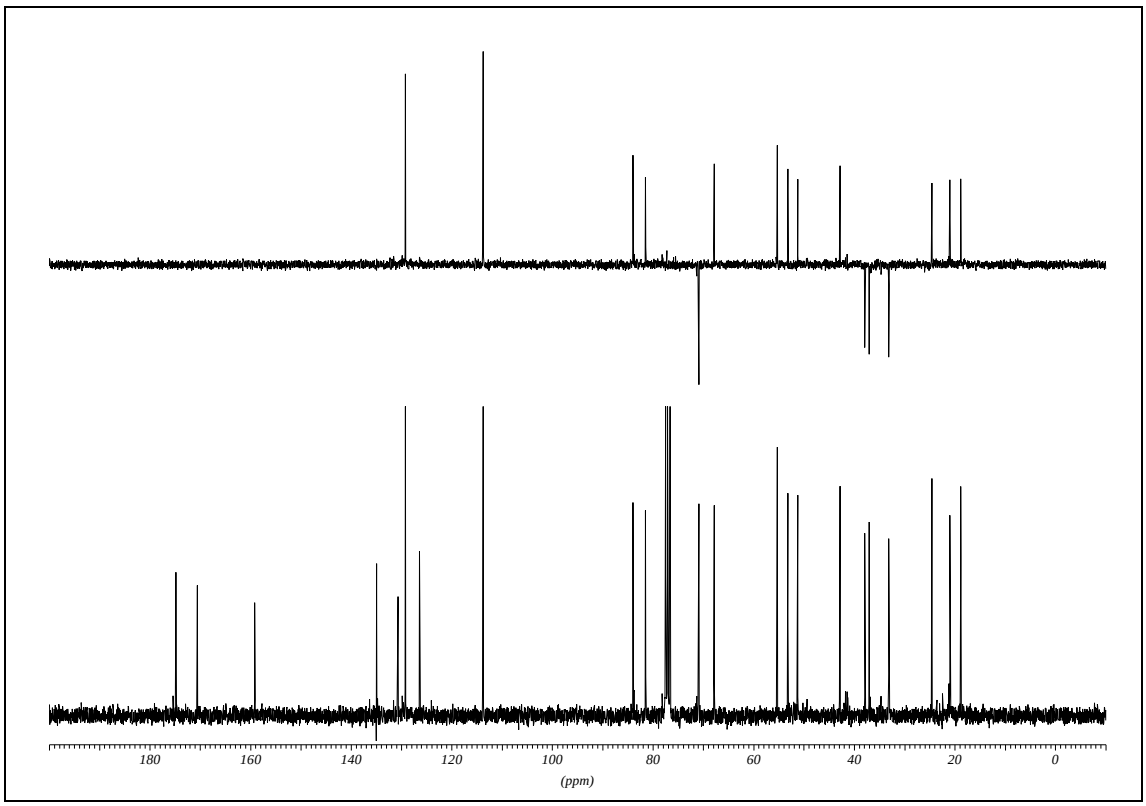
(3aR,4S,8S,9S,9aS,9bR)-8-(4-methoxybenzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (56)



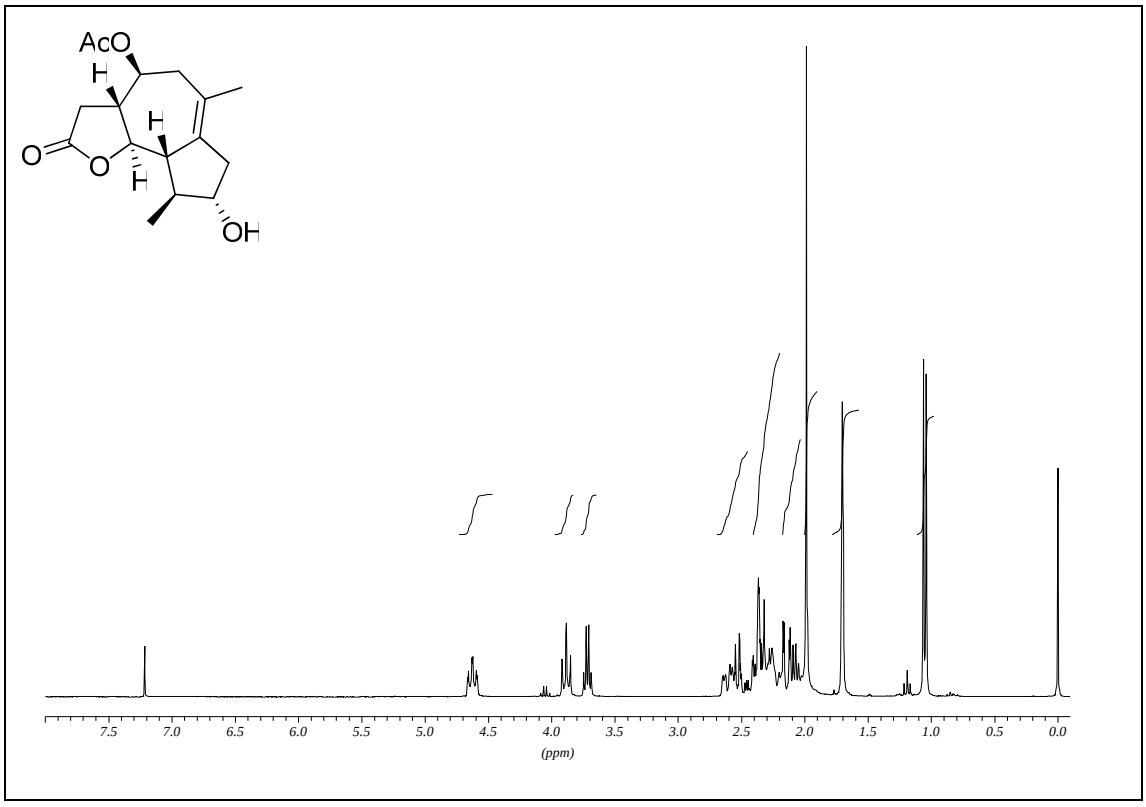


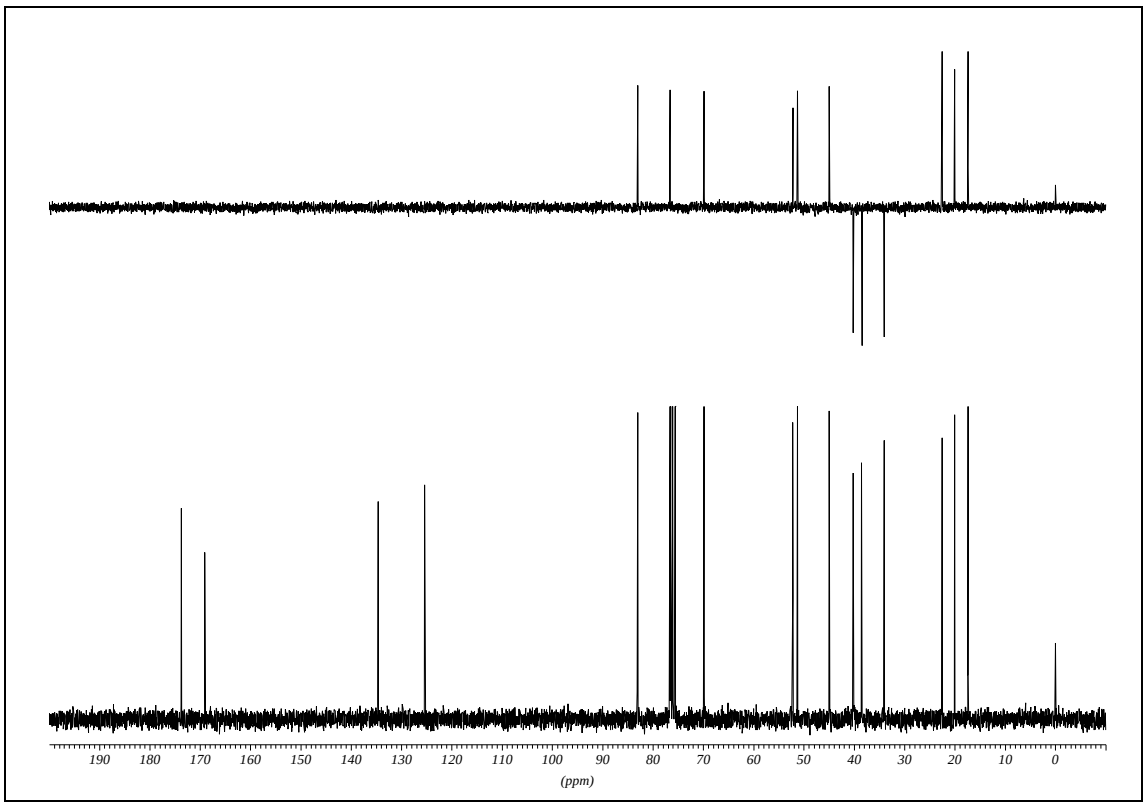
(3aR,4R,8S,9S,9aS,9bR)-8-(4-methoxybenzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5, 7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (*epi* 56)



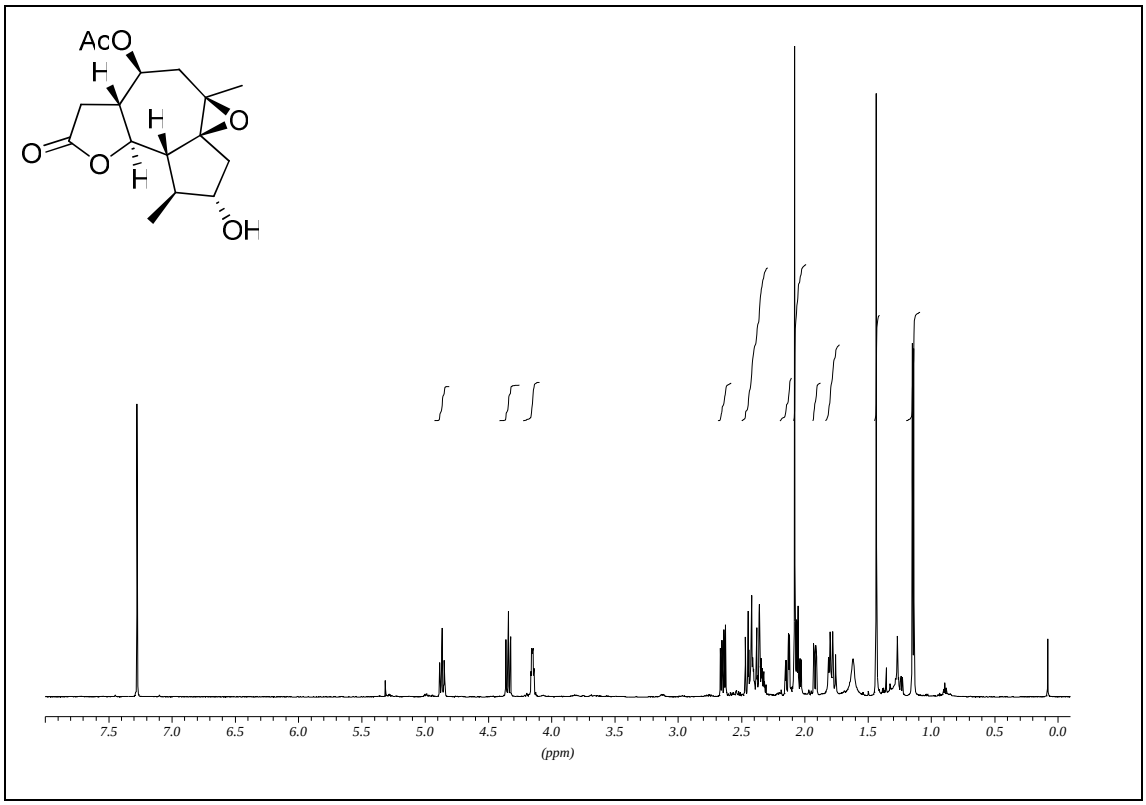


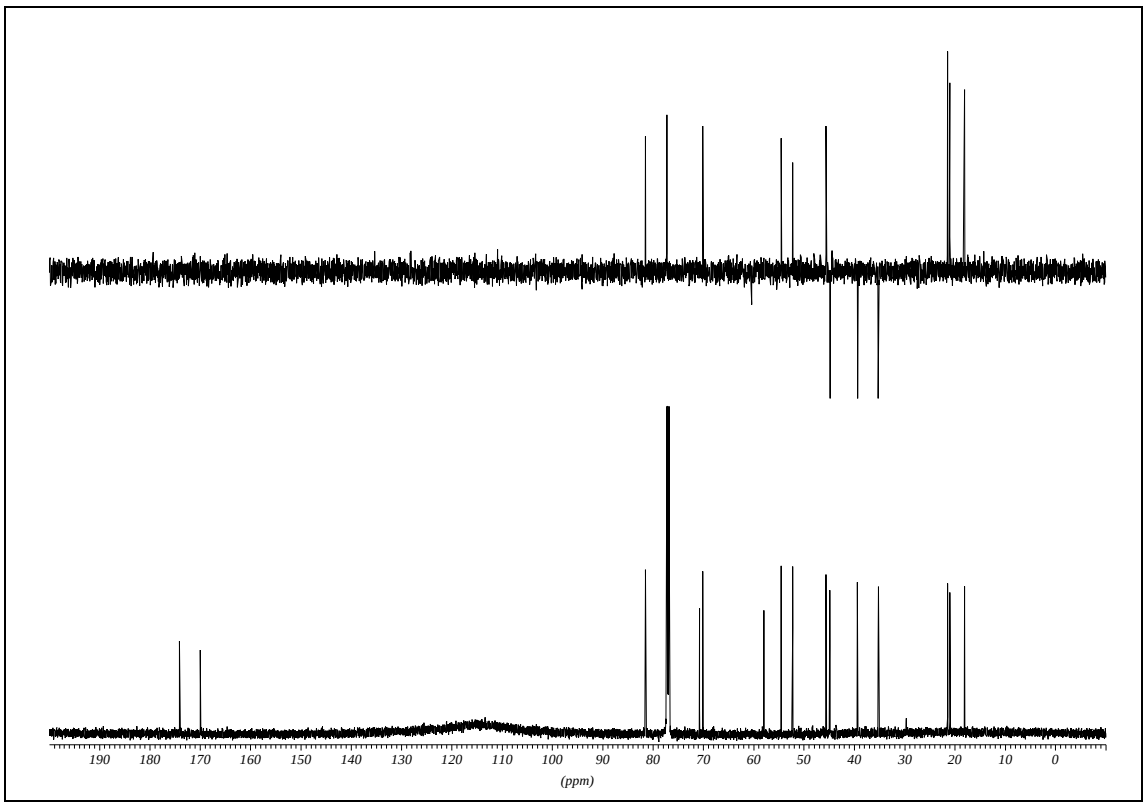
(3aR,4S,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydro-azuleno[4,5-b]furan-4-yl acetate (60)



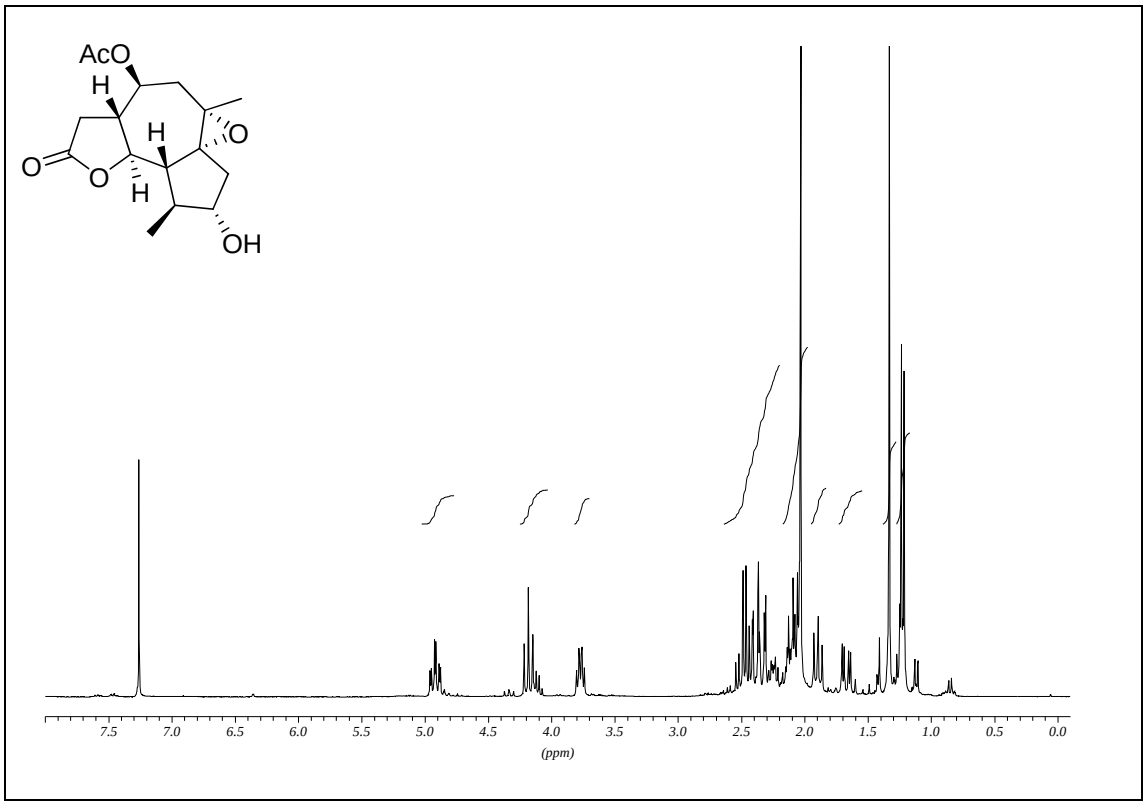


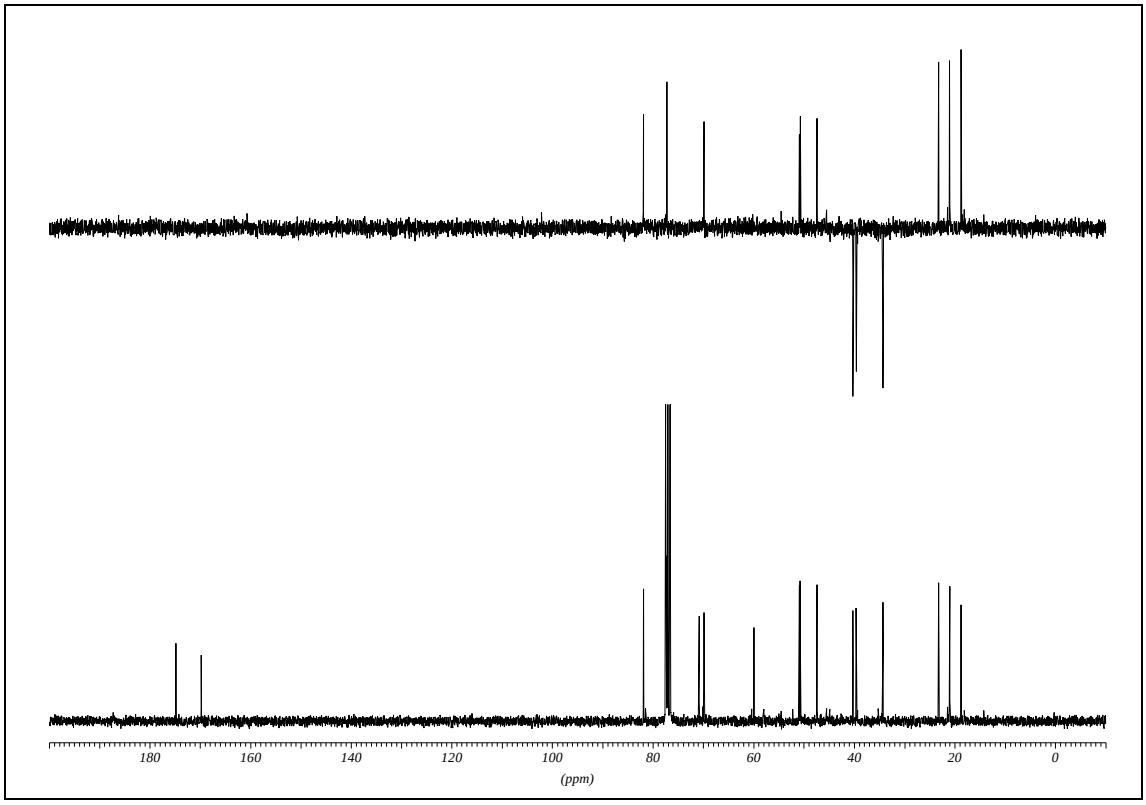
(3aR,4S,6S,6aR,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (61)



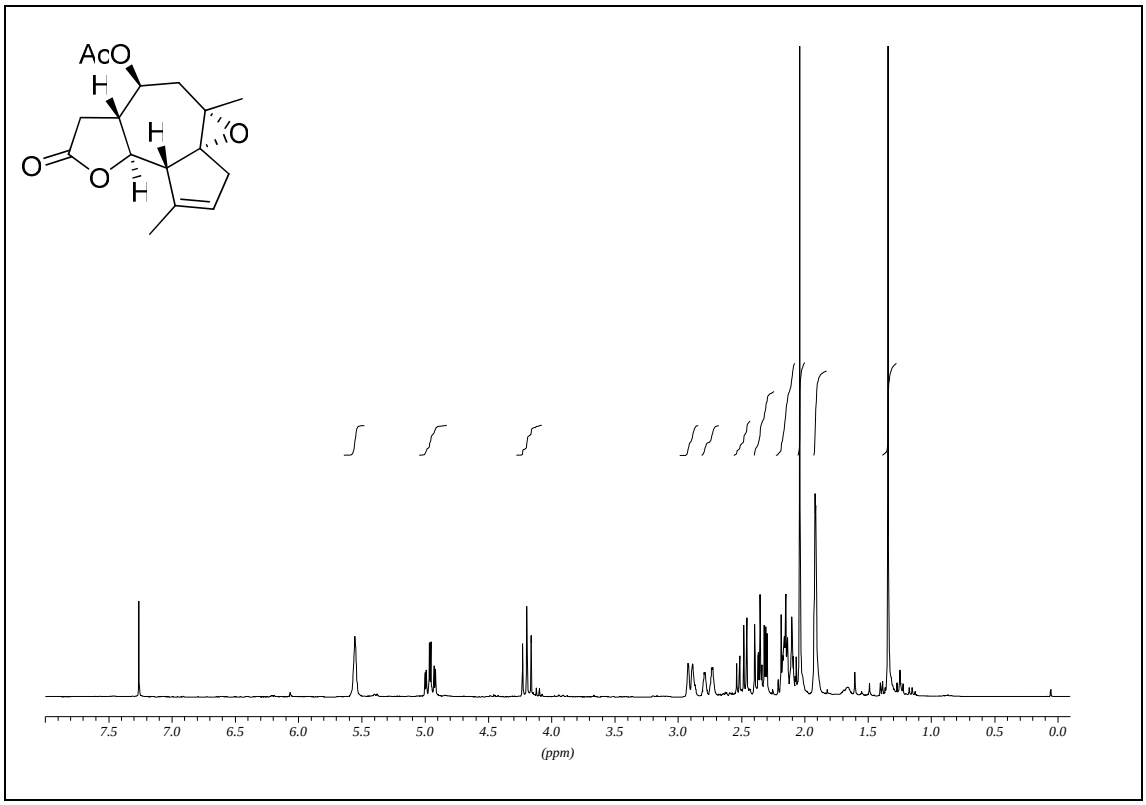


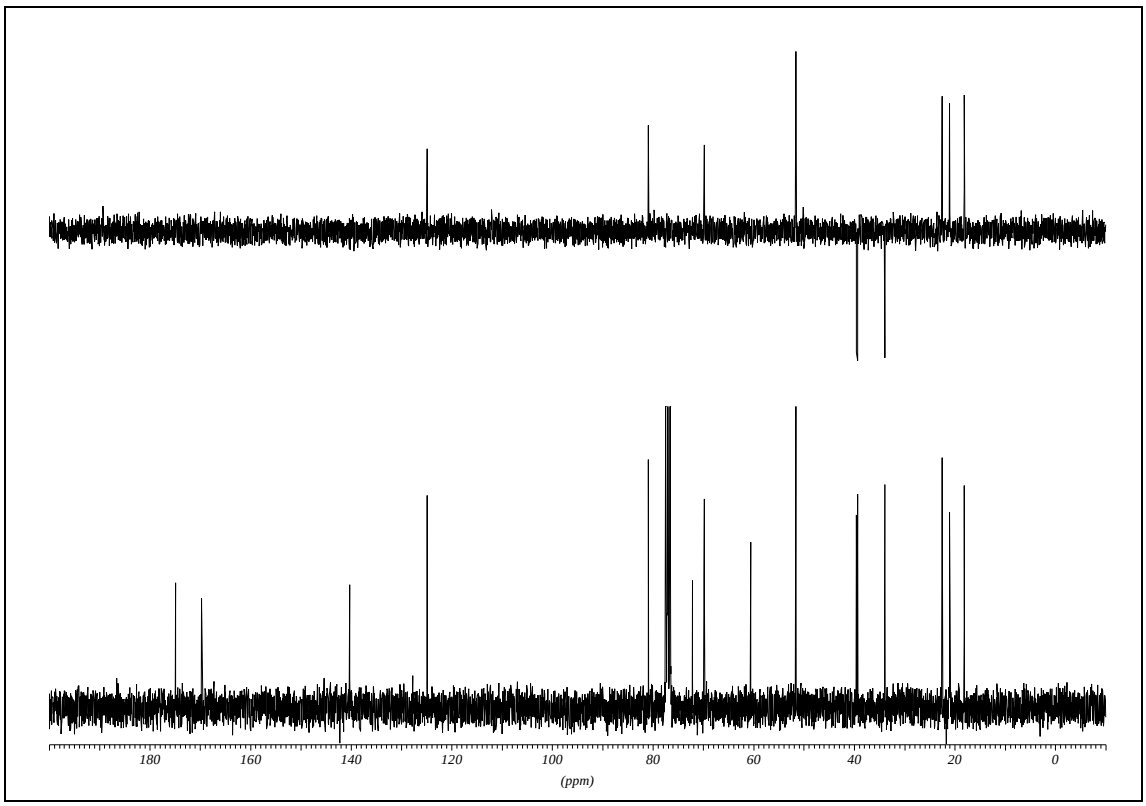
(3aR,4S,6R,6aS,8S,9S,9aS,9bR)-8-hydroxy-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (62)



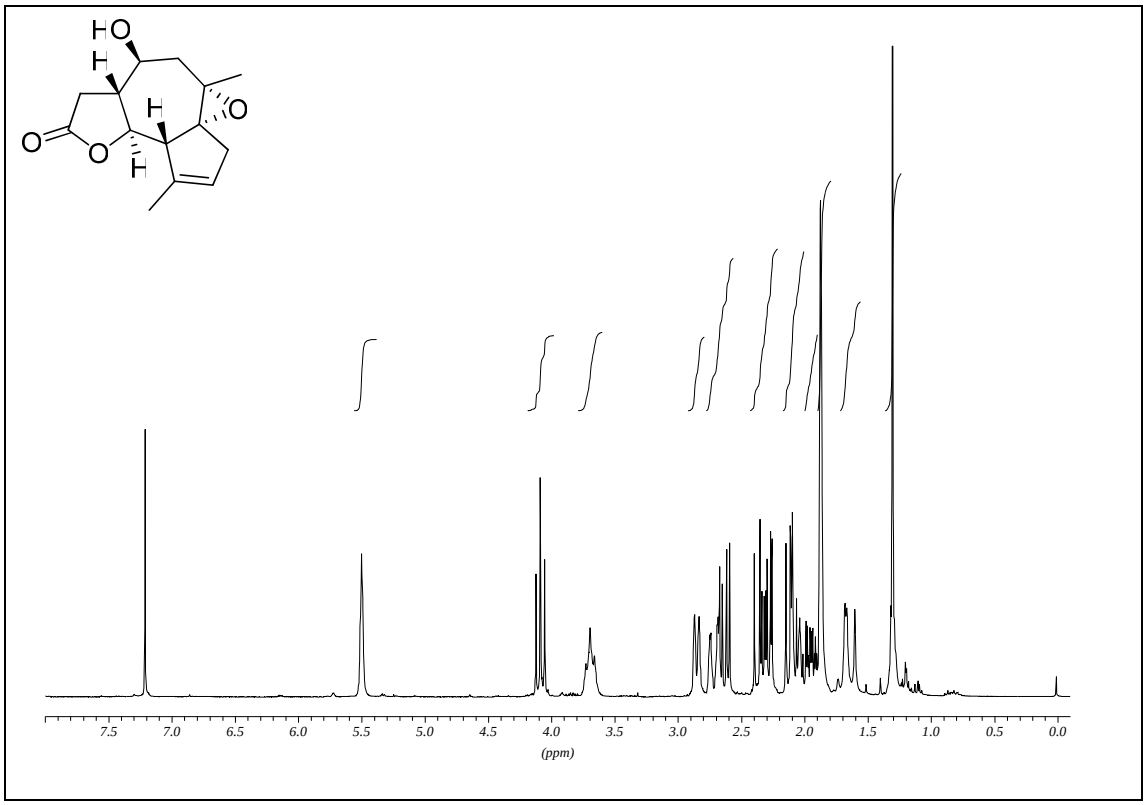


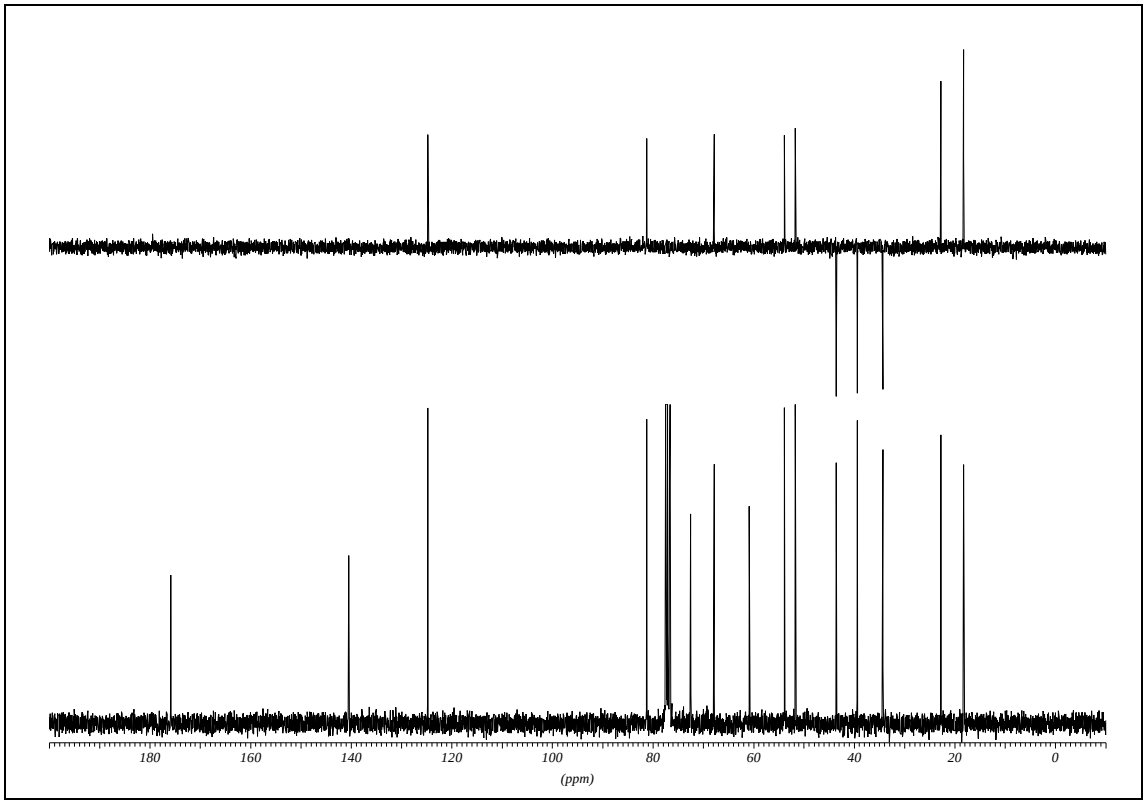
(3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (70)



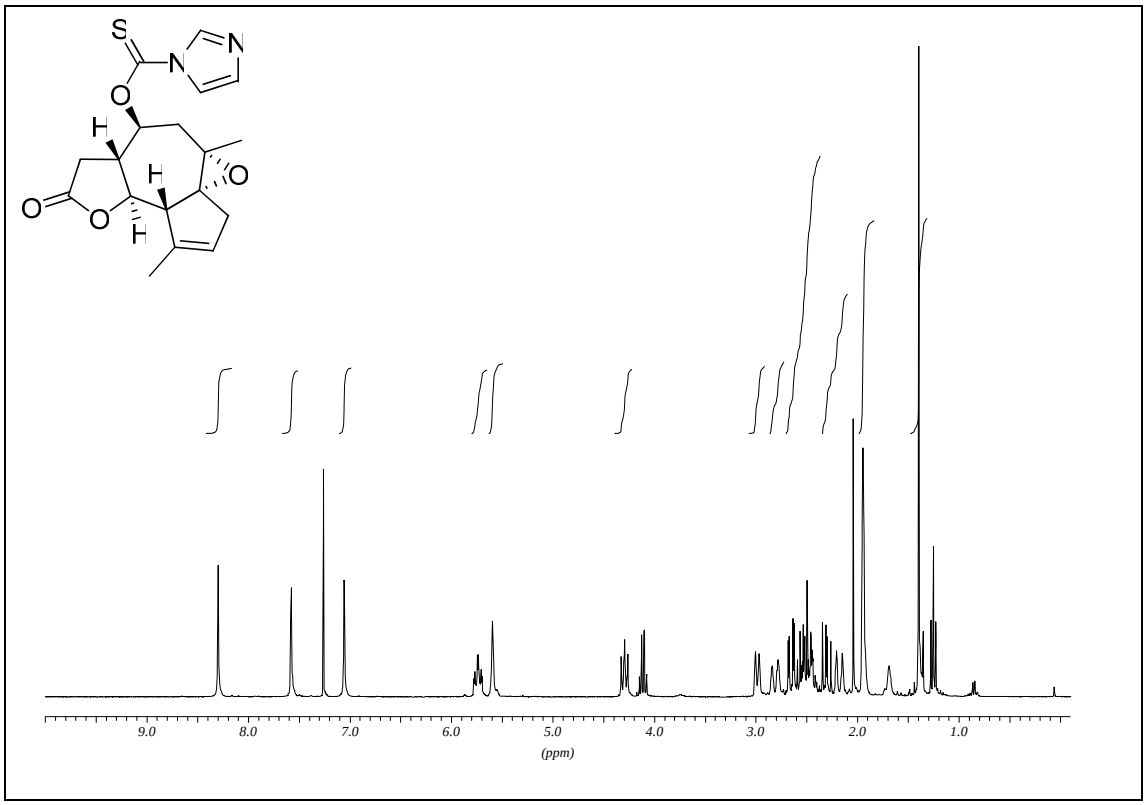


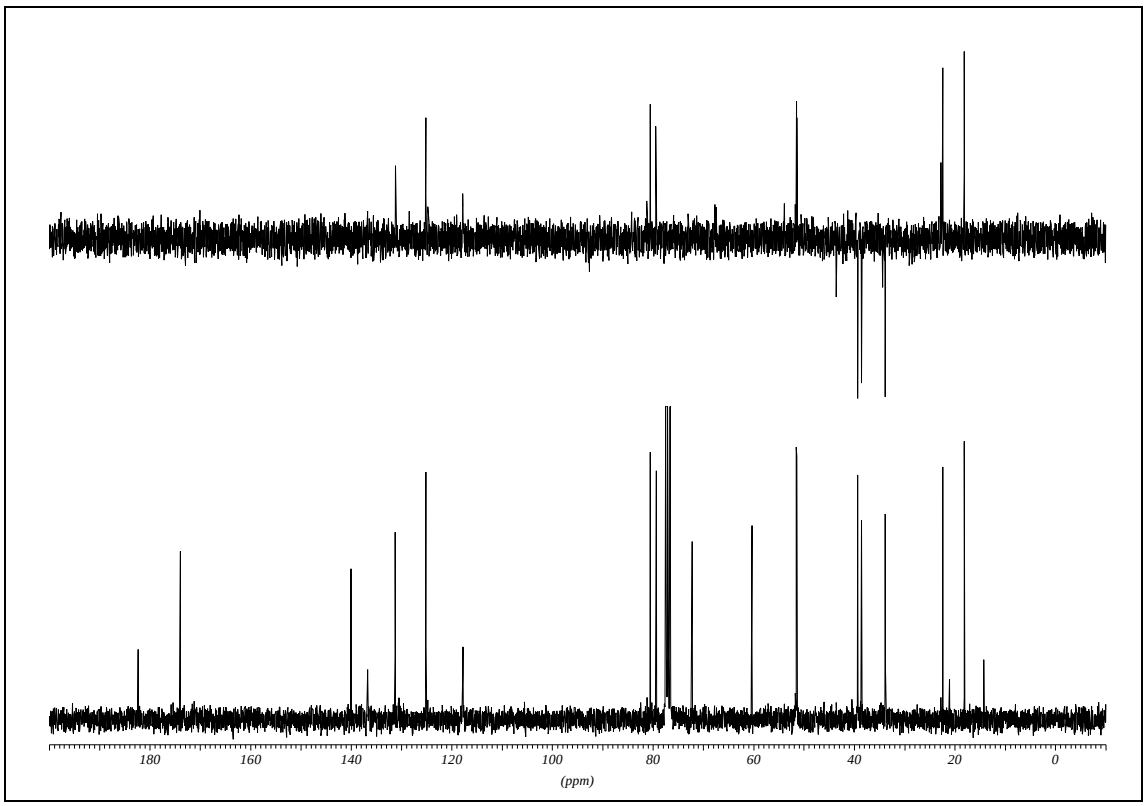
(3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl hydroxide (72)



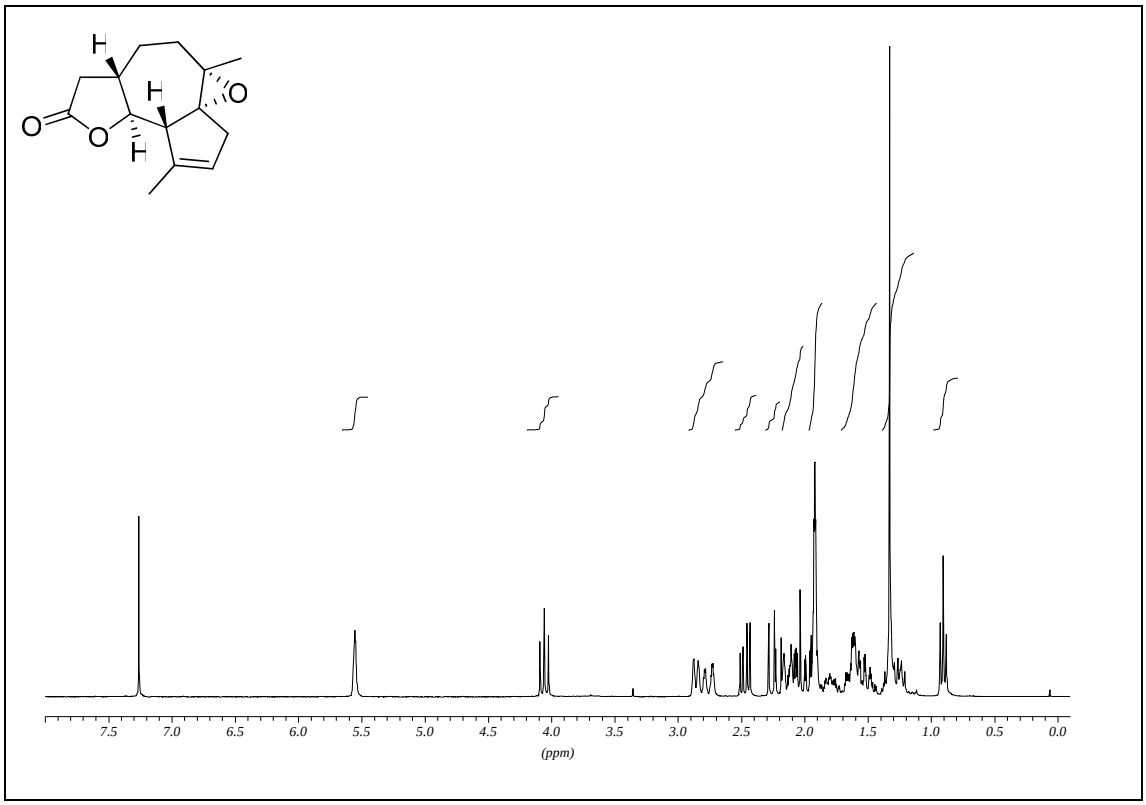


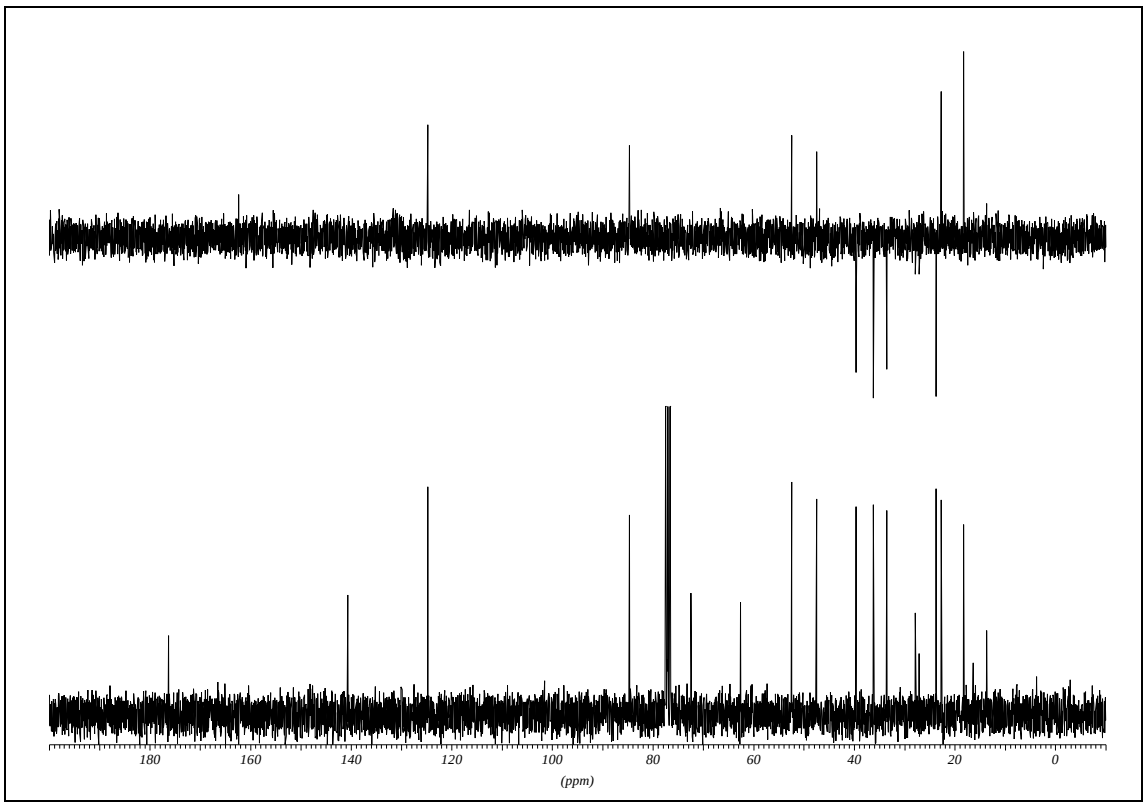
(3aR,4S,6R,6aS,9aS,9bR)-8-en-6,9-dimethyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl-1´H-imidazole-1´-carbothioate (74)



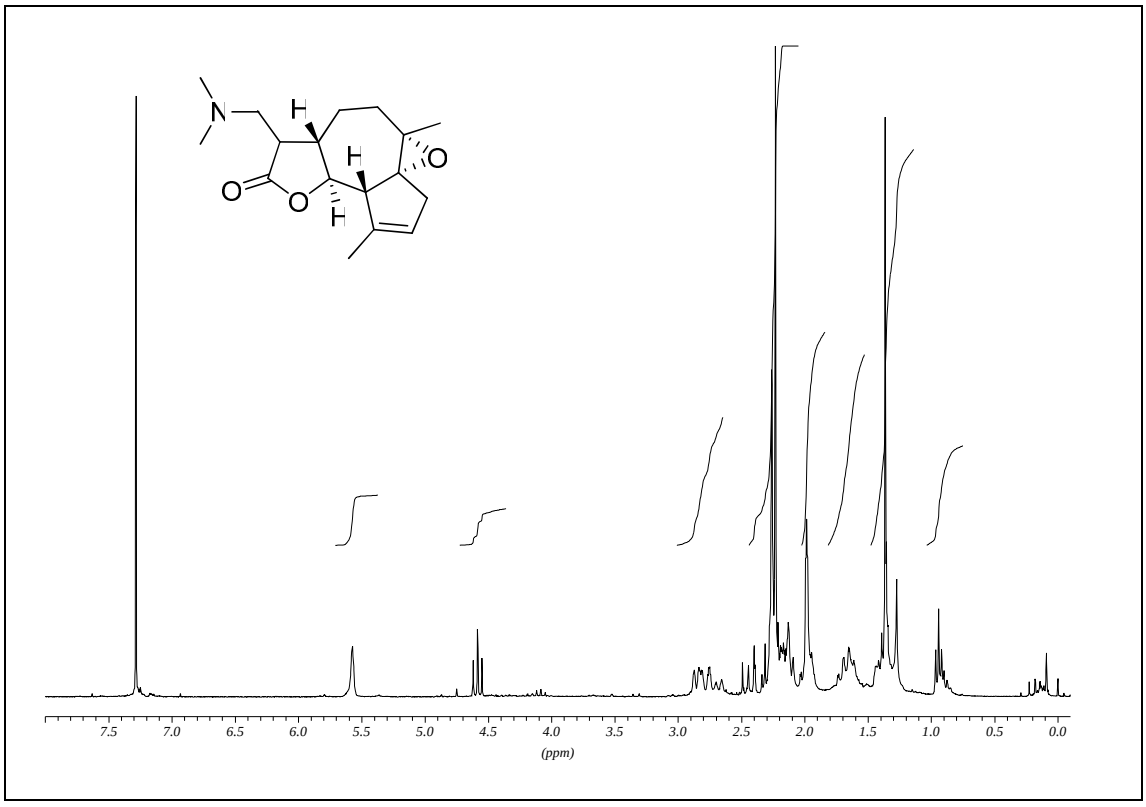


(3[1]R,4aS,6aS,9aS,9bR)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3H-chromeno[5,6-b]furan-8(4aH)-one (75)

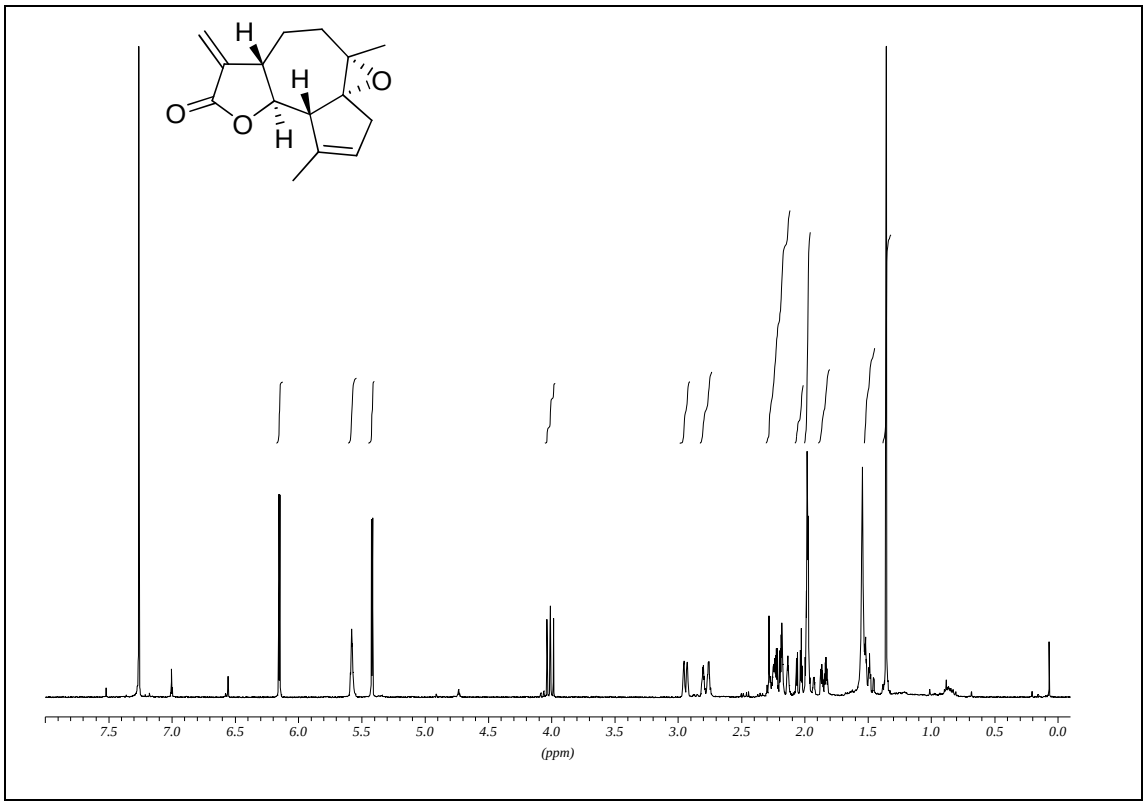




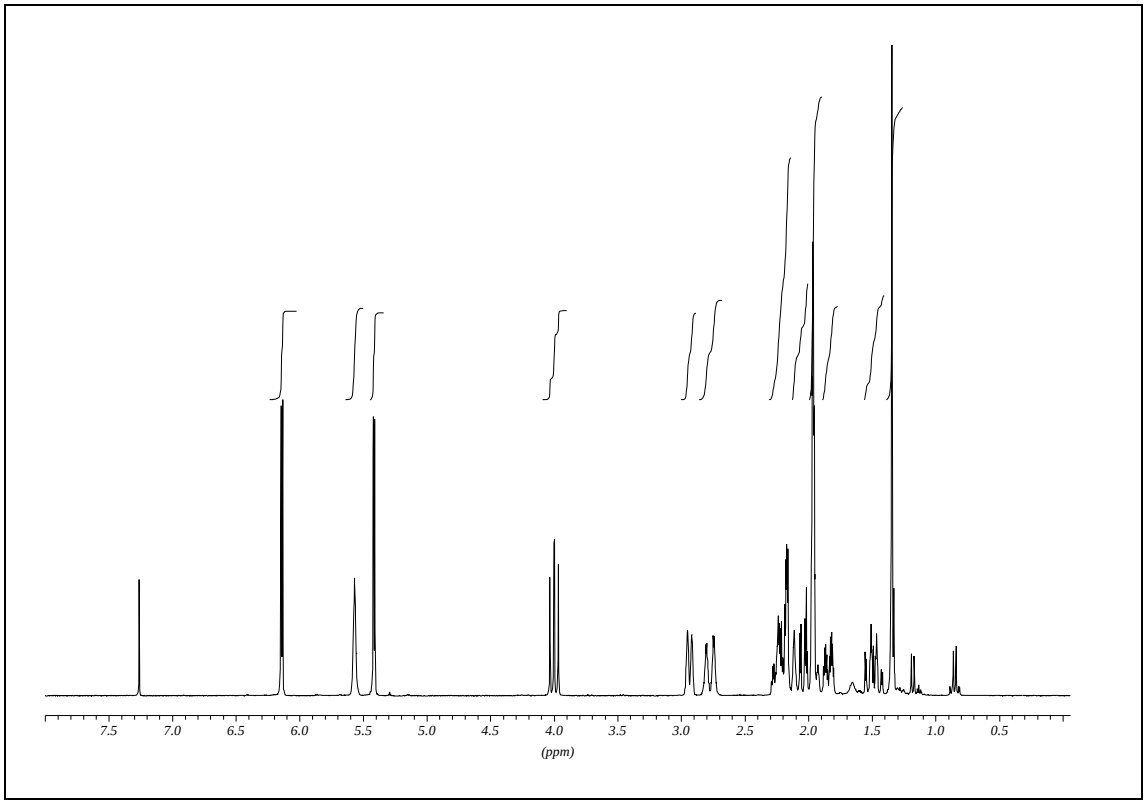
(3[1]R,4aS,6aS,9aS,9bR)-7-((dimethylamino)methyl)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3H-chromeno[5,6-b]furan-8(4aH)-one (77)



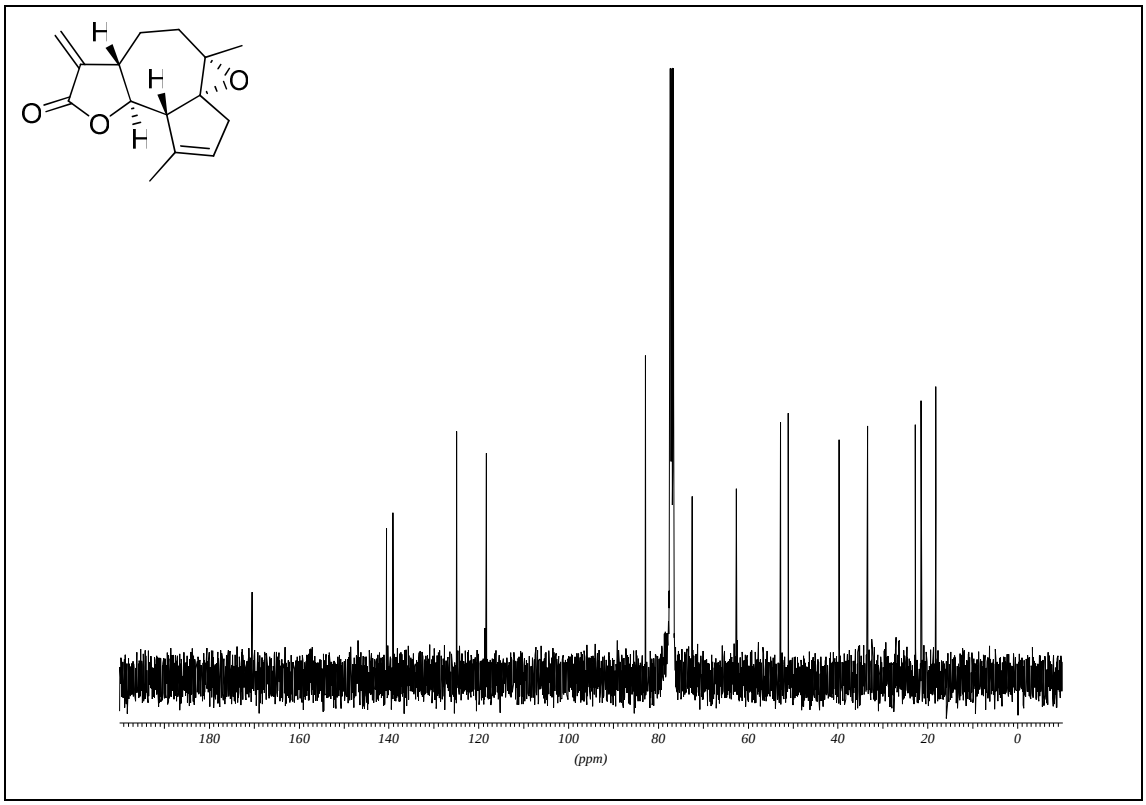
(+)-Arglabin (11) (synthetic sample), $[\alpha]_D^{23}$ = 81.0 (c = 0.3, $CHCl_3$)



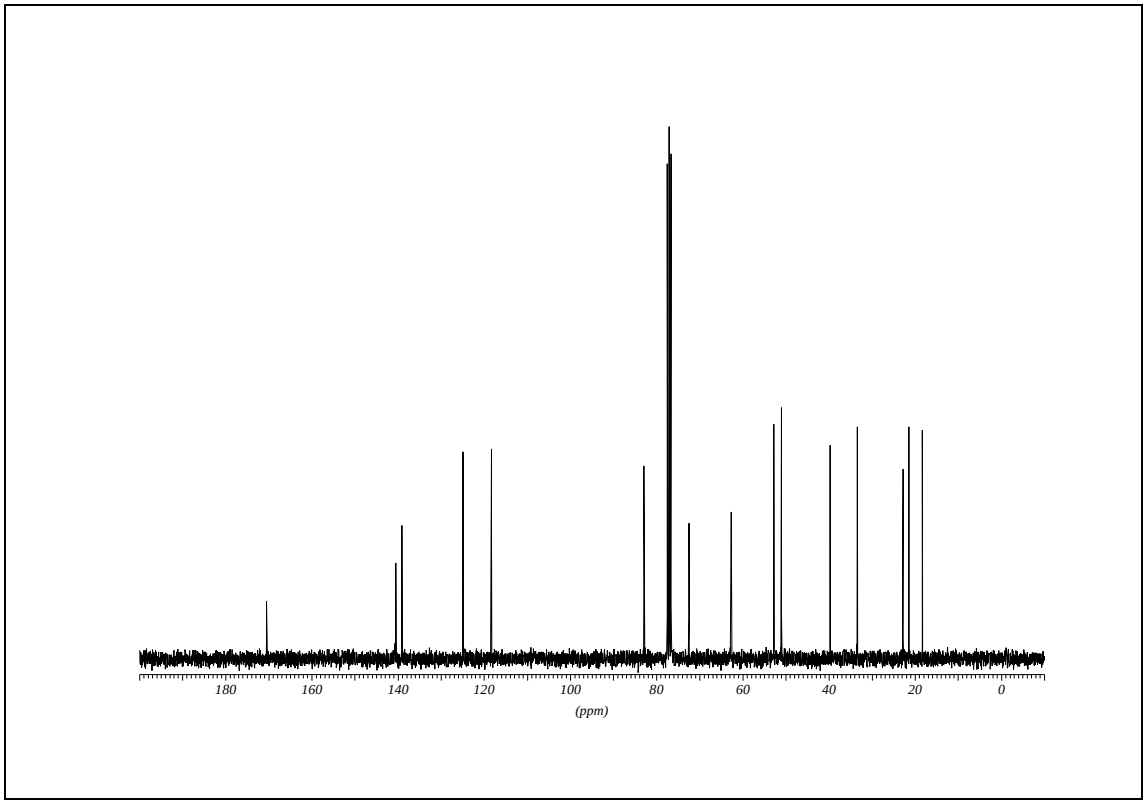
(+)-Arglabin (isolated sample), $[\alpha]_D^{23}$ = 82.1 (c = 0.3, $CHCl_3$)



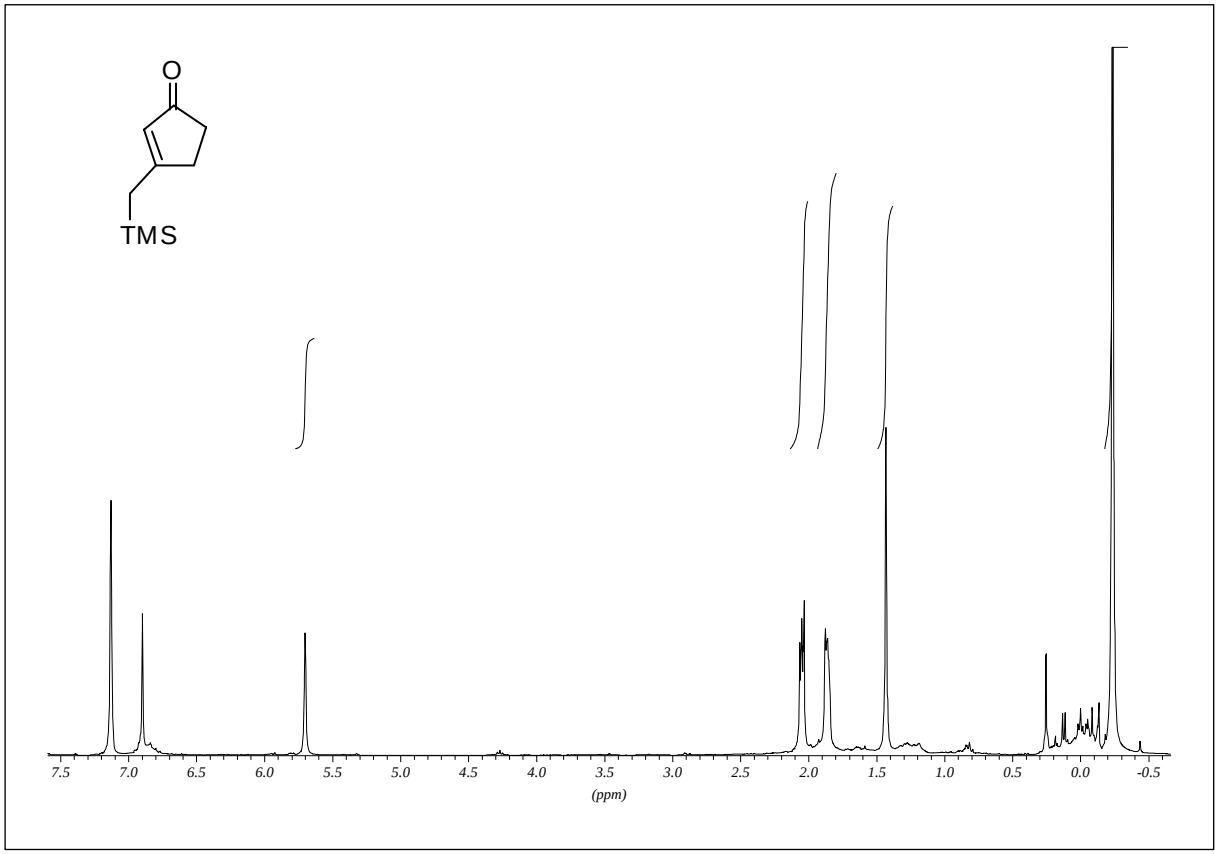
(+)-Arglabin (synthetic sample), $[\alpha]_D^{23}$ = 81.0 (c = 0.3, $CHCl_3$)

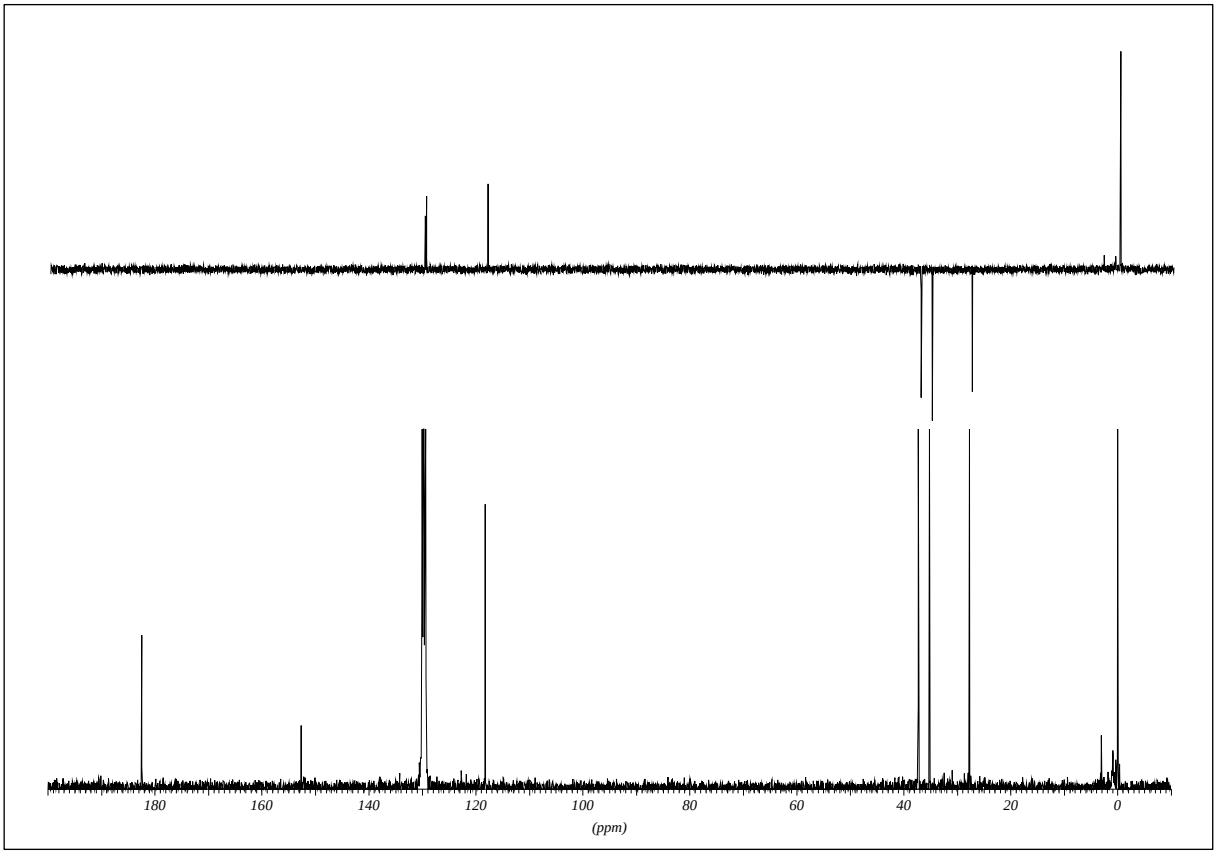


(+)-Arglabin (isolated sample), $[\alpha]_D^{23}$ = 82.1 (c = 0.3, $CHCl_3$)

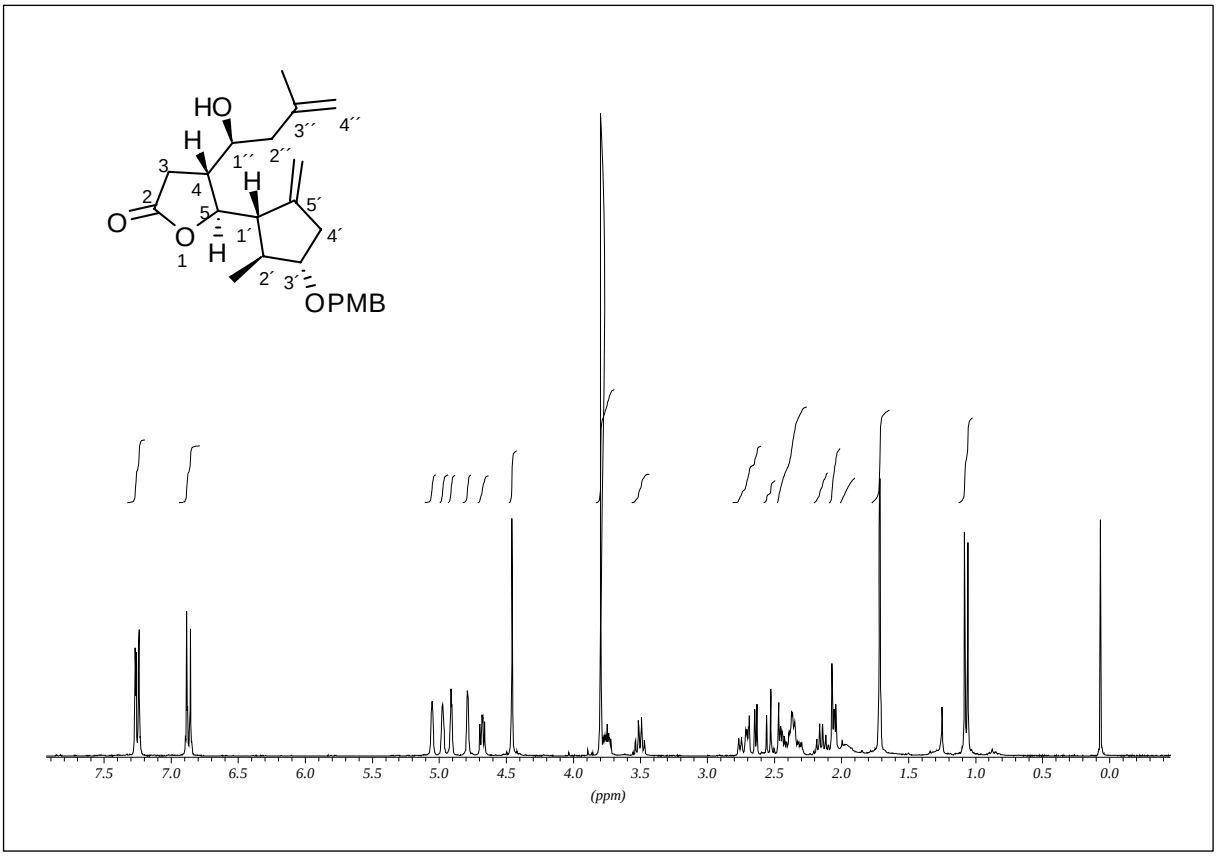


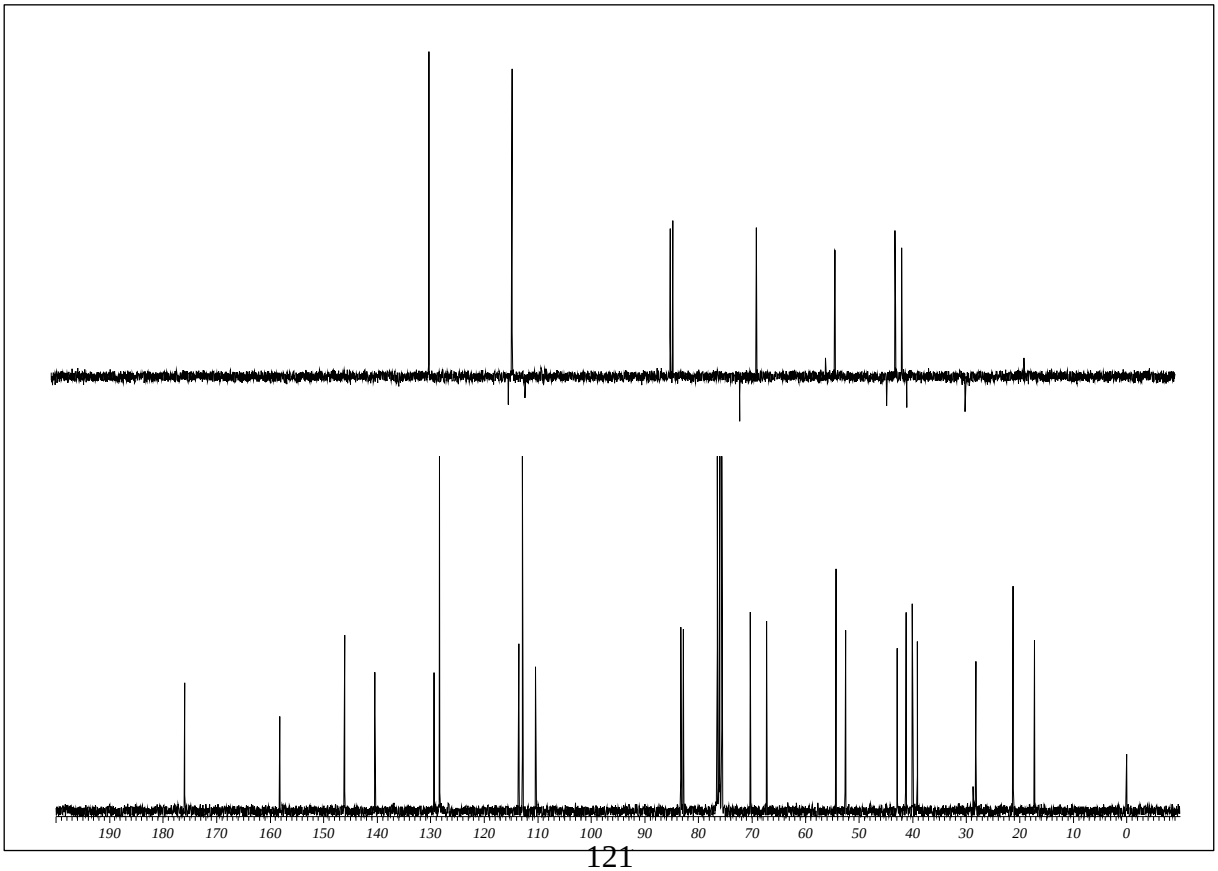
3-((trimethylsilyl)methyl)cyclopent-2-enone (86)



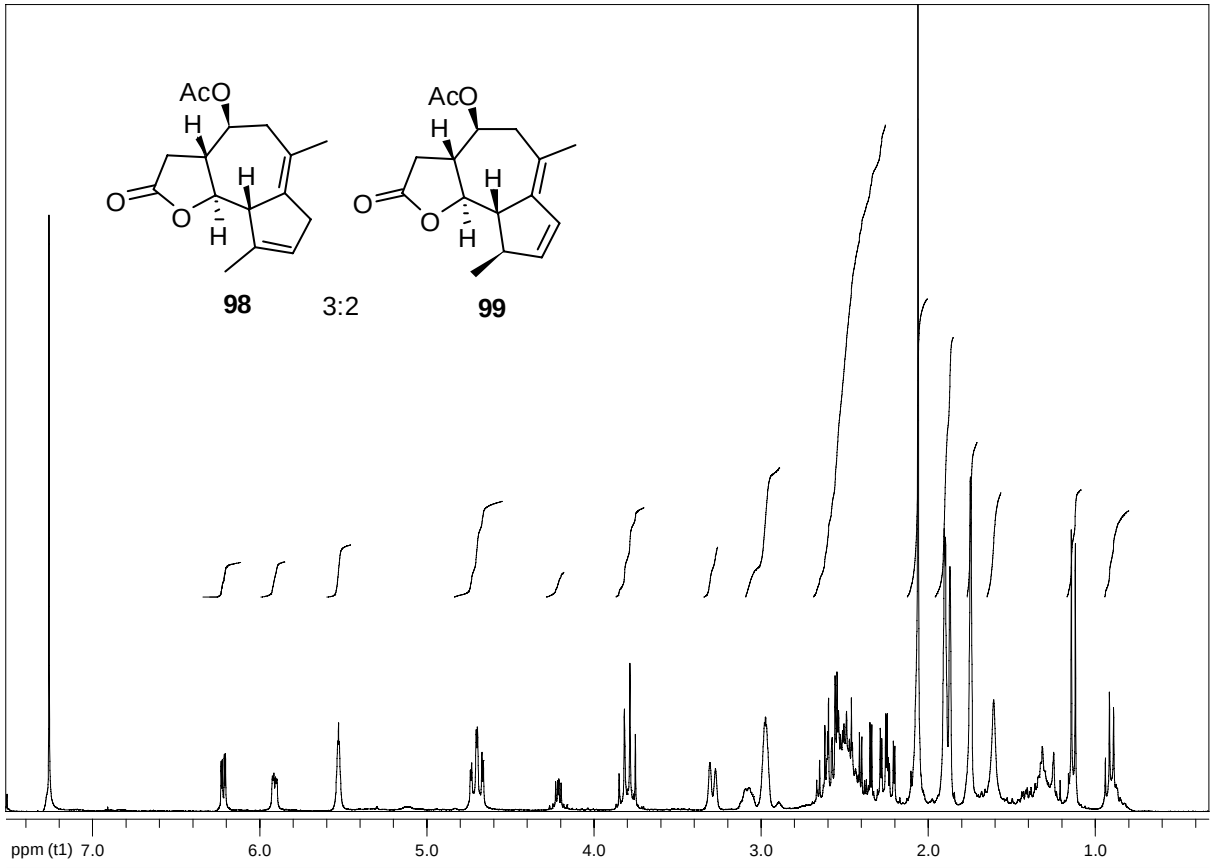


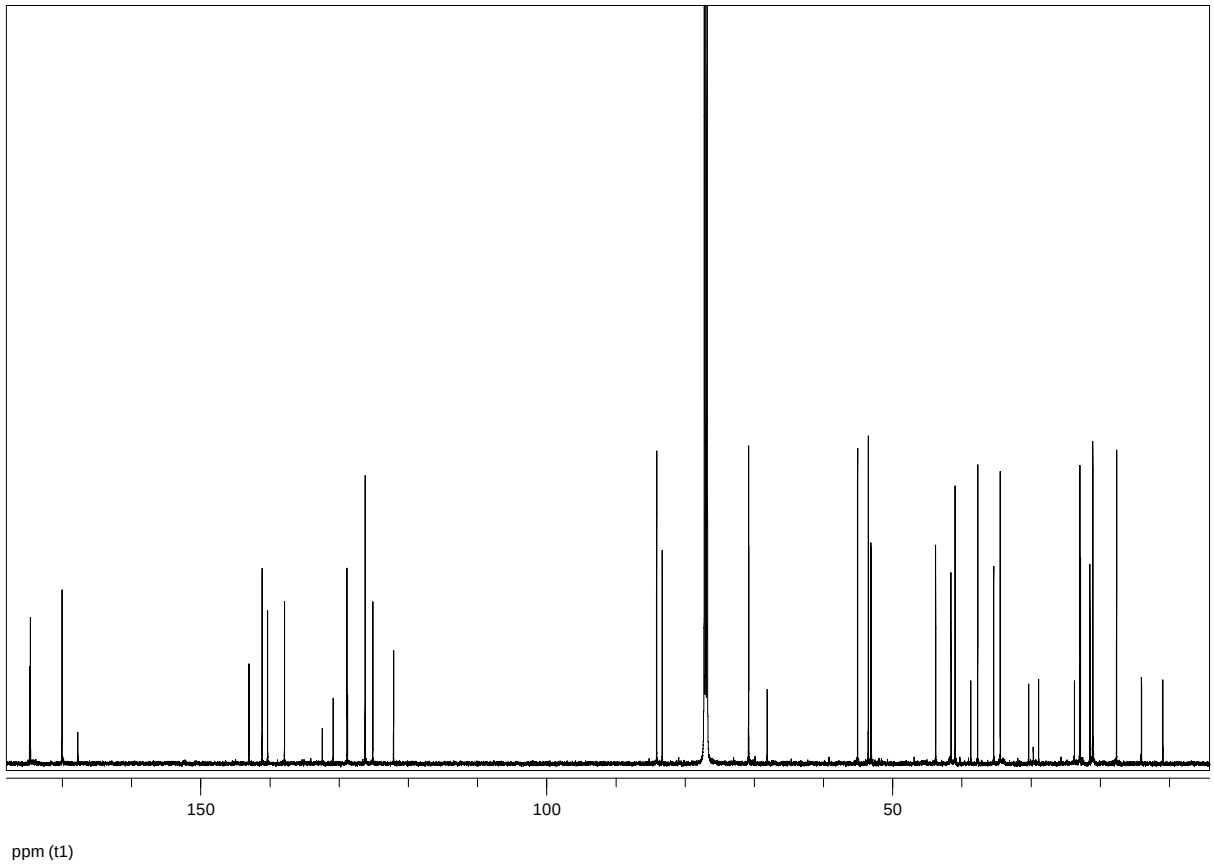
(4*R*,5*R*)-4-((S)-1´´-hydroxy-3´´-methylbut-3´´-enyl)-5-((1´*S*,2´*S*,3´*S*)-3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl)dihydrofuran-2(3H)-one (1´´ *S*: 1´´ *R* = 96:4) (54)



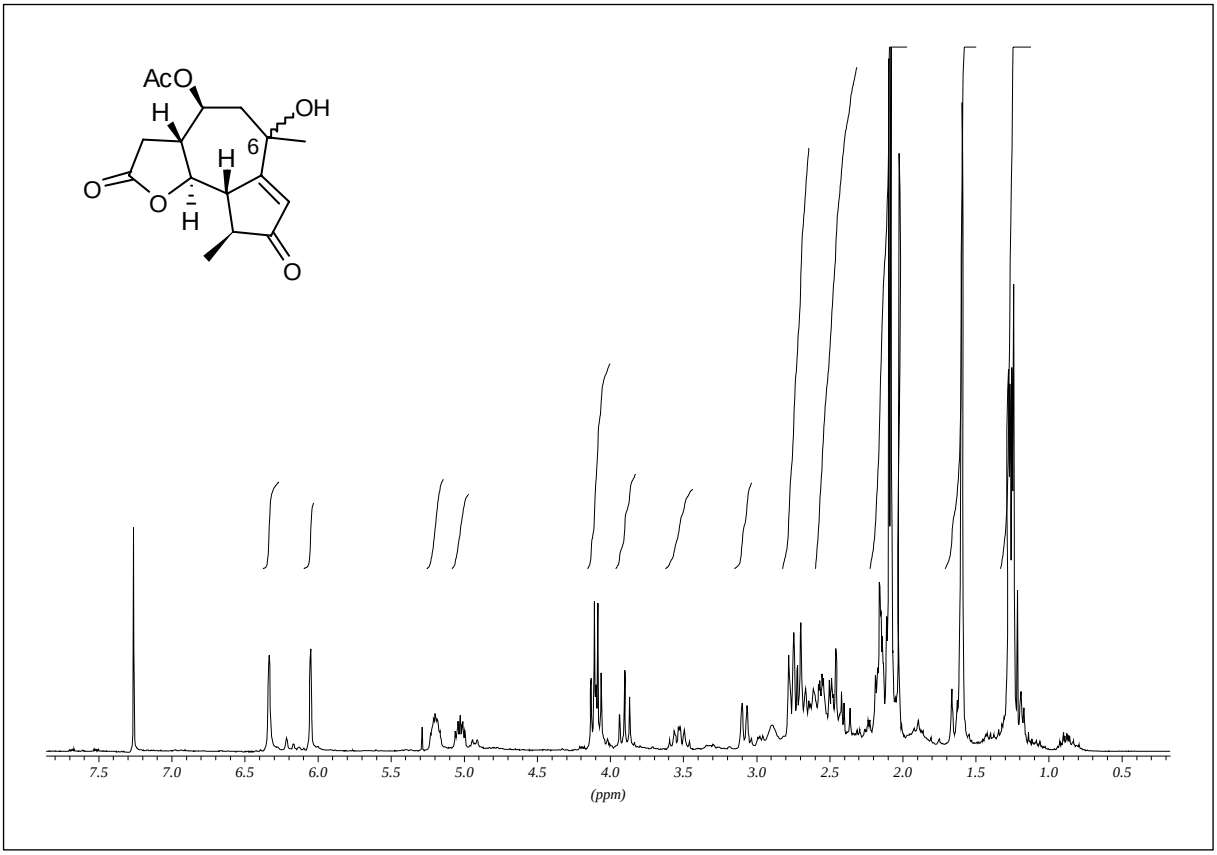


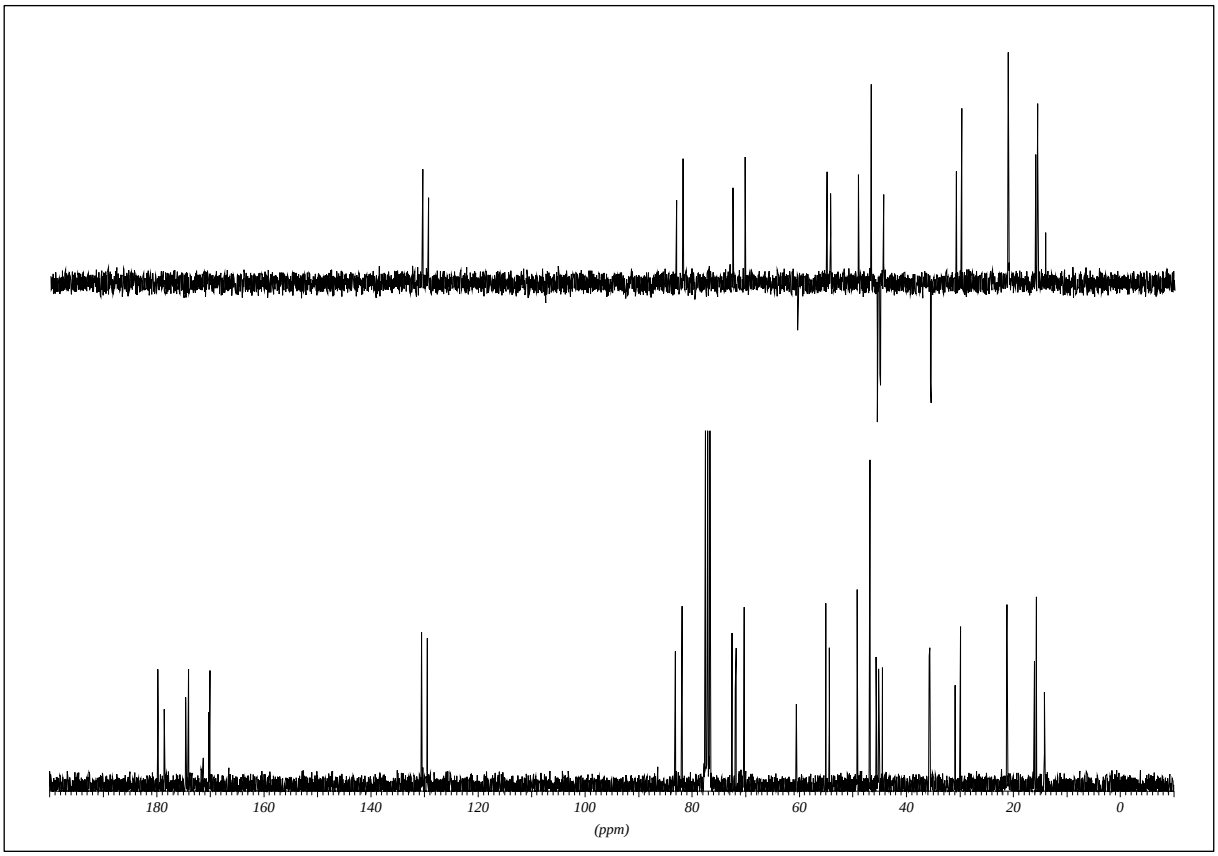
(3aR,4S,9aS,9bR,Z)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (98) and (3aR,4S,9R,9aS,9bR,Z)-6,9-dimethyl-2-oxo-2,3,3a,4,5,9,9a,9b-octahydroazuleno[4,5-b]furan-4-yl acetate (99)



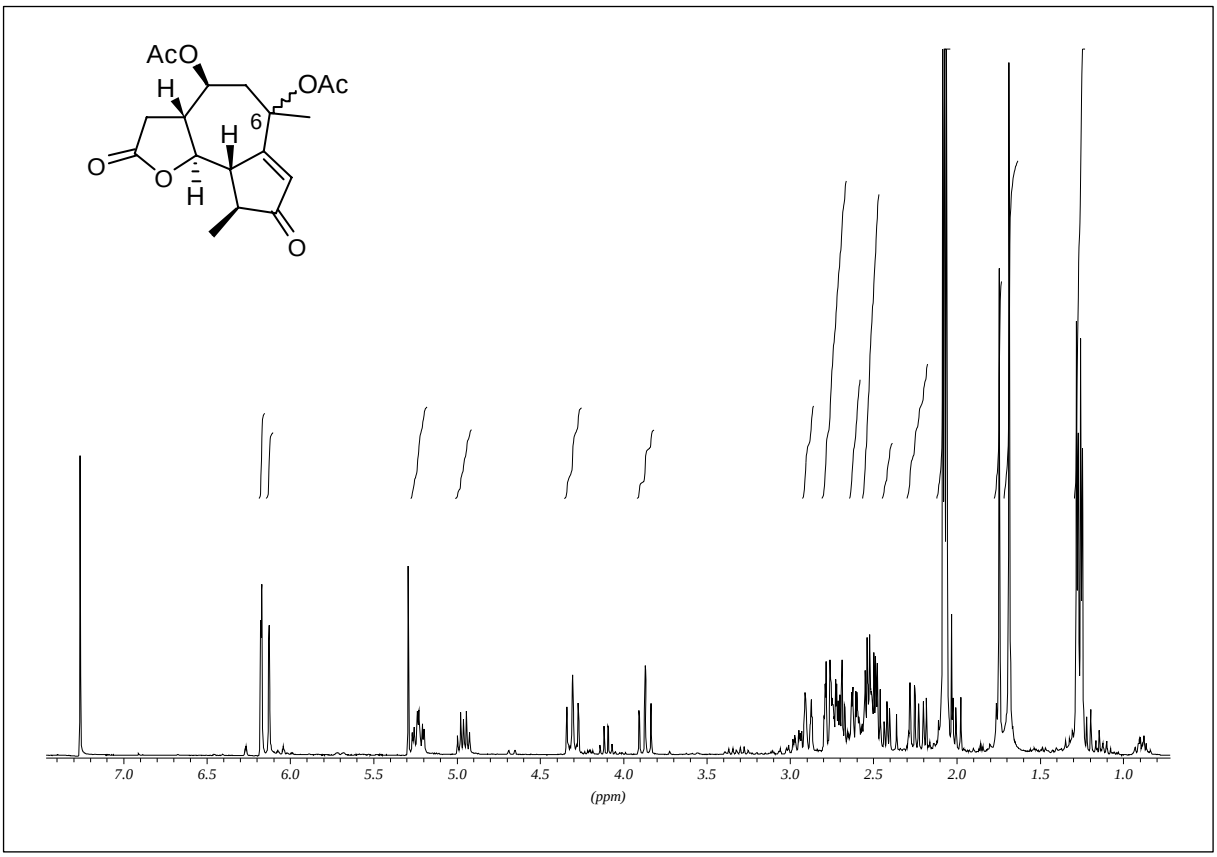


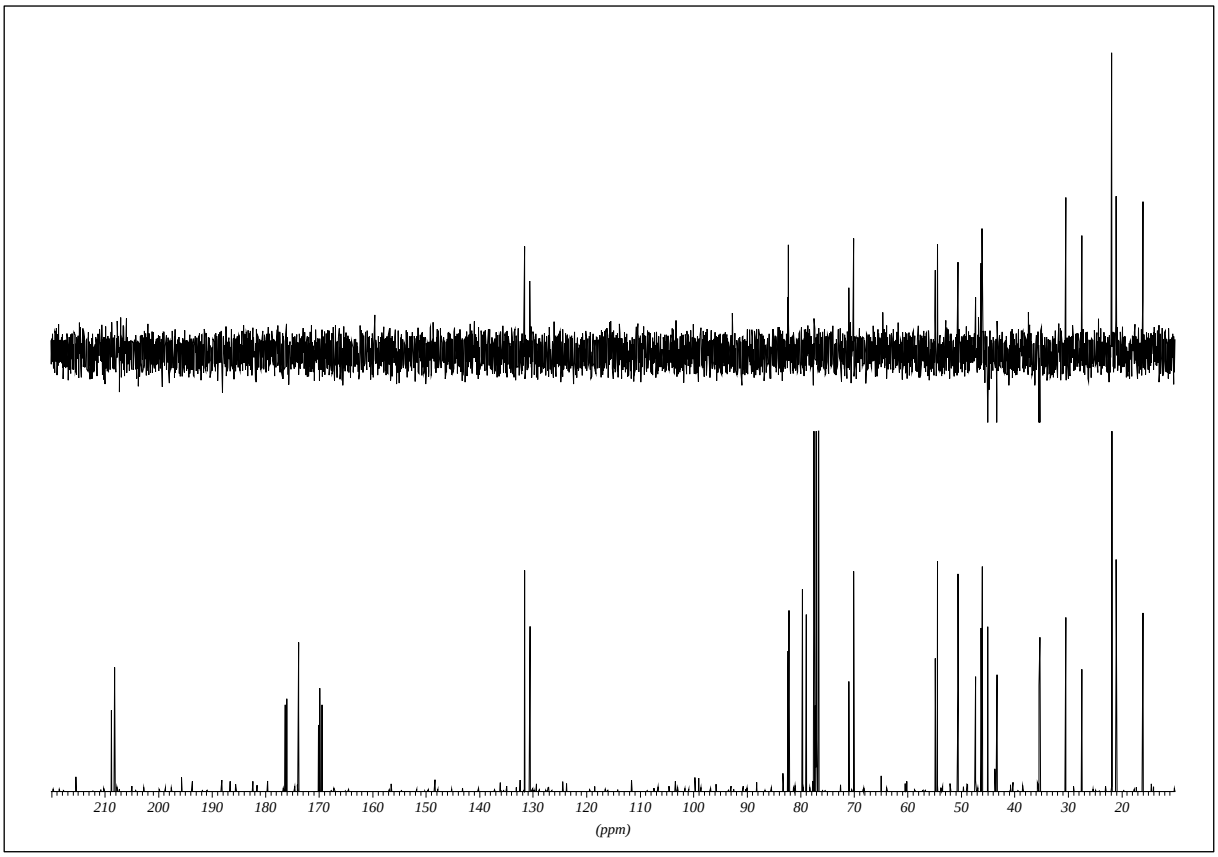
3aR,4S,6R,9S,9aS,9bR)-6-hydroxy-6,9-dimethyl-2,8-dioxo-2,3,3a,4,5,6,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (6 *R*: 6 *S*=1:1) (101)



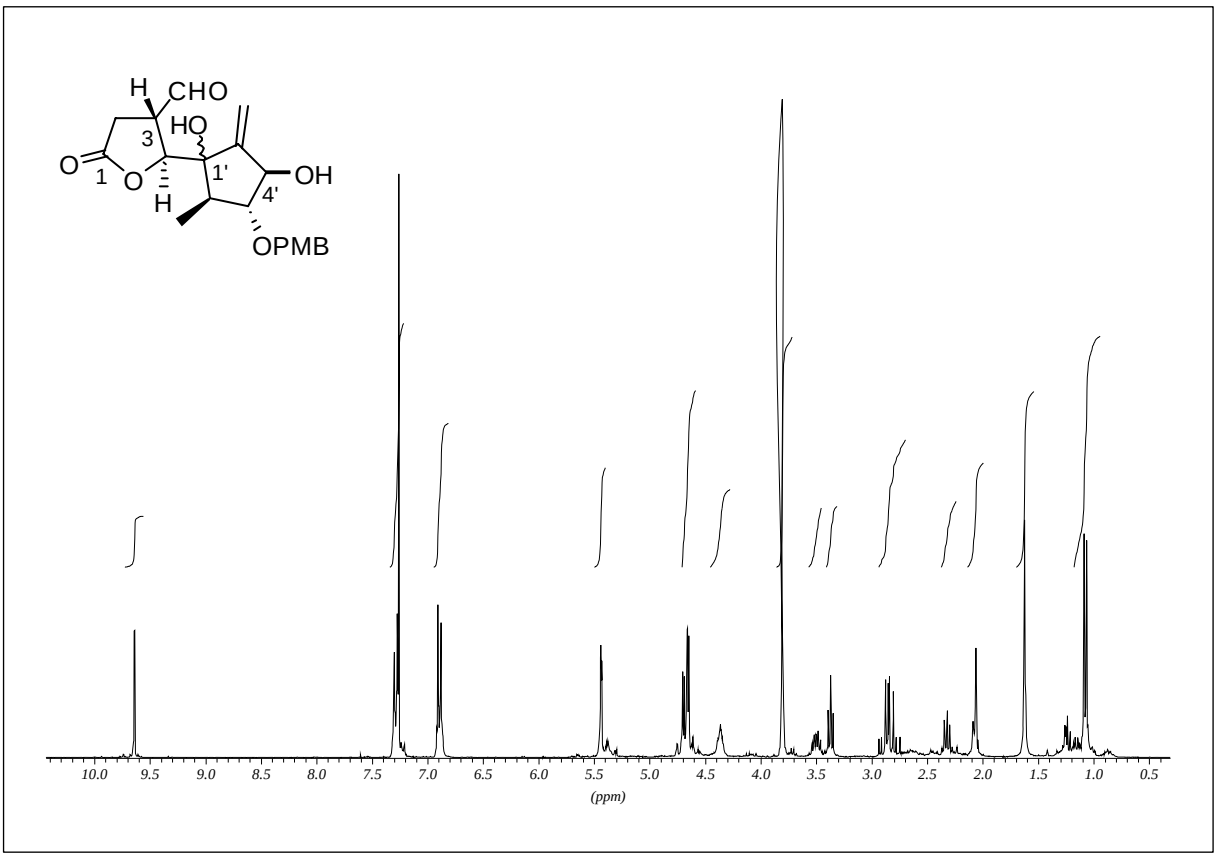


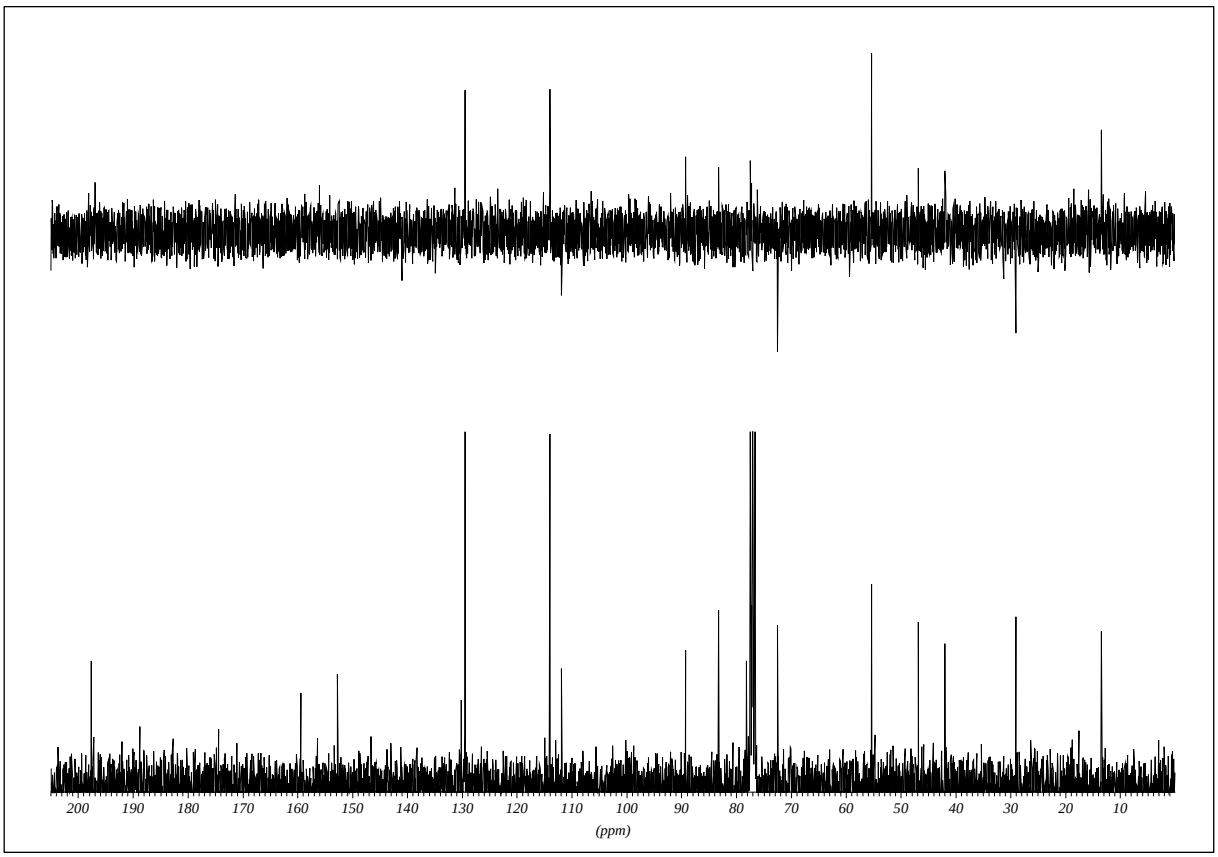
(3aR,4S,6R,9S,9aS,9bR)-6,9-dimethyl-2,8-dioxo-2,3,3a,4,5,6,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4,6-diyl diacetate (6 *R*: 6 *S*=1:1) (120)



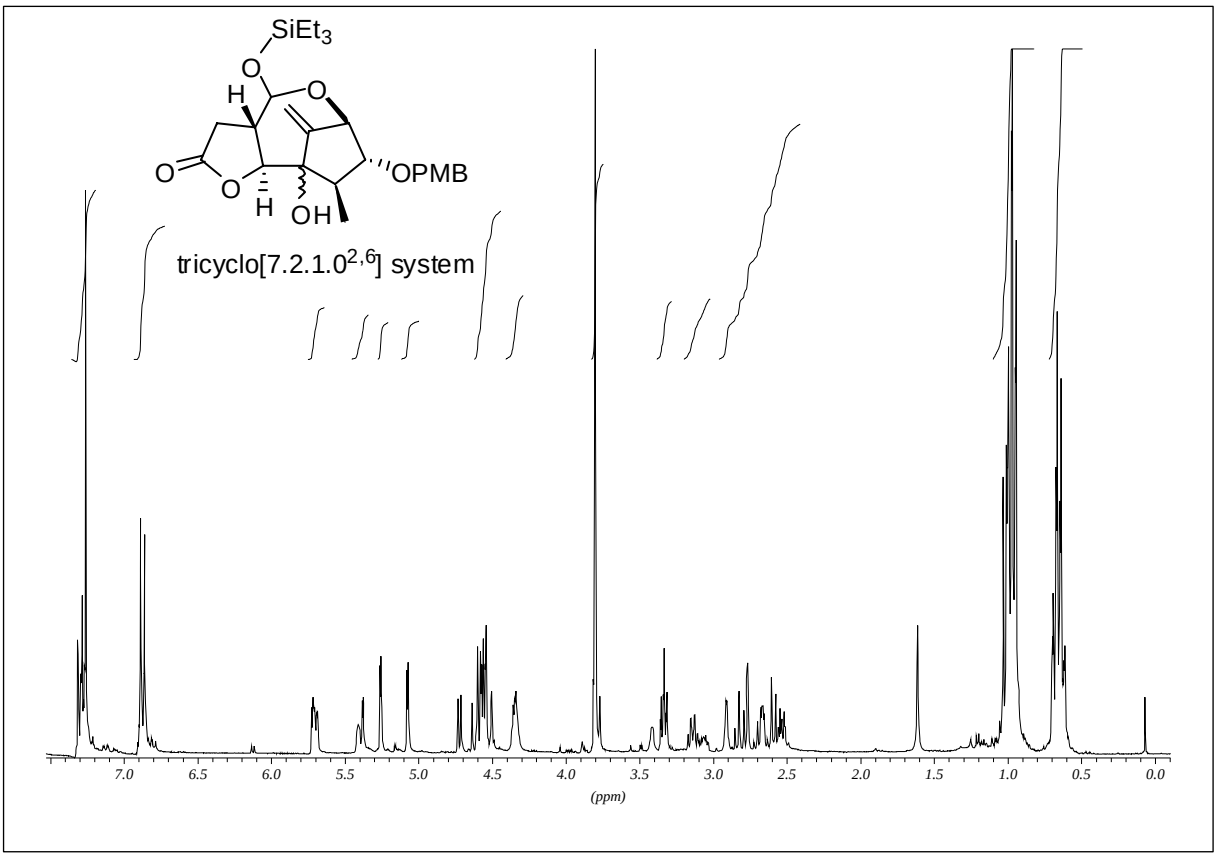


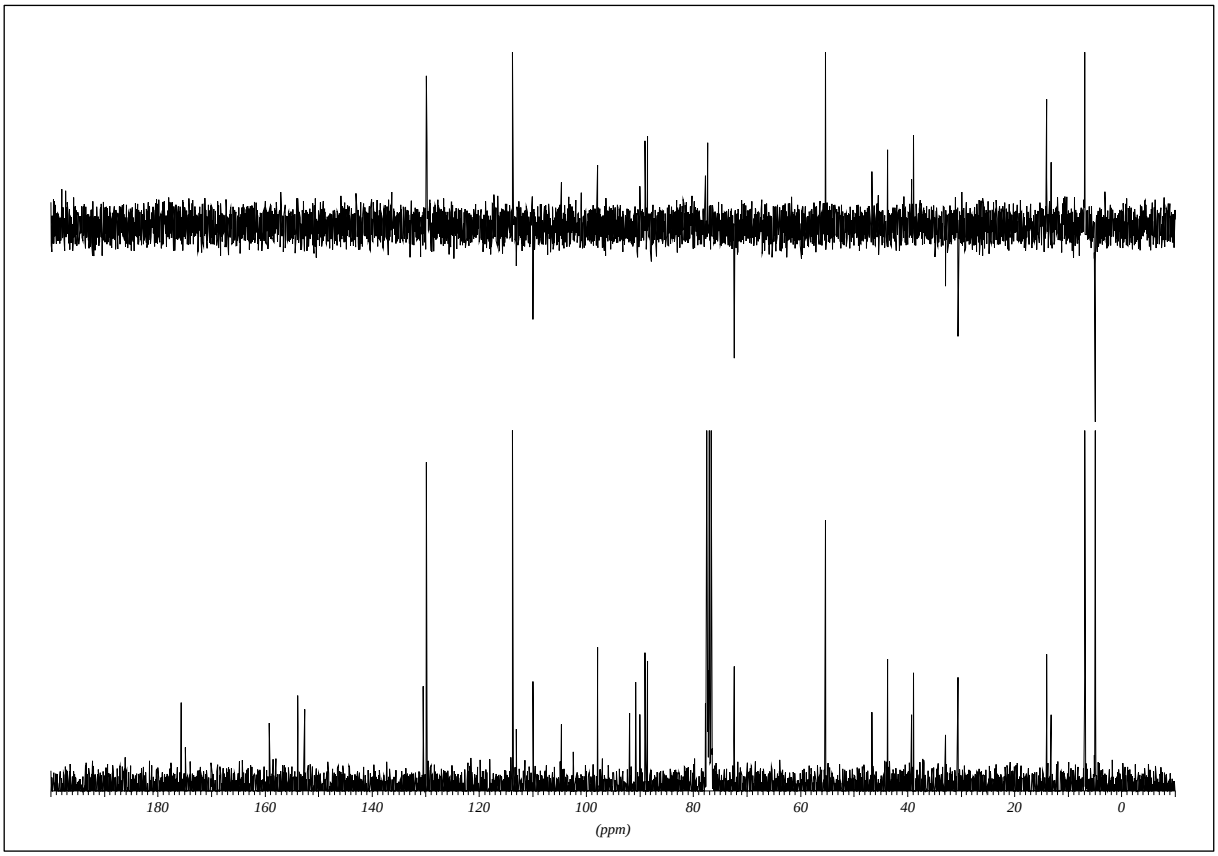
(2*R*,3*S*)-2-((1´*S*,2´*S*,3´*S*)- 1`,5`,-dihydroxy 3´-(4-methoxybenzyloxy)-2´-methyl-5´-methylenecyclopentyl) Oxotetrahydrofuran-3-carbaldehyde (102)



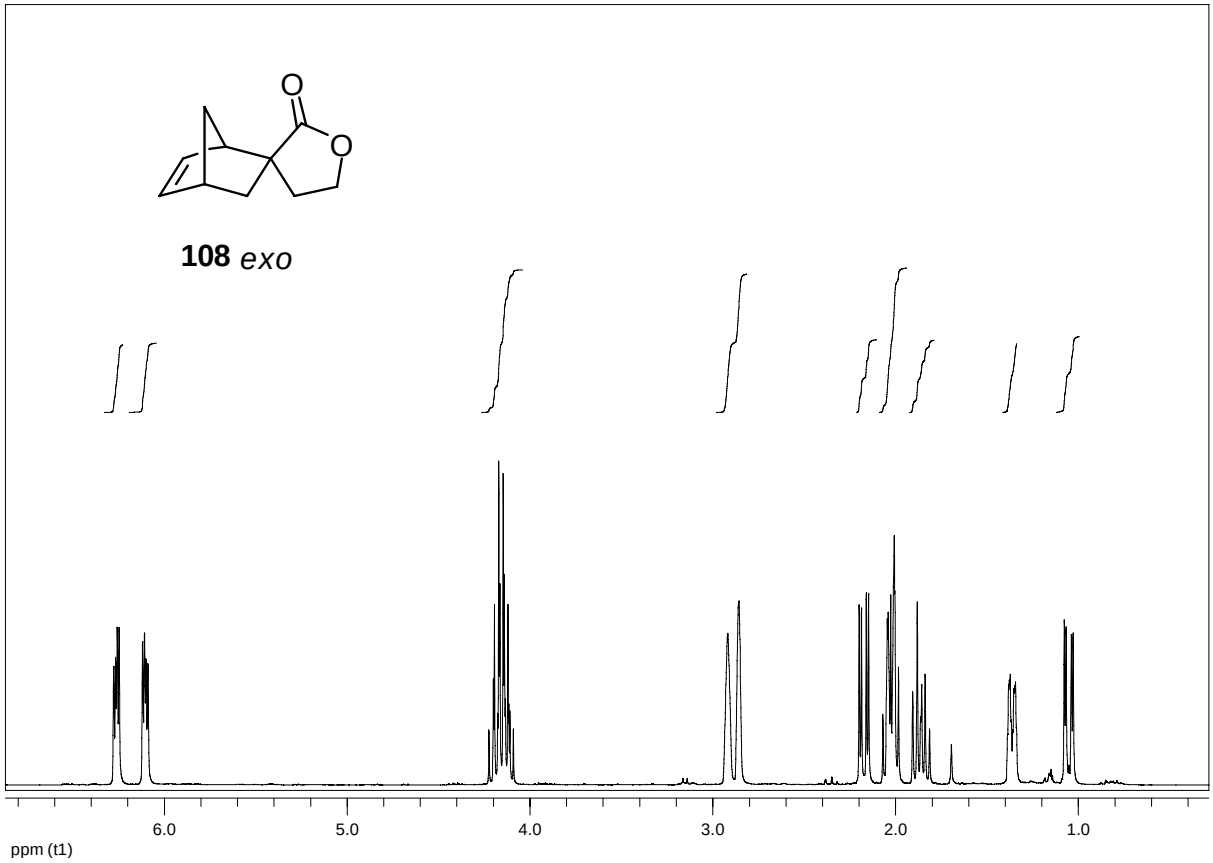


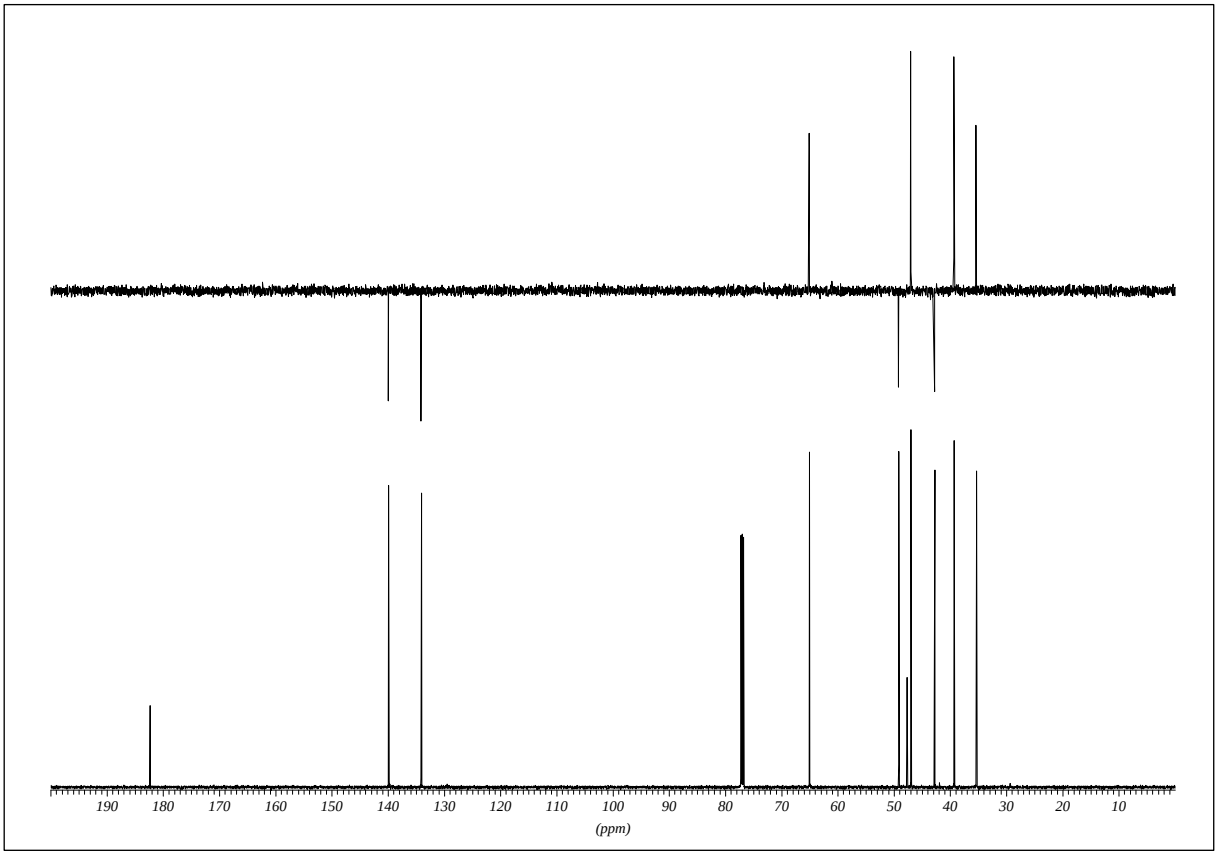
Compound 103



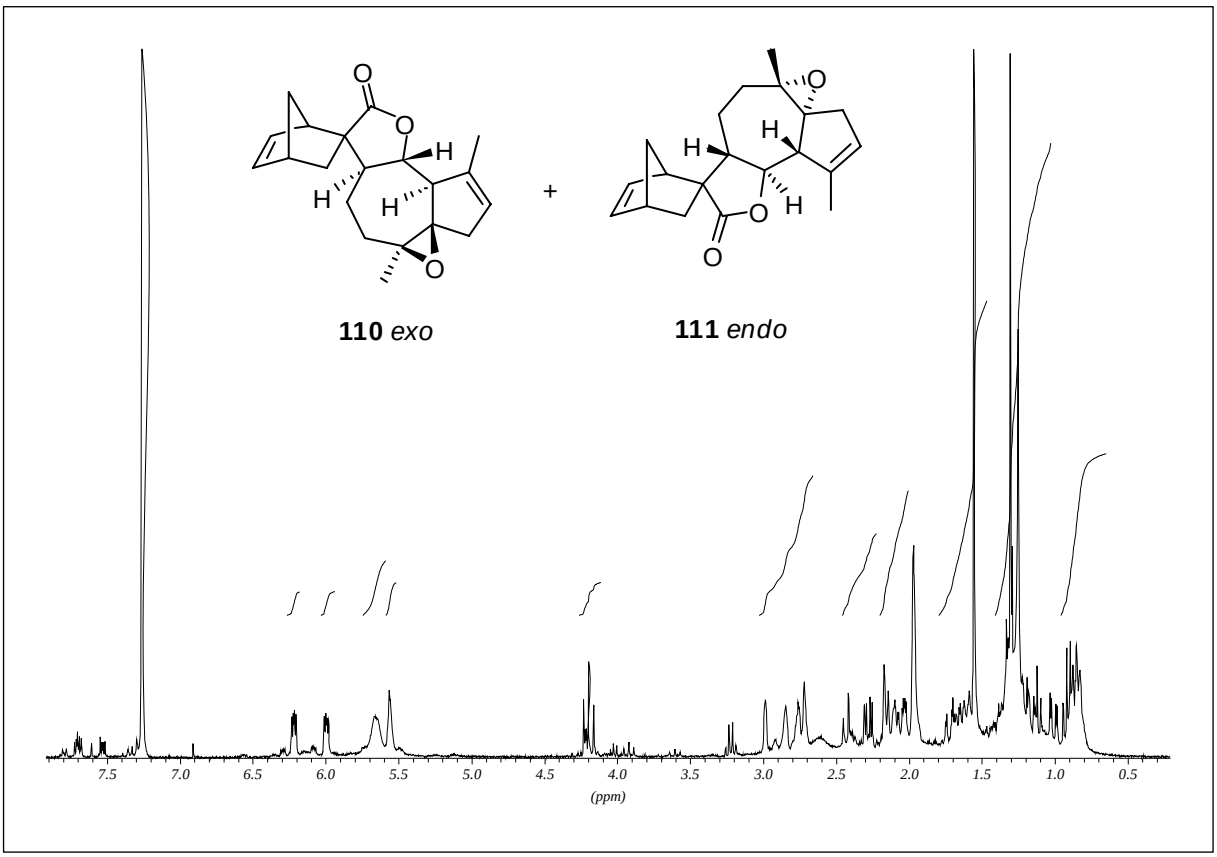


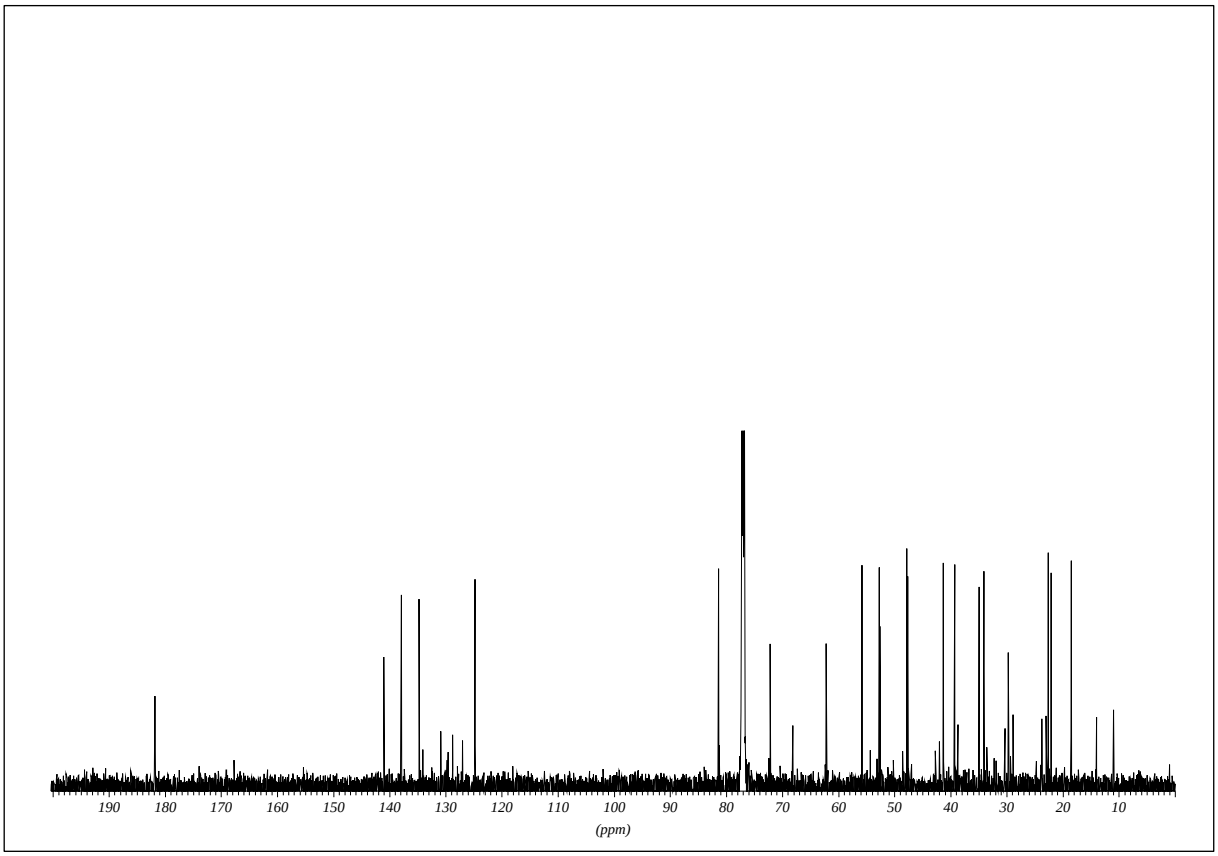
4',5'-dihydro-2'H-spiro[bicyclo[2.2.1]hept[5]ene-2,3'-furan]-2'-one (108, *exo*)



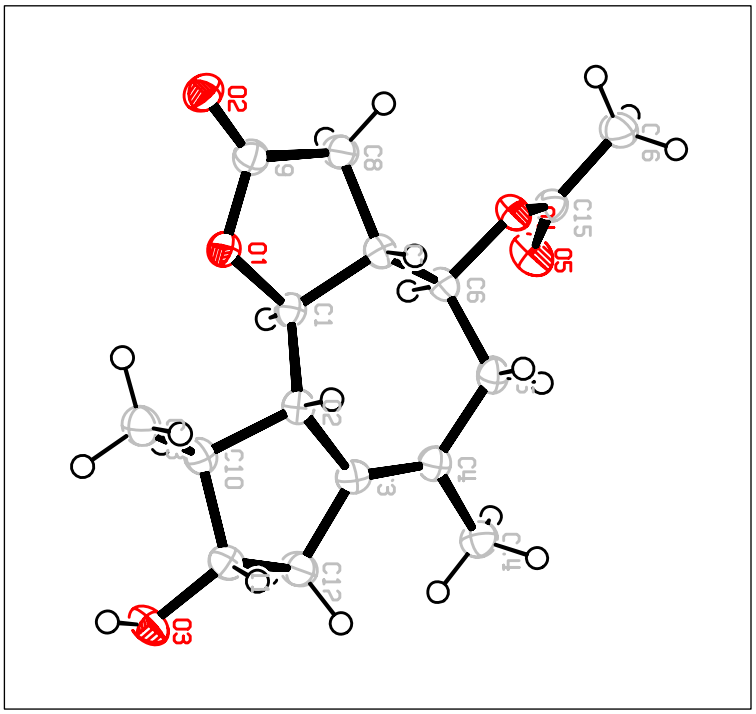


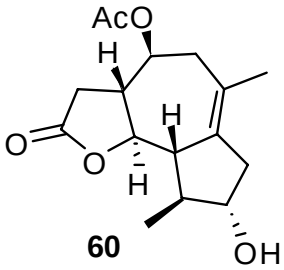
Compounds 110 (*exo*) and 111 (*endo*)





13.2 X-ray data





60

Crystal data and structure refinement for f226.

Crystal Data Table 1 .

Empirical formula ;	C16 H22 O5
Formula weight ;	294.34
Crystal size ;	0.380 x 0.160 x 0.060 mm
Crystal description ;	rod
Crystal colour ;	colourless
Crystal system;	Orthorhombic
Space group ;	P 21 21 21
Unit cell dimensions	a = 6.7210(5) A alpha = 90 deg. b = 11.3264(8) A beta = 90 deg. c = 20.238(2) A gamma = 90 deg.
Volume ;	1540.6(2) A^3
Z, Calculated density ;	4, 1.269 Mg/m^3
Absorption coefficient ;	0.094 mm^{-1}

F(000) ;	632

Data Collection

Measurement device type;	STOE-IPDS diffractometer
Measuremnet method;	rotation
Temperature;	123(1) K
Wavelength;	0.71073 A
Monochromator;	graphite
Theta range for data collection;	3.19 to 26.95 deg.
Index ranges;	-8<=h<=8, -14<=k<=14, -25<=l<=25
Reflections collected /unique;	24284 / 3335 [R(int) = 0.0304]
Reflections greater	I>2\s(I);2912
Absorption correction ;	None
Max. and min. transmission ;	0.994 and 0.965

Refinement;

Refinement method;	Full-matrix least-squares on F^2
Hydrogen treatment;:	
Data / restraints / parameters;	3335 / 0 / 193
Goodness-of-fit on F^2;	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0324, wR2 = 0.0751
R indices (all data)	R1 = 0.0375, wR2 = 0.0764
Absolute structure parameter;	-0.1(7)
Largest diff. peak and hole;	0.274 and -0.142 e.A^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for f226.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom; x; y; z; U(eq)

O(1);7067(2);653(1);1482(1);26(1)

O(2);5807(2);-2233(1);964(1);33(1)

O(3);7936(2);2702(1);3361(1);32(1)

O(4);11610(1);207(1);-203(1);26(1)

O(5);14926(2);203(1);-27(1);36(1)

C(1);8757(2);164(1);1398(1);22(1)

C(2);8212(2);1381(1);1672(1);22(1)

C(3);10013(2);2226(1);1701(1);23(1)

C(4);11385(2);2443(1);1230(1);23(1)

C(5);11431(2);1888(1);537(1);26(1)

C(6);11272(2);542(1);489(1);22(1)

C(7);9198(2);101(1);654(1);22(1)

C(8);8743(2);-1206(1);506(1);26(1)

C(9);7052(2);-1454(1);982(1);25(1)

C(10);7420(2);1348(1);2397(1);24(1)

C(11);7917(2);2592(1);2654(1);25(1)

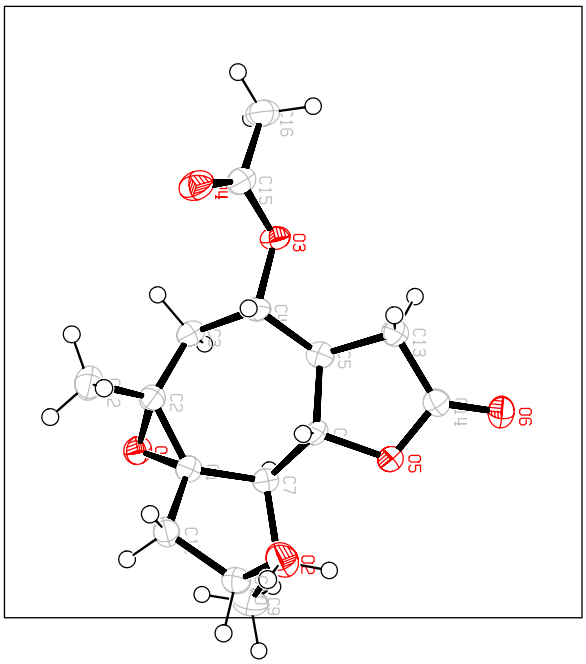
C(12);9991(2);2836(1);2378(1);28(1)

C(13);5232(2);1013(1);2491(1);31(1)

C(14);13024(2);3350(1);1326(1);29(1)

C(15);13523(2);51(1);-391(1);25(1)

C(16);13655(3);-311(1);-1109(1);33(1)



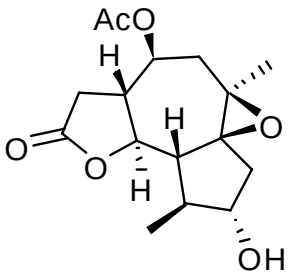


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Table 1. Crystal data and structure refinement for f227.

Crystal Data .

Empirical formula ;C16 H22 O6

Formula weight ;310.34

Crystal size ;0.32 x 0.18 x 0.06 mm

Crystal description ;flat prism

Crystal colour ;colourless

Crystal system;Orthorhombic

Space group ;P 21 21 21

Unit cell dimensions ;a = 7.8751(7) A alpha = 90 deg.
;b = 9.9609(8) A beta = 90 deg.
;c = 20.630(2) A gamma = 90 deg.

Volume ;1618.3(2) A^3

Z, Calculated density ;4, 1.274 Mg/m^3

Absorption coefficient ;0.097 mm^{-1}

F(000) ;664

Data Collection ;

Measurement device type ;STOE-IPDS diffractometer

Measuremnet method ;rotation

Temperature ;123(1) K

Wavelength ;0.71073 A

Monochromator ; graphite

Theta range for data collection ;2.77 to 26.87 deg.

Index ranges ;-10<=h<=9, -12<=k<=12, -26<=l<=26

Reflections collected / unique ;24731 / 3442 [R(int) = 0.0634]

Reflections greater I>2\s(I);2863

Absorption correction ;None

Refinement ;

Refinement method ;Full-matrix least-squares on F^2

Hydrogen treatment ;:

Data / restraints / parameters ;3442 / 0 / 202

Goodness-of-fit on F^2 ;1.052

Final R indices [I>2sigma(I)] ;R1 = 0.0528, wR2 = 0.1541

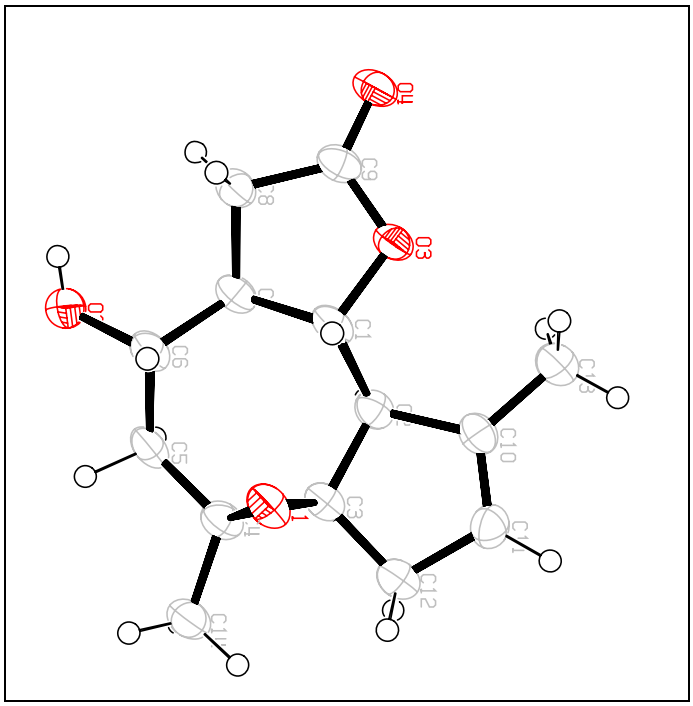
R indices (all data) ;R1 = 0.0620, wR2 = 0.1580

Absolute structure parameter ;0.0(15)

Largest diff. peak and hole ;0.346 and -0.310 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for f227.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom;	;x	;y	z ;	U(eq)
O(1);	-2202(3);	2566(2);	5165(1);	30(1)
O(2);	-3005(3);	169(2);	7062(1);	37(1)
O(3);	2042(2);	5005(2);	6434(1);	28(1)
O(4);	205(3);	6629(2);	6736(1);	36(1)
O(5);	1220(2);	416(2);	6883(1);	27(1)
O(6);	3551(2);	244(2);	7499(1);	32(1)
C(1);	-2158(4);	1968(3);	5815(1);	25(1)
C(2);	-1988(4);	3452(3);	5731(1);	26(1)
C(3);	-248(4);	4125(3);	5767(1);	28(1)
C(4);	628(3);	4034(3);	6429(1);	25(1)
C(5);	1465(3);	2676(3);	6524(1);	26(1)
C(6);	180(3);	1513(2);	6602(1);	23(1)
C(7);	-679(3);	1012(3);	5982(1);	26(1)
C(8);	-1557(4);	-372(3);	6064(1);	30(1)
C(9);	-1803(5);	-1089(3);	5407(2);	42(1)
C(10);	-3288(4);	-27(3);	6376(1);	31(1)
C(11);	-3820(4);	1310(3);	6048(1);	29(1)
C(12);	-3489(4);	4356(3);	5870(2);	36(1)
C(13);	2539(4);	2478(3);	7140(1);	26(1)
C(14);	2547(3);	962(3);	7214(1);	26(1)
C(15);	1634(4);	6285(3);	6596(1);	29(1)
C(16);	3167(4);	7191(3);	6562(2);	38(1)



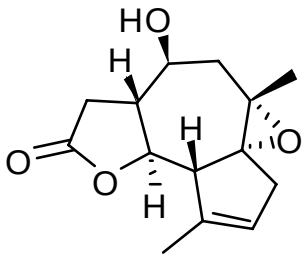


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Table 1. Crystal data and structure refinement for g027.

Crystal Data .

Empirical formula ;C14 H18 O4

Formula weight ;250.28

Crystal size ;0.230 x 0.180 x 0.010 mm

Crystal description ;plate

Crystal colour ;colourless

Crystal system;Orthorhombic

Space group ;P 21 21 21

Unit cell dimensions ;a = 5.94400(10) A alpha = 90 deg.
;b = 7.17110(10) A beta = 90 deg.
;c = 29.1130(5) A gamma = 90 deg.

Volume ;1240.94(3) A^3

Z, Calculated density ;4, 1.340 Mg/m^3

Absorption coefficient ;0.801 mm^-1

F(000) ;536

Data Collection ;

Measurement device type ;Oxford Diffraction Gemini Ultra

Measuremnet method ;omega-scan

Temperature ;123 K

Wavelength ;1.54184 A

Monochromator ; graphite

Theta range for data collection ;3.04 to 51.66 deg.

Index ranges ;-5<=h<=6, -7<=k<=6, -29<=l<=29

Reflections collected / unique ;12707 / 1357 [R(int) = 0.0477]

Reflections greater I>2\s(I);1176

Absorption correction ;Semi-empirical from equivalents

Max. and min. transmission ;1.00000 and 0.78410

Refinement ;

Refinement method ;Full-matrix least-squares on F^2

Hydrogen treatment ;:

Data / restraints / parameters ;1357 / 0 / 213

Goodness-of-fit on F^2 ;1.024

Final R indices [I>2sigma(I)] ;R1 = 0.0267, wR2 = 0.0611

R indices (all data) ;R1 = 0.0322, wR2 = 0.0623

Absolute structure parameter ;-0.1(3)

Largest diff. peak and hole ;0.097 and -0.128 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for g027. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom; x; y; z ; U(eq)

O(1);-7763(2);-2634(2);-1302(1);37(1)

O(2);-3511(3);-5108(2);-2302(1);42(1)

O(3);-1727(3);335(2);-1459(1);34(1)

O(4);1070(3);1176(2);-1923(1);41(1)

C(1);-3537(4);-1043(3);-1455(1);33(1)

C(2);-4000(5);-1667(3);-969(1);31(1)

C(3);-6148(4);-2833(3);-932(1);31(1)

C(4);-6764(4);-4459(3);-1212(1);34(1)

C(5);-5353(5);-5228(4);-1600(1);37(1)

C(6);-4457(4);-3894(3);-1962(1);34(1)

C(7);-2688(4);-2574(3);-1779(1);32(1)

C(8);-1384(5);-1425(4);-2130(1);35(1)

C(9);-486(4);147(3);-1846(1);34(1)

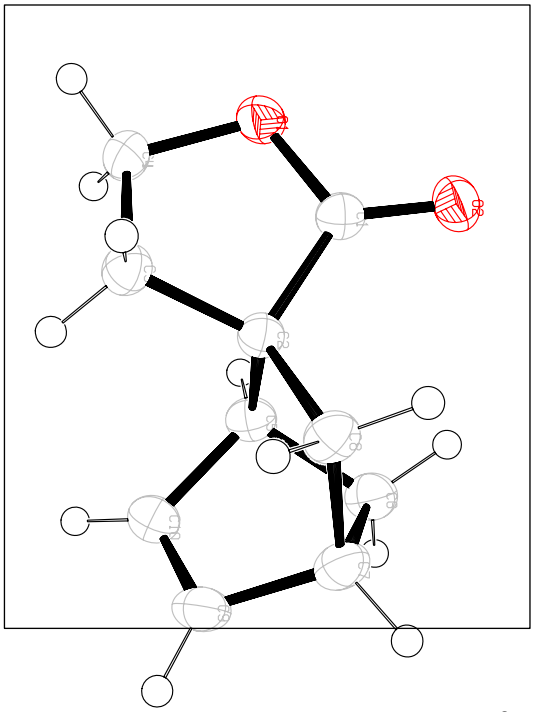
C(10);-4357(4);-198(3);-600(1);33(1)

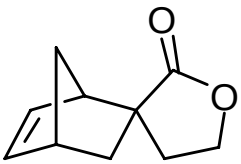
C(11);-6056(5);-670(3);-327(1);37(1)

C(12);-7123(5);-2476(4);-458(1);37(1)

C(13);-2841(4);1436(3);-524(1);45(1)

C(14);-8362(4);-5883(3);-1014(1);41(1)





exo

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Table 1. Crystal data and structure refinement for i009.

Crystal Data .

Empirical formula ;C10 H12 O2

Formula weight ;164.20

Crystal size ;0.430 x 0.370 x 0.020 mm

Crystal description ;plate

Crystal colour ;colourless

Crystal system;Orthorhombic

Space group ;P 21 21 21

Unit cell dimensions ;a = 6.9823(2) A alpha = 90 deg.
;b = 10.4959(3) A beta = 90 deg.
;c = 11.1686(4) A gamma = 90 deg.

Volume ;818.50(4) A^3

Z, Calculated density ;4, 1.332 Mg/m^3

Absorption coefficient ;0.740 mm^-1

F(000) ;352

Data Collection ;

Measurement device type ;Oxford Diffraction Gemini Ultra

Measuremnet method ;omega-scan

Temperature ;123 K

Wavelength ;1.54184 A

Monochromator ; graphite

Theta range for data collection ;5.78 to 66.76 deg.

Index ranges ;-7<=h<=8, -12<=k<=11, -13<=l<=12

Reflections collected / unique ;5896 / 1429 [R(int) = 0.0364]

Reflections greater I>2\s(I);1367

Absorption correction ;Semi-empirical from equivalents

Max. and min. transmission ;1.00000 and 0.79960

Refinement ;

Refinement method ;Full-matrix least-squares on F^2

Hydrogen treatment ;:

Data / restraints / parameters ;1429 / 0 / 109

Goodness-of-fit on F^2 ;1.082

Final R indices [I>2sigma(I)] ;R1 = 0.0348, wR2 = 0.0906

R indices (all data) ;R1 = 0.0364, wR2 = 0.0918

Absolute structure parameter ;0.5(3)

Largest diff. peak and hole ;0.141 and -0.195 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for i009. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom; x; y; z ; U(eq)

O(1);-720(2);2830(1);8895(1);29(1)

O(2);1351(2);4430(1);8776(1);32(1)

C(1);998(2);3325(1);8585(1);24(1)

C(2);2222(2);2319(1);7976(1);23(1)

C(3);1336(2);1102(2);8482(2);27(1)

C(4);-763(2);1472(1);8610(2);29(1)

C(5);1956(2);2488(2);6571(1);27(1)

C(6);3510(2);3496(2);6316(2);30(1)

C(7);5134(2);2669(2);6813(2);30(1)

C(8);4416(2);2491(2);8128(1);27(1)

C(9);4745(3);1427(2);6172(2);32(1)

C(10);2864(3);1323(2);6023(2);32(1)

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2. From Aromatics to Guaianolides (Oral presentation)
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1. Enantioselective Synthesis of Arglabin, **Srinivas Kalidindi**.; Won Boo Jeong.; Andreas Schall.; Rakeshwar Bandichhor.; Bernd Nosse.; Oliver Resier.
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