Studies Towards the Total Synthesis of Biological Active γ-Butyrolactones

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

Dr. rer. nat.

an der Fakultät für Chemie und Pharmazie

der Universität Regensburg

vorgelegt von

Andreas Schall

aus

Runding

Regensburg 2007

Die Arbeit wurde angeleitet von:	Prof. Dr. O. Reiser
Promotionsgesuch eingereicht am:	25. Mai 2007
Promotionskolloquium am:	26. Juni 2007
Prüfungsausschuss:	Vorsitz: Prof. Dr. H. Krienke
	1. Gutachter: Prof. Dr. O. Reiser
	2. Gutachter: Prof. Dr. B. König
	3. Prüfer: Prof. Dr. S. Elz

Der experimentelle Teil der vorliegenden Arbeit wurde unter der Leitung von Herrn Prof. Dr. Oliver Reiser in der Zeit von Oktober 2003 bis Mai 2007 am Institut für Organische Chemie der Universität Regensburg sowie in der Gruppe von Prof. Dr. Paul Hanson, University of Kansas, angefertigt,

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 family…

"If you want to build a ship,
don't drum up the men to gather wood,
divide the work and give orders.
Instead, teach them to yearn for the vast and endless sea."

Antoine de Saint-Exupéry (1900 - 1944)

Table of Content

1. Approaches to the total synthesis of biological active guaianolides with a *trans*-annulated lactone moiety

1.1 Introduction

Guaianolides, consisting of a tricyclic 5,7,5-ring system represent a large subgroup of naturally occurring sesquiterpene lactones exhibiting significant biological activity.[1,2] Plants containing such compounds 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.

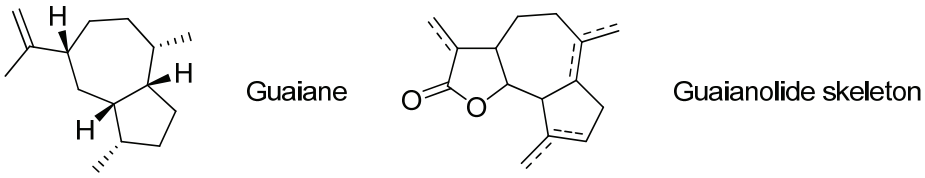


Figure 1. Skeletal relationships.

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 (Figure 1). With only a few exceptions the hydroazulene core is also *cis*-fused in the 5,7,5-tricyclic carbon skeleton, while the γ-butyrolactone ring is *trans*-annulated in approximately 85% of all known guaianolides.[3]

This interesting class of natural products shows a broad range of biological activity (Figure 2) stimulating the development of research towards their total synthesis. Although several strategies especially towards monocyclic γ-butyrolactones are reported to date,[4-10] only a few groups succeeded in the total synthesis of guaianolides.[10-14]

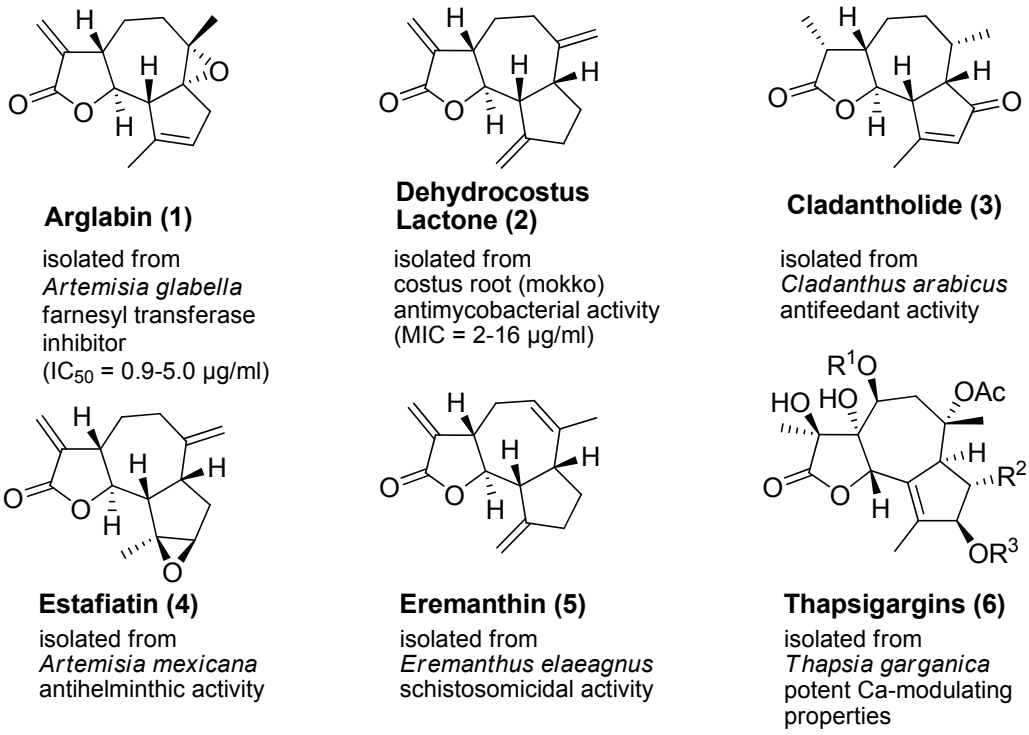
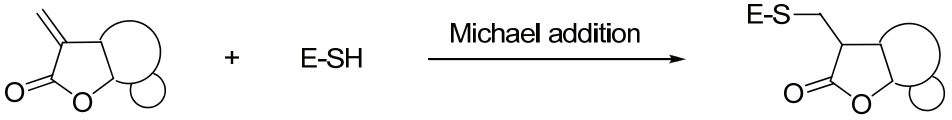


Figure 2. Some guaianolides, representing the structural diversity of this class of compounds.

The structure-activity relationship (SAR) of α-methylene sesquiterpene lactones was intensively studied.[15-20] It was shown that these compounds can react by conjugate addition of various biological nucleophiles such as cystein or thiol-containing enzymes (E-SH) (Scheme 1). Consequently, α-methylene sesquiterpene lactones are good alkylation agents manifesting their biological activity but also their cytotoxicity.



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

There is further evidence, that compounds of this type inhibit cellular enzyme activity and do not show DNA-alkylating properties.[18,21-26] Furthermore it is assumed that the residual substitution pattern of the guaianolides determines the specificity and the resulting biological activity.[11]

1.2 Biosynthesis of guaianolides

1.2.1 The mevalonate pathway

Since ancient times various oils with intensive and mostly delightful fragrances were extracted from numerous plants. In the beginning direct distillation and later on steam distillation were common techniques to afford the essential oils, which mainly consisted of terpenes. Until now more than 30,000 terpenes from all sources have been identified, making them a large and structurally highly diverse family of natural products. It was early recognized that terpenes are formally derived from C_5-isoprene units (**7**), but that isoprene (**8**) itself, a metabolite produced naturally, is not involved in their formation (Figure 3).

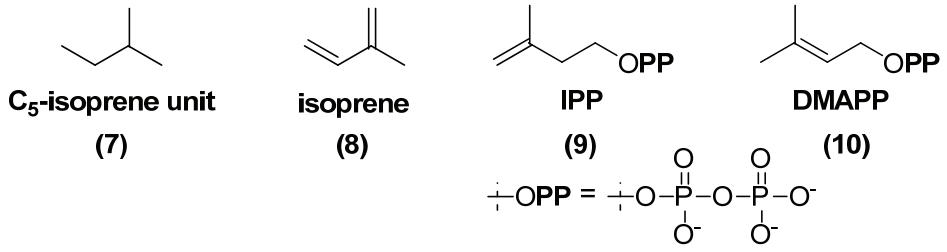
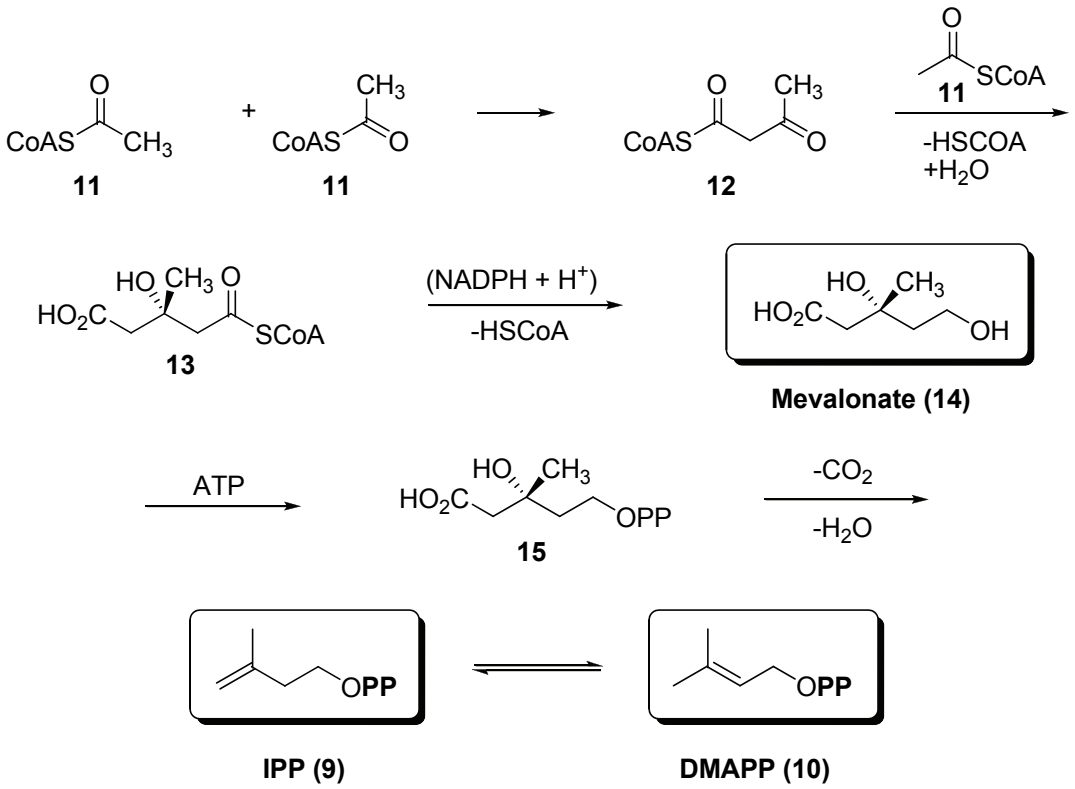


Figure 3. Comparsion of C_5-units.

The biochemically active isoprene units are isopentenyl-pyrophosphate (IPP, **9**) and γ,γ-dimethylallyl-pyrophosphate (DMAPP, **10**). These important precursors are formed via certain biochemical pathways that have been extensively studied over the last 50 years leading to the generally accepted mevalonate (MVA) biosynthesis pathway of terpenes in organisms.[27-30] More recently a second biosynthetic route was discovered in plants also leading to IPP (**9**) and DMAPP (**10**) as the final products.[30-32] This so called mevalonate independent pathway or methylerythritol-phosphate pathway (MEP) is only found in a few plants and microorganisms. It was also recognized that the MVA-pathway is located in the cytosol and the MEP-pathway takes place in the plastids (chloroplasts, leukoplasts, etc.). Furthermore, in organisms equipped with both pathways, a limited exchange of intermediates between MVA and MEP also appears. This may explain why the MEP pathway was completely overlooked until labeling experiments revealed its existence.[33-36]

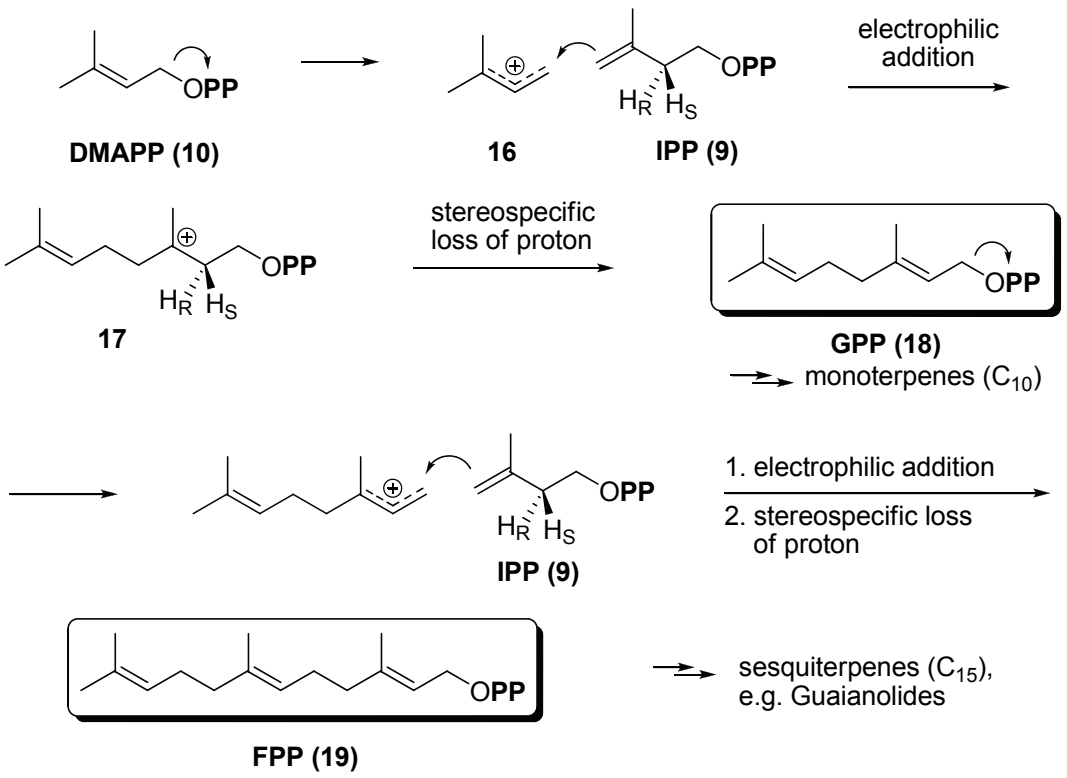
The biosynthesis in the cytosol starts with the assembly of three molecules of activated acetic acid (acetyl-CoA) (**11**) by an initial Claisen-condensation and a subsequent aldol reaction to give β-hydroxy-β-methyl-glutaryl-CoA (**13**) (Scheme 2).



Scheme 2. MVA pathway for the biosynthesis of IPP (**9**) and DMAPP (**10**).

Reduction with NADPH+H^+ releases mevalonic acid (Mevalonate, MVA, **14**), which is then activated by means of ATP to the pyrophosphomevalonate (**15**). Decarboxylation and elimination leads to isopentenyl-pyrophosphate (IPP, **9**), further isomerization of the double bond to dimethylallylpyrophosphate (DMAPP, **10**).

To construct the basic backbones of terpenes, prenyltransferases connect IPP (**9**) and its isomer DMAPP (**10**) in a head to tail fashion (Scheme 3). In a first step DMAPP (**10**) is therefore ionized to an allylic cation **16**, to which the double bond of IPP (**9**) can add resulting in a tertiary cation **17**. Subsequent stereoselective loss of a proton introduces selectively a new *trans* substituted double bond and releases geranylpyrophosphate (GPP, **18**), a fundamental precursor for the biosynthesis of monoterpenes (e.g. menthol).



Scheme 3. Biosynthesis of GPP (**18**) and FPP (**19**).

For the biosynthesis of sesquiterpenes the C_{10}-skeleton of GPP (**18**) has to be extended by addition of a further C_5-IPP (**9**) unit according to the isoprene rule[37-39] ($(C_5)_n$, n = 3 for sesquiterpenes) which was first discovered by Otto Wallach in 1887 but largely ignored until Leopold Ruzicka recognized its general significance. Repeating the electrophilic addition of IPP (**9**) and stereospecific elimination (Scheme 3) gives rise to farnesylpyrophosphate (FPP, **19**), the precursor for linear and cyclic sesquiterpenes and sesquiterpene lactones.

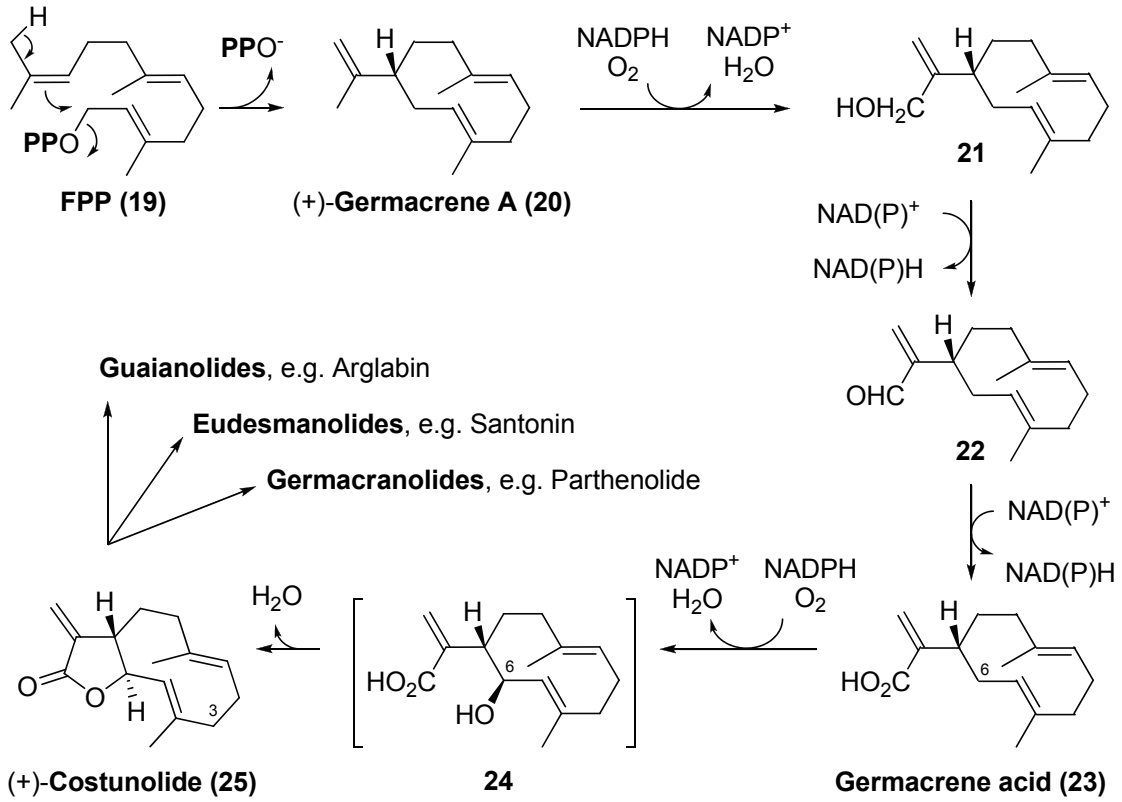
1.2.2 Biosynthesis of guaianolides

The further assembly of guaianolides used in nature has been intensively investigated by *de Kraker et al.* based on the biosynthetic route of sesquiterpene lactones in chicory which is reasonable to assume to be also valid for other plant species (Scheme 4).[40-43] According to these studies, cyclization of FPP (**19**) yields (+)-Germacrene A (**20**). Because of the double bond configuration in FPP (**19**) two (*E*)-substituted double bonds are incorporated within the 10-membered ring system of **20**.

Oxidation of the isopropenyl side chain by (+)-Germacrene A hydroxylase to the primary alcohol **21** and further oxidations by $NAD(P)^+$-dependent dehydrogenases afford

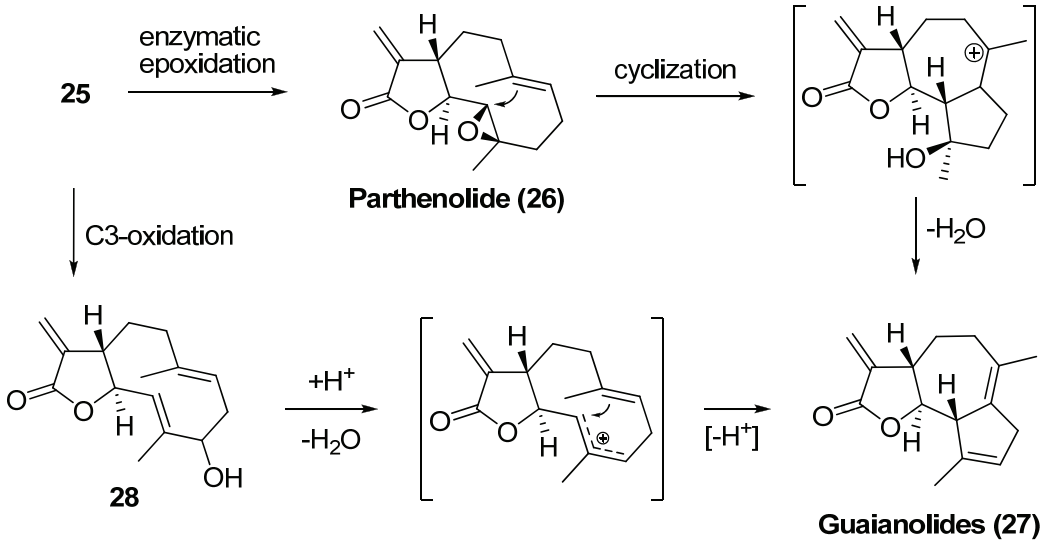
Germacrene acid (**23**). It was further demonstrated that hydroxylation on the C6-position and subsequent lactonization yields (+)-Costunolide (**25**).

This intermediate is seen as a branching point in the biosynthesis of sesquiterpene lactones, because here the pathways for the formation of guaianolides, eudesmanolides and germacranolides are considered to divide.



Scheme 4. Biosynthesis of (+)-Costunolide (**25**).

Quite a number of stereospecific biomimetic transformations of germacranolides and their derivatives into eudesmanolides and guaianolides have been reported in literature.[44-52] Based upon these studies it is postulated that the second cyclization of germacranolides towards the guaianolide skeleton is directed by epoxidations or hydroxylations of the costunolide skeleton **25**. Enzymatic epoxidation on C4-C5 position directly affords Parthenolide (**26**) (Scheme 5). This interesting germacranolide is a highly active antimigraine agent isolated from feverfew and magnolia and also shows anti-inflammatory and anti-tumor activities.[53-55] *Trans*-annular cyclization of the strained ring system in **26** and subsequent elimination completes the guaianolide skeleton **27**.[56]



Scheme 5. Guaianolides (**27**) via cyclizations starting from (+)-Costunolide **(25)**.

In addition to the above described route also an alternative pathway is proposed: Enzymatic introduction of a hydroxy group at C3-position in (+)-Costunolide (**25**) affords **28**. Subsequent dehydration and cyclization also leads to the guaianolide skeleton **27**.[43]

Further oxidation steps on the 5,7,5-membered ringsystem of **27** introduce many different functionalities: Epoxides (e.g. found in Arglabin (**1**) or Estafiatin (**4**)) or the introduction of hydroxy groups (see Thapsigargins (**6**)) on various positions contributes to the diversity and complexity of this interesting and biologically important class of natural products. Esterification or glycosylation[57] of the later also broadens the structural variety of the guaianolides.

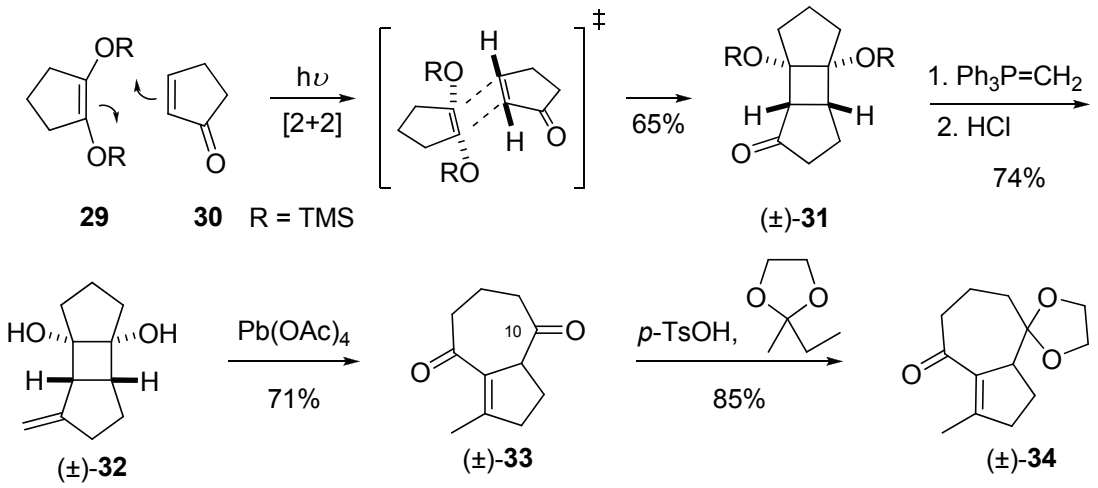
In summary, nature has proven a tremendous creativity in the construction of the guaianolides with respect to their structures and biological functions. For an organic chemist now the question arises how to find synthetic entries towards these natural products. Even with modern state of the art techniques in organic synthesis at hand, the complexity of the core-structure and the high substitution pattern still makes the class of the guaianolides a challenging and exciting target.

1.3 Racemic approaches towards guaianolides

1.3.1 Total synthesis of (±)-Compressanolide and (±)-Estafiatin

Although there are some reports in literature dealing with the synthesis of pseudo-guaianolides[1] or of guaianolide related compounds,[58-61] to the best of our knowledge the first total synthesis of a guaianolide with a *trans*-annulated lactone moiety was reported by *Vandewalle et al*.[62-64] in 1982. On the basis of a novel, flexible and convergent route towards substituted hydroazulenes the total synthesis of various sesquiterpene lactones has been achieved.[65]

As the starting point the photochemical addition of 1,2-bis[trimethylsiloxy]-cyclopentene (**29**) to cyclopentenone (**30**) affords the 5,4,5-membered ring system (±)-**31** as a single diastereomer, in which the five-membered rings are *anti*-oriented to each other (Scheme 6).



Scheme 6. Synthesis of key intermediate (±)-**34**.

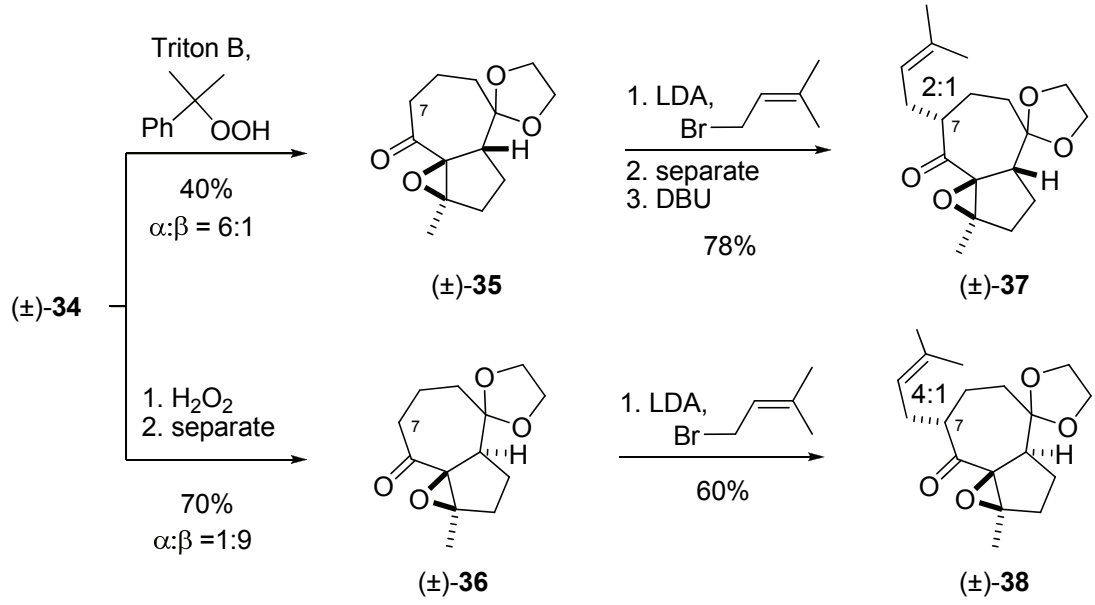
Subsequent Wittig-reaction and TMS-deprotection set the stage for ring expansion by oxidative cleavage of the diol (±)-**32**, giving rise to (±)-**33** in which the *exo*-methylene double bond had concurrently migrated in conjugation to the carbonyl group. Acid catalyzed acetalization chemoselectively protected the more reactive carbonyl group on C-10 to afford the racemic key intermediate (±)-**34**, which allowed access to a number of different sesquiterpene lactones.

With the substituted hydroazulene (±)-**34** in hands the group of Vandewalle started out for the total synthesis of (±)-Compressanolide (**44**),[62] a guaianolide first isolated from *Michelia compressa*.[66] Furthermore a small variation of this route allowed the synthesis of

(±)-Estafiatin (**4**),[62,64] a natural product first isolated by Romo and co-workers from *Artemisia mexicana* (Willd).[67]

The opening step entails the epoxidation of the double bond in the 5-membered ring of (±)-**34** (Scheme 7, top). Controlled by steric hindrance (shielding of the β-face by the bulky ketal protecting group) the bulkiest reagent gave the best selectivity of 6:1 for the desired α-epoxide (±)-**35**.

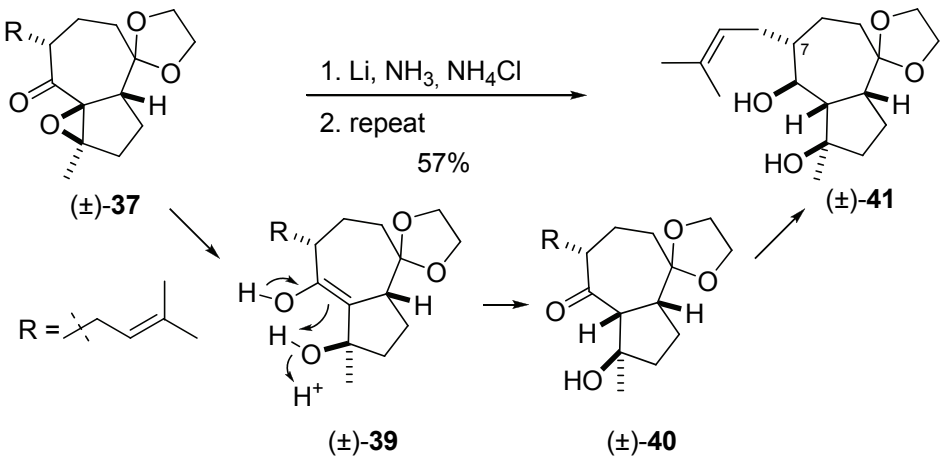
In contrast, epoxidation of the key intermediate (±)-**34** using H_2O_2 afforded the epoxide in better yield and a 1:9 ratio, this time approaching from the β-face (Scheme 7, bottom) forming the now desired *trans*-fused 5,7-membered ring system (±)-**36**.



Scheme 7. Stereoselective epoxidation and alkylation.

The next key step in the synthesis is the selective introduction of the prenyl-sidechain at the C7-position which is later on used for the formation of the lactone moiety. Attempts to introduce this arm by kinetic controlled deprotonation/alkylation already in the key intermediate (±)-**34** failed, but alkylation of epoxide (±)-**35** afforded the desired product (±)-**37** in a 2:1 ratio (β:α). Base induced equilibration of the undesired epimer led again to an approx. 1:1 ratio, providing the possibility to recycle the unwanted epimer. Alkylation of (±)-**36** on C-7 also introduced the prenyl-sidechain and afforded (±)-**38** in a 4:1 ratio.

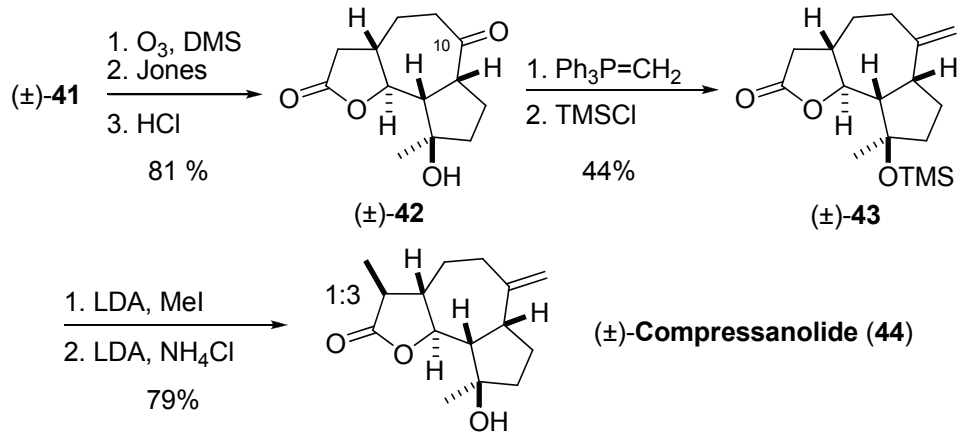
The selective reductive opening of the epoxide in (±)-**37** is the next crucial reaction, installing three stereocenters present in (±)-Compressanolide (**44**) within one step. This complex sequence starts with a reductive cleavage of the epoxide present in (±)-**37** and a fast protonation of the resulting enolate (±)-**39** (Scheme 8).



Scheme 8. Stereoselective reduction sequence.

Intramolecular tautomerization to ketone (±)-**40** by intramolecular proton transfer from the near by hydroxy group leads to a less strained *cis*-annulated hydroazulene ring system. Subsequent *in situ* reduction gives rise to the more stable equatorial alcohol (±)-**41**, *trans* to the vicinal prenyl-sidechain at the C7-position.

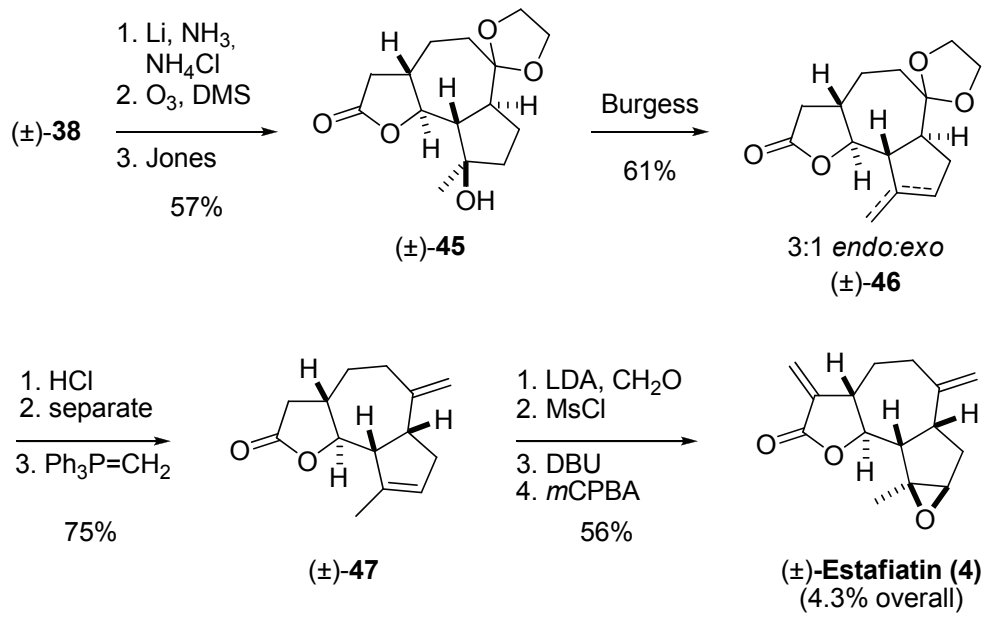
The *trans*-lactone moiety in (±)-**42** is obtained by ozonolysis and Jones-oxidation of the prenyl-side chain completing the guaianolide skeleton (Scheme 9). Acid deprotects the masked ketone and a Wittig-reaction introduces the *exo*-methylenic double bond at the C10-position of (±)-**43**, a very common structural feature of sesquiterpene lactones.



Scheme 9. Final steps towards (±)-Compressanolide (**44**).

The resulting tertiary alcohol was protected, before α-methylation unfortunately afforded a mixture of 1:4 for the undesired isomer of (±)-**44**. Equilibration by kinetic protonation of the enolate improved the ratio only slightly to 1:3 towards (±)-Compressanolide (**44**).

Applying the stereoselective reduction on (±)-**38** as described above (Scheme 8) and subsequent oxidation gave rise to the all-*trans* substituted 5,7,5-ring system (±)-**45** (Scheme 10).

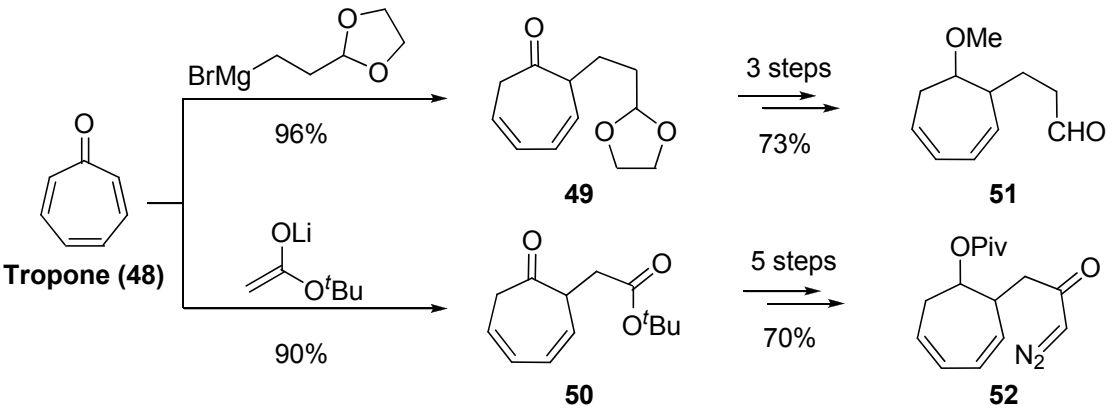


Scheme 10. Finals steps in the synthesis of (±)-Estafiatin (**4**).

The regioselective elimination of the tertiary alcohol present in (±)-**45** proved to be difficult: As classical methods for the dehydration failed, only the application of Burgess-reagent resulted in a 3:1 *endo:exo* elimination towards (±)-**46**. Acidic deprotection of the ketal also is accompanied with an equilibration of the resulting ketone to 3:1 for the desired more stable *cis*-connected endocyclic alkene (±)-**47**. Subsequent Wittig-olefination and α-methylenation followed by epoxidation of the more reactive trisubstituted endocyclic double bond finally afforded (±)-Estafiatin (**4**) in 4.3% overall yield.

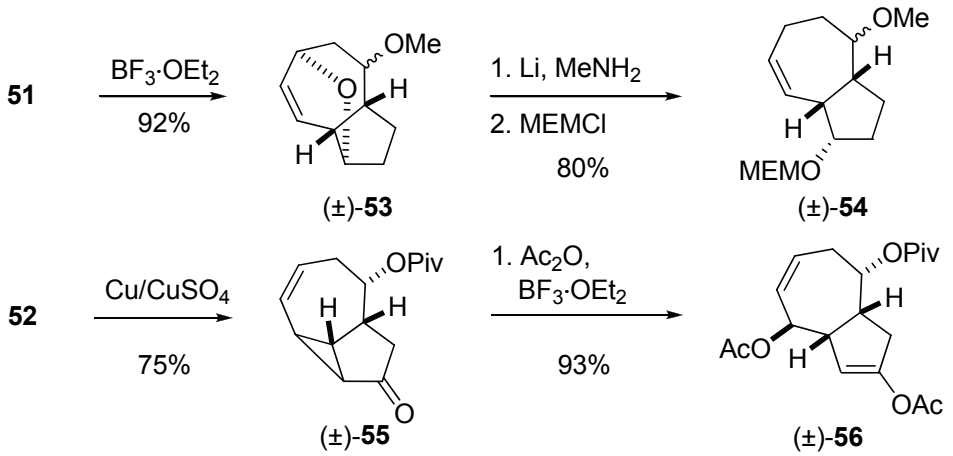
1.3.2 Total synthesis of (±)-Dehydrocostus Lactone and (±)-Grosshemin

Four years later *Rigby et al.*[68,69] reported the racemic synthesis of three further guaianolides ((±)-Dehydrocostus Lactone (**2**) (IC_{50} = 14 µM, CTL cells[70]), (±)-Estafiatin (**4**) and (±)-Grosshemin (**62**) starting from commercially available 2,4,6-cycloheptatrienone (Tropone) (**48**). Similar to the Vandewalle-approach described above, the first target was also the construction of the hydroazulene core. Utilizing the 7-membered ringsystem already present in Tropone (**48**), 1,8-addition of appropriate nucleophiles afforded the alkylated products **49** and **50**, which were further converted into the aldehyde **51** and the diazocompound **52**, respectively (Scheme 11).



Scheme 11. Functionalization of Tropone (**48**) by *Rigby et al.*

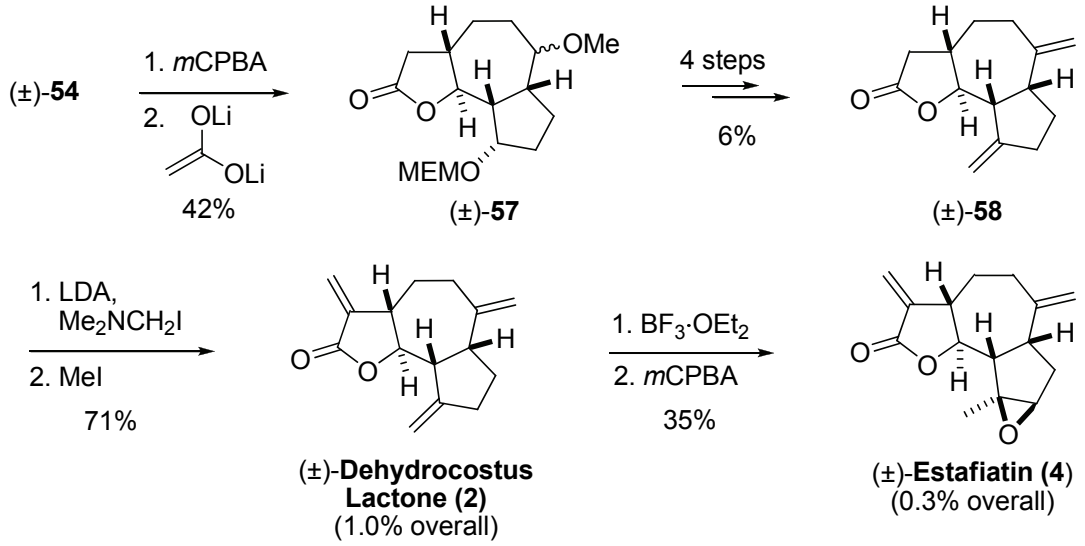
The required *cis*-fused hydroazulene ring system is then formed via a Lewis-acid mediated cyclization on **51** and subsequent reductive opening of the resulting epoxide (±)-**53** releasing the next key-intermediate (±)-**54** in the synthesis of (±)-Estafiatin (**4**) (Scheme 12, top).



Scheme 12. Formation of *cis*-fused hydroazulene systems.

Alternatively an intramolecular cyclopropanation in **52** gives rise to the tricyclic system (±)-**55** which is then opened by a Lewis-acid mediated homoconjugate addition reaction releasing the intermediate (±)-**56** for the synthesis of (±)-Grosshemin (**62**) (Scheme 12, bottom).

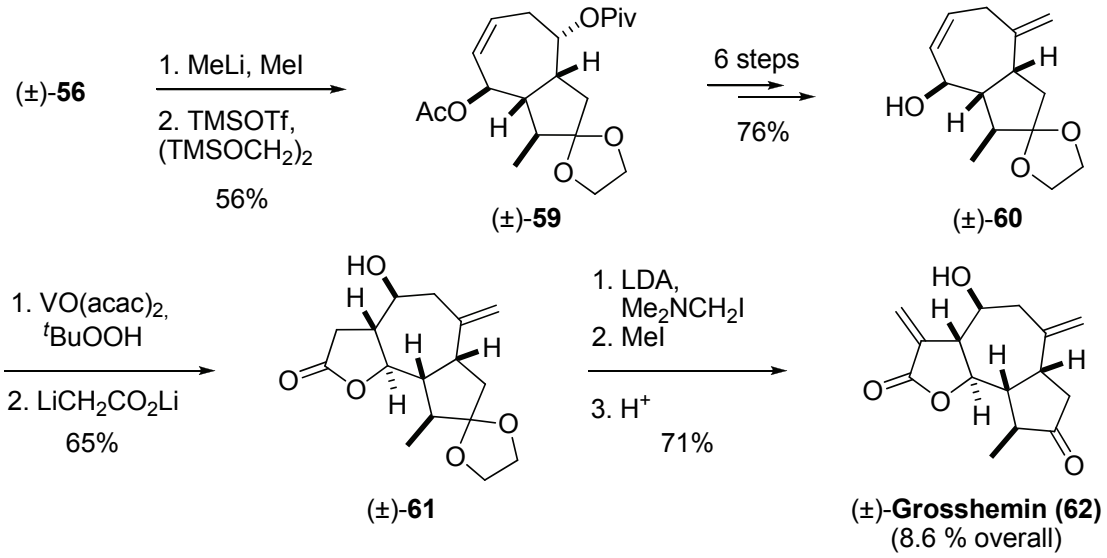
To introduce the *trans*-fused lactone moiety, the double bond in (±)-**54** was first selectively epoxidized (approach of peracid from the less hindered upper face) and then the epoxide was opened with the appropriate lithium-organyle closing the ring to lactone (±)-**57** (Scheme 13). Functional group transformation leads in 4 steps to the diene (±)-**58**.



Scheme 13. Final steps towards (±)-Dehydrocostus Lactone (**2**) and (±)-Estafiatin (**4**).

The still missing α-*exo*-methylenic group is introduced via a Mannich-type reaction to yield (±)-Dehydrocostus Lactone (**2**) in 1.0% overall yield. The structural closely related (±)-Estafiatin (**4**) was then obtained in 0.3% overall yield by selective isomerization of the double bond present in (±)-**2** towards the more stable tetrasubstitution and subsequent regio- and stereoselective epoxidation.

Using the hydroazulene key intermediate (±)-**56** Rigby and coworkers started out for the synthesis of (±)-Grosshemin (**62**), first isolated by *Rybalko et al.* from *Grossheimia macrocephala*.[71] The methyl group present in (±)-Grosshemin (**62**) was selectively introduced via alkylation by methyliodid approaching over the less hindered upper face of (±)-**56** (Scheme 14).



Scheme 14. Final steps towards (±)-Grosshemin (**62**).

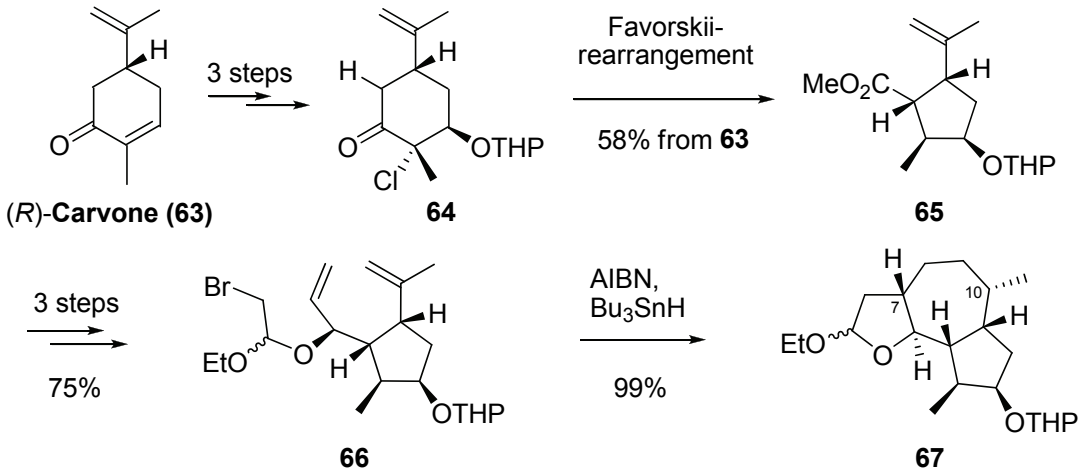
Further six steps including functional group transformation and Wittig olefination lead to allylalcohol (±)-**60**. The *trans*-fused lactone ring is introduced by directed epoxidation via the allylic alcohol and subsequent epoxide opening as shown in (±)-**61**. Again a Mannich-type reaction introduced the α-*exo*-methylene group at the lactone ring and finalized the synthesis of (±)-Grosshemin (**62**) in 8.6% overall yield.

1.4 Stereoselective total synthesis of guaianolides

1.4.1 Total synthesis of (+)-Cladantholide and (-)-Estafiatin

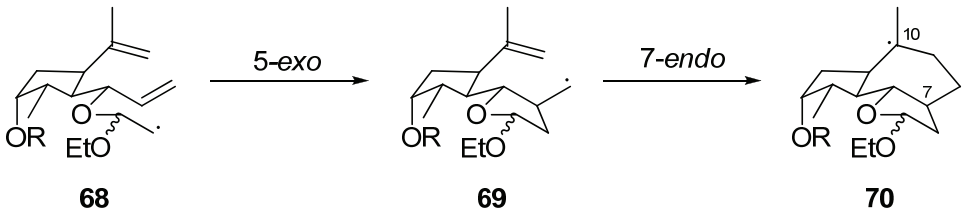
A very elegant stereoselective approach towards two members of the guaianolide family via a radical cyclization cascade was reported by Lee and co-workers,[72] who succeeded in the total synthesis of (+)-Cladantholide (**3**) (isolated from *Cladanthus arabicus* (L.) Cass.)[73] and (-)-Estafiatin (**4**) starting from (*R*)-Carvone (**63**).

In three steps the chlorohydrin derivative **64** was synthesized, which was subjected to a stereoselective Favorskii-rearrangement to afford the highly substituted cyclopentane-carboxylate **65** (Scheme 15). Three more steps were necessary to obtain the bromoacetal **66**, which was set up for a radical cyclization being initiated by AIBN/Bu_3SnH under standard high-dilution conditions. **67** was obtained in quantitative yield and perfect diastereoselectivity with respect to the newly created stereocenters at the C7- and the C10-position.



Scheme 15. Favorskii-rearrangement and radical cyclization.

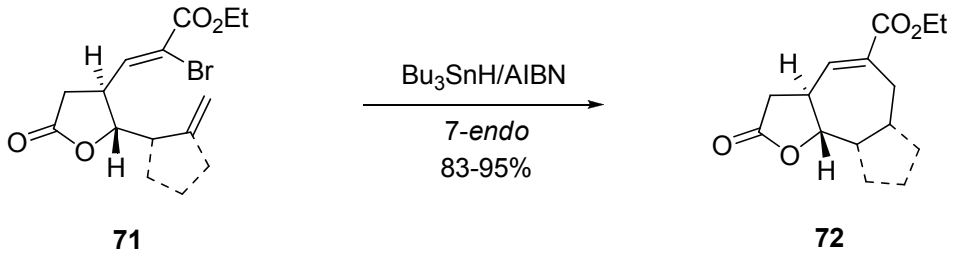
The stereochemical outcome of this highly selective and efficient cascade can be explained by conformational analysis of the substrate (Scheme 16): The most stable conformation of the cyclopentane ring in **68** is represented with three substituents in equatorial positions, and the attached sidechains are oriented chairlike.



Scheme 16. Conformational analysis of **68** and radical cyclization.

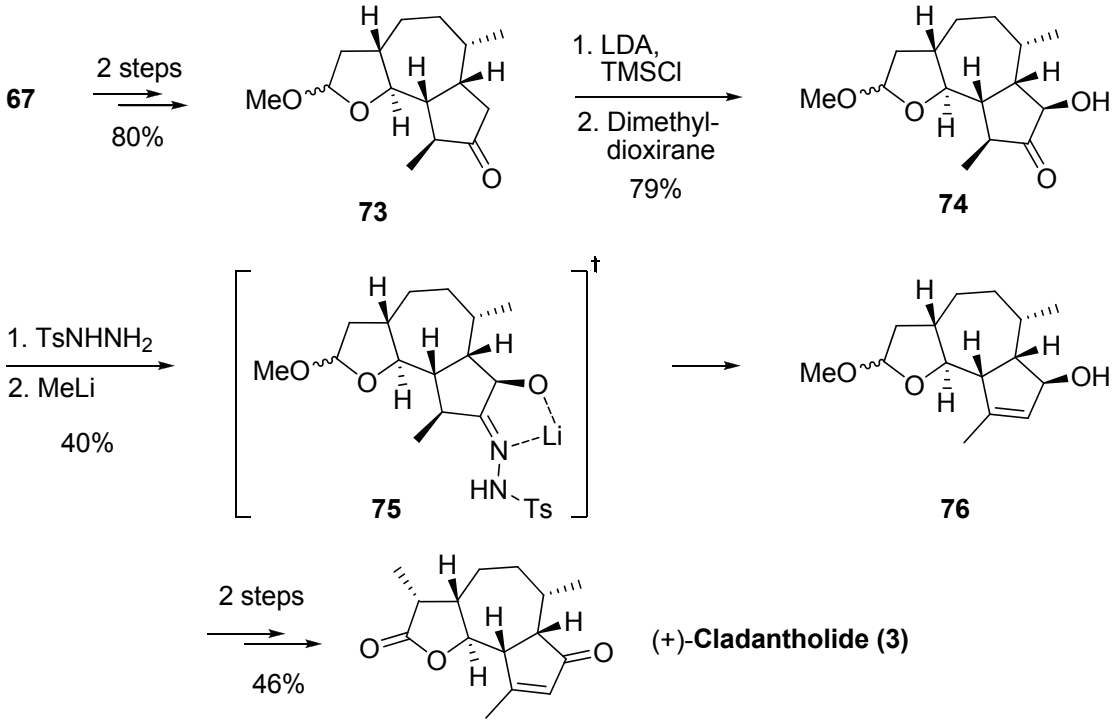
Consequently 5-*exo*-cyclization of the primary radical onto the opposite double bond forms the *trans* cyclic acetal **69** setting the correct stereochemistry on C7. Subsequent 7-*endo* cyclization affords the tertiary radical **70**, while the alternative kinetically favored 6-*exo* pathway was not observed. Final hydrogen addition setting the correct stereocenter at C10 must have occurred from the α-face, which is presumable sterically less hindered.

The high preference for the 7-membered ring formation by radical cyclization was also observed by Reiser and co-workers during their investigations on model systems towards the synthesis of bi- and tricyclic sesquiterpene lactones of the xanthanolide and guaianolide family (Scheme 17).[74]



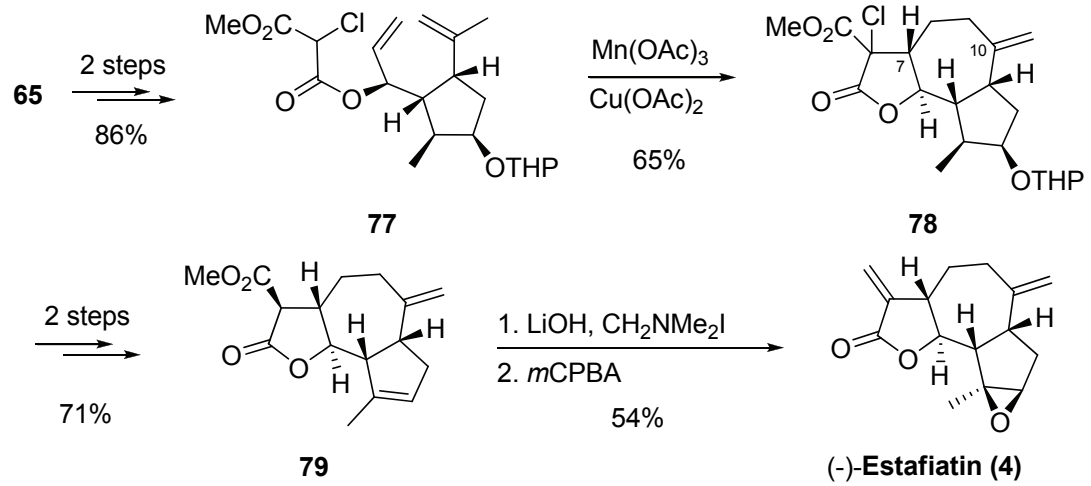
Scheme 17. 7-*endo* cyclization by *Reiser et al.*

To finalize the synthesis of (+)-Clandantholide (**3**) *Lee et al.* had to transform **67** to the ketoacetal **73**, in which the introduction of a hydroxy group adjacent to the ketogroup yields α-hydroxyketone **74** (Scheme 18).



Scheme 18. Synthesis of (+)-Cladantholide (**3**).

Applying the Shapiro-protocol to **74** resulted in the regioselective introduction of the C=C-double bond to give the allylalcohol **76**. It was argued, that the reaction proceeds through an intermediate **75**, in which the lithium coordinates with the first nitrogen of the hydrazone and the adjacent hydroxy group. Consequently, excess base can only deprotonate next to the methyl group, affording the trisubstituted double bond in **76**. Finally, oxidation and stereoselective α-methylation completed the synthesis of (+)-Cladantholide (**3**).



Scheme 19. Synthesis of (-)-Estafiatin (**4**).

65 has also been the starting point for the synthesis of (-)-Estafiatin (**4**) (Scheme 19), for which again a radical cascade cyclization has been the key step. In difference to the reductive conditions employed for the transformation of **66** to **67**, the cyclization of **77** to **78** was carried out under oxidative conditions, being initiated by hydrogen rather than halogen abstraction of the α-halo-carbonyl functionality. Reductive dechlorination and dehydration proceeded uneventfully to **79** and subsequent α-methylenation using Eschenmoser´s salt and selective epoxidation of the *endo* double bond afforded (-)-Estafiatin (**4**).

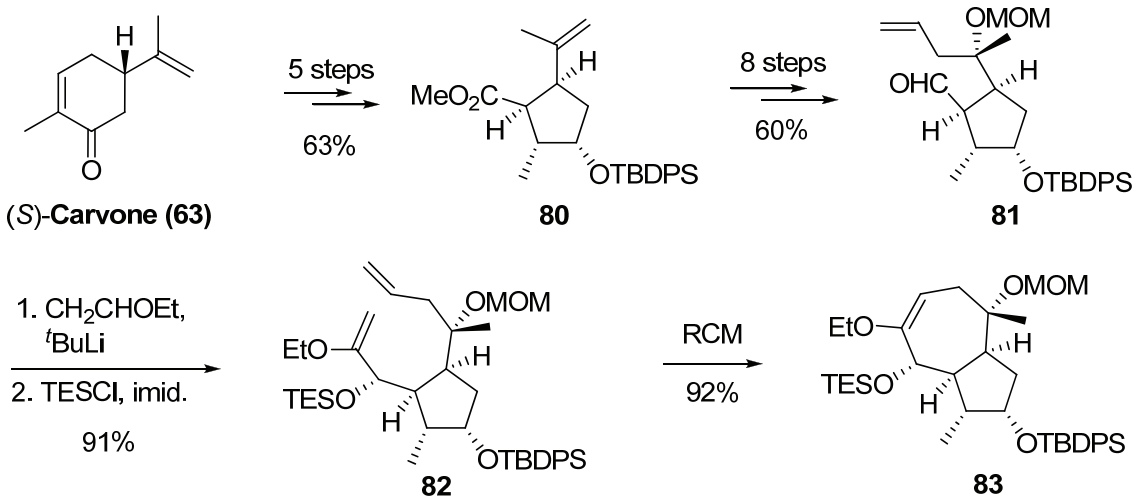
1.4.2 Synthesis of the Thapsigargins by Ley et al.

A powerful demonstration of modern organic synthesis was shown by Ley and co-workers with their total synthesis of the Thapsigargins (**6**).[75-77] Although extracts from the root of *Thapsia garganica* L. were used for a long time as treatment for rheumatic pains and pulmonary disorders, the identification and characterization of the active principles was not reported until 1980.[78,79] The potent biological activities reach from histamine liberation[80] to selective Ca^{2+}-modulating properties[81-83] on subnanomolar concentrations.

The outstanding activity and the complex molecular structure consisting of a polyoxygenated 5,7,5-core structure which is further functionalized with eight stereogenic centers and up to four different ester groups, makes this class of guaianolides to an especially challenging target for total synthesis.

The overall strategy towards the Thapsigargins (**6**) was again to construct the hydroazulene core first and subsequently functionalize it towards the target.

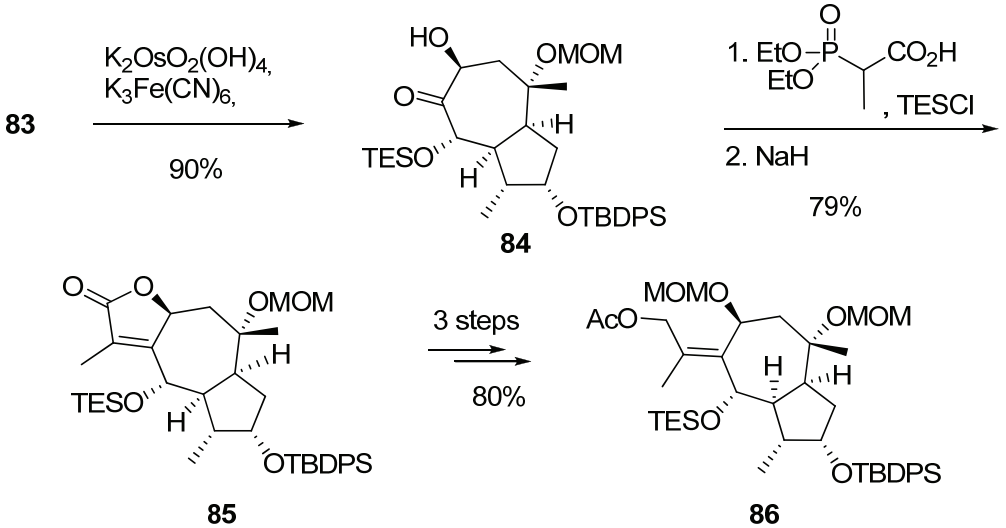
Therefore Ley and co-workers started from (*S*)-Carvone (**63**) following a similar route as described above for *Lee et al*.[72] Within five steps **80** was reached and further eight high yielding steps lead to aldehyde **81** with already one allyl sidearm installed (Scheme 20).



Scheme 20. Ring closing metathesis as an essential key step.

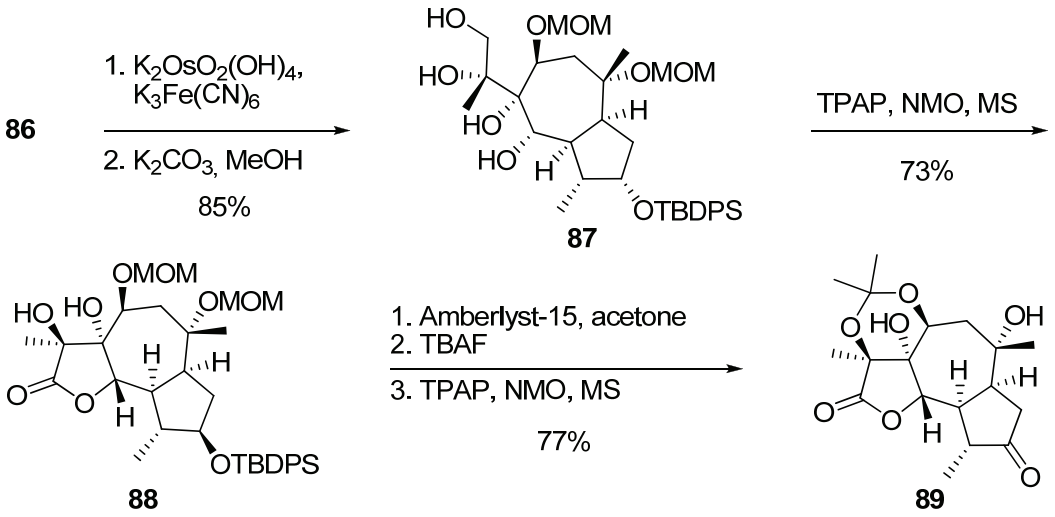
The second arm for the ring closing metathesis key step was introduced using the lithium anion of ethylvinylether. Following strictly the Felkin-Anh model diene **82** was generated as a single diastereomer. The bicyclic hydroazulene ringsystem was then constructed by ring closing metathesis affording **83** in high yield.

The convex half space of the double bond present in **83** is shielded by the bulky TES protecting group and so osmylation results in good selectivity (16:1) for the concave attack releasing **84** (Scheme 21).



Scheme 21. Facial selective osmylation.

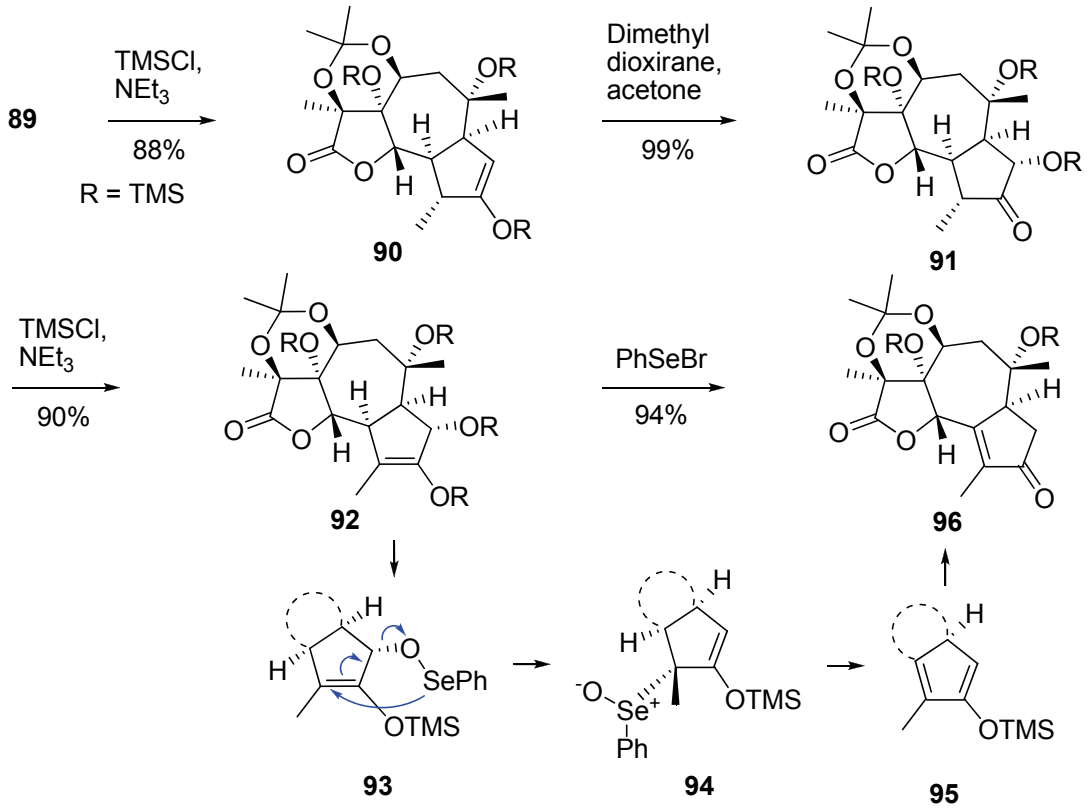
Esterification of the resulting alcohol and subsequent intramolecular Horner-Wadsworth-Emmons reaction provided the butenolide **85** which was within 3 steps transformed into **86**. Further functionalization of **86** towards the highly oxygenated core system of the targets was performed by selective dihydroxylation of the side chain to yield **87** (Scheme 22). The desired *trans*-annulated lactone **88** was formed after selective oxidation of the primary alcohol.



Scheme 22. Dihydroxylation and completion of the tricyclic framework.

Until this point already 23 steps were necessary, but this process required five chromatographic steps only, providing a nice possibility to assemble material in 11% overall yield to this point in multiple gram quantities. After MOM deprotection the acetonide **89** was formed stabilizing the already complex system.

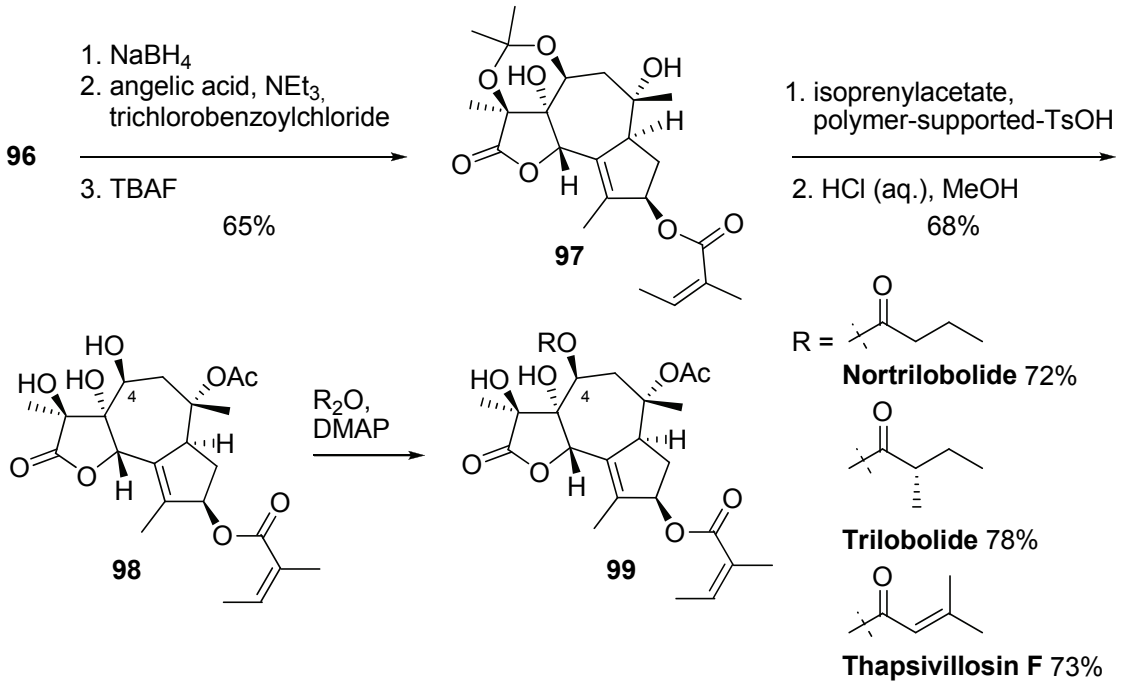
The next target was the modification of the cyclopentane ring. Kinetic enolisation of **89** followed by oxidation from the less hindered concave face provided α-siloxy-ketone **91** (Scheme 23).



Scheme 23. Synthesis of conjugated ketone by selenium elimination.

Again, enolisation, this time to the opposite side, afforded highly functionalized **92**, the starting point for a complex unanticipated catalytic selenium reaction. The opening step in this sequence is supposed to be a selenation of the TMS protected secondary alcohol **92**, because this seems to be the least hindered position. Subsequent 2,3-sigmatropic rearrangement affords a selenoxide **94** which is able to undergo *syn*-elimination in direction towards the 7-memberd ringsystem. Hydrolysis of the resulting enolether **95** releases the conjugated ketone **96**.

To complete the synthesis Ley and co-workers still had to set the last stereocenter in the cyclopentane ring of **96** by stereoselective reduction (4:1 selectivity, again by steric controlled attack from the concave face). Esterification with angelic acid of the resulting alcohol and removal of the TMS protecting groups afforded the diol **97** (Scheme 24). Selective acetyl protection of the more reactive hydroxy group via a polymer supported reagent installed the second ester group in **98**.

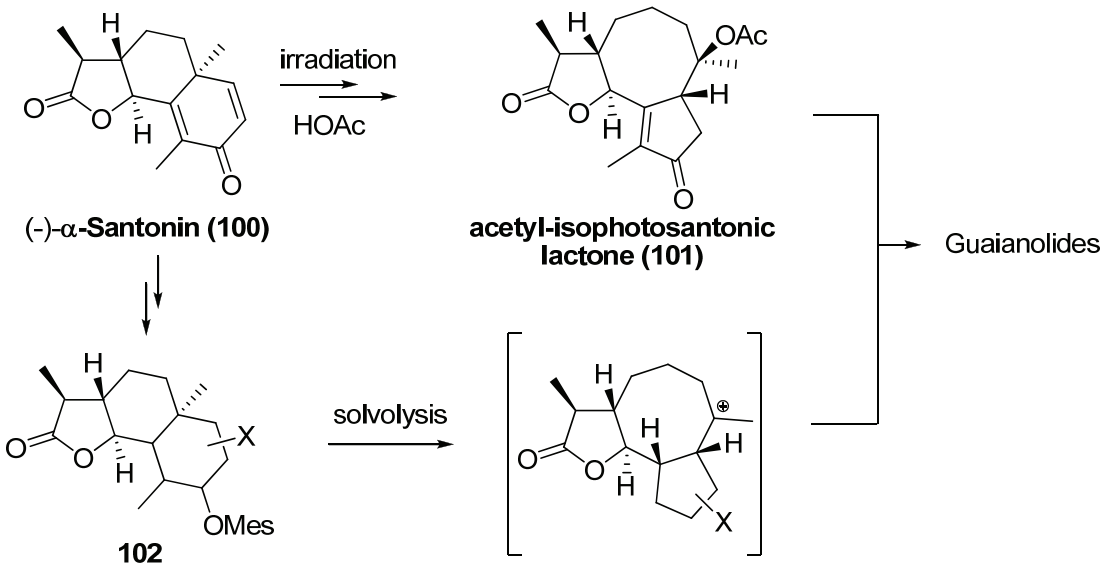


Scheme 24. Final synthetic steps towards the Thapsigargins.

Removal of the acetal protection provided the triol **98**. Esterification of the more reactive secondary alcohol on the C-4 position finally afforded three members of the Thapsigargin family.

1.5 Hemi-Synthesis starting from Santonin

First isolated by *Kahler et al.* in 1830 [84,85] it was a long and exciting way to elucidate the full structure of (-)-α-Santonin (**100**).[85-90] Commercially available by extraction,[91] this eudesmanolide provides a perfect starting point for the synthesis of various sesquiterpene lactones (Scheme 25). *Abe et al.*[92-94] and *Marshall et al.*[95] also succeeded in the total synthesis starting from a hexahydronaphtalene skeleton or 3-methyl-benzoic acid, respectively.



Scheme 25. Structure and rearrangement of (-)-α-Santonin (**100**).

Despite its own biological activity, the most important feature of (-)-α-Santonin (**100**) is the possibility to rearrange the 6,6,5-eudesmanolide skeleton to a hydroazulene carbon backbone (Scheme 25). The light induced rearrangement of **100** is one of the longest known photochemical organic reactions.[96] The cross conjugated dienone rearranges upon irradiation in the presence of acetic acid towards acetyl-isophotosantonic lactone **101** and serves as a classic example for photochemical rearrangements, although it was a long way to completely understand this reaction.[85,96-99] Furthermore was found that solvolysis of methanesulfonates **102** also provides an entry to the 5,7,5-ringsystem of the guaianolides.

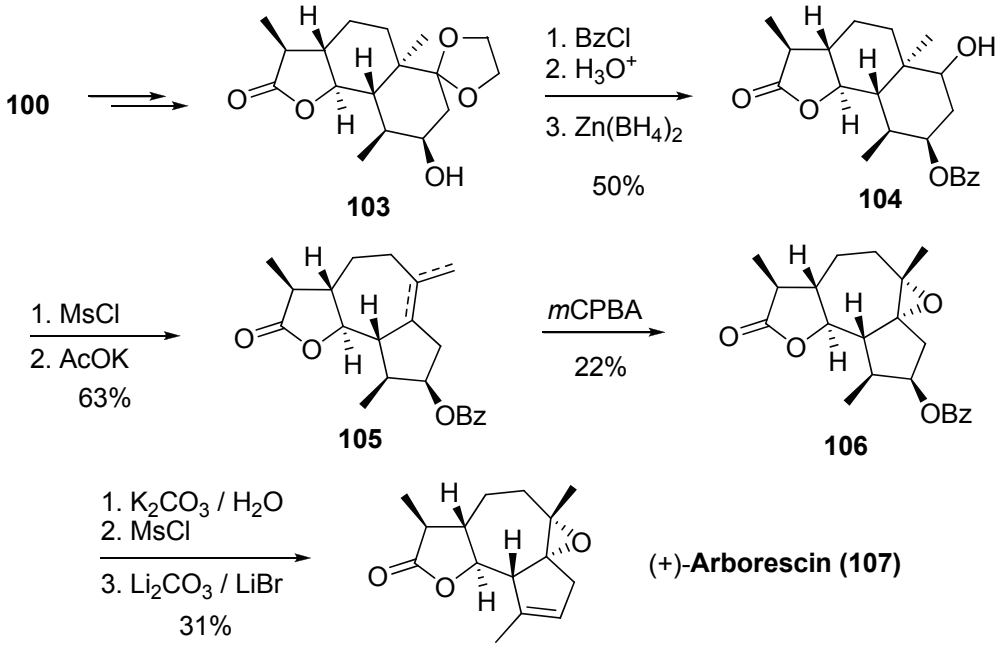
1.5.1 Syntheses by Ando et al.

Ando et al. were able to synthesize more than ten guaianolides starting from (-)-α-Santonin (**100**). Preparing suitable derivatives of this available natural product and subsequent solvolytic rearrangement offers a very interesting and efficient entry towards the guaianolides.

1.5.2 Synthesis of (+)-Arborescin

(+)-Arborescin (**107**) was first isolated by Meisels and Weizmann from *Artemisia arboresces (Compositae)*, a plant used for contraceptive purpose by the ancient Greeks and Arabs.[100] The proposed structure by *Herout et al.*[101] was later on confirmed by X-ray analysis.[102]

In an opening step *Ando et al.*[103] transformed (-)-α-Santonin (**100**) into the eudesmanolide **103** (Scheme 26). Protecting group transformation and reduction afforded the alcohol **104**.



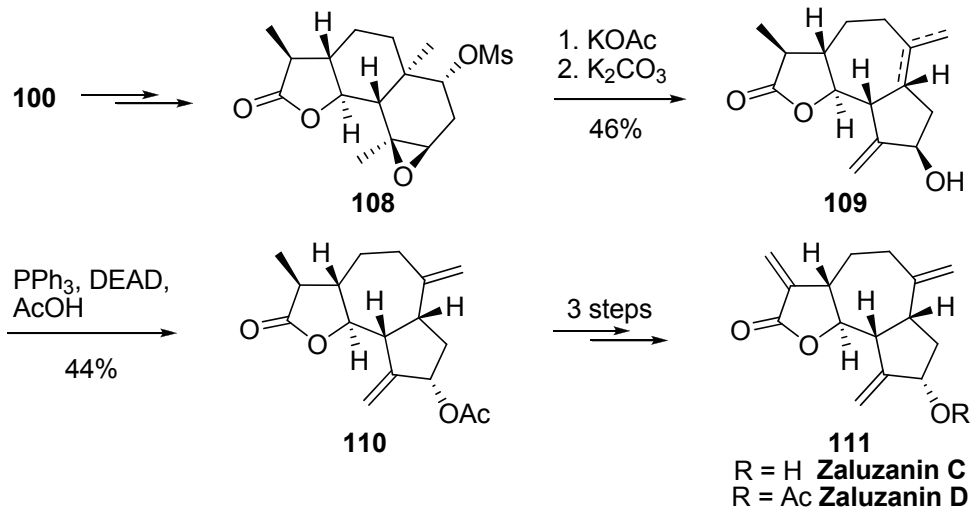
Scheme 26. Synthesis of (+)-Arborescin (**107**).

Mesylation and solvolytic rearrangement resulted in a mixture of olefins **105**, which was rectified by selective epoxidation of the tetrasubstituted double bond of the *endo*-isomer. The approach of the epoxidizing agent from the sterically less hindered down face sets the right stereochemistry for the epoxide. Subsequent deprotection and elimination afforded (+)-Arborescin (**107**) with a *trans* annulation of the cyclopentane ring.

1.5.3 Synthesis of Zaluzanines

A similar approach was used for the synthesis of different Zaluzanines (**111**).[104,105] These guaianolides were originally isolated from *Zaluzania augusta* and *Zaluzania triloba*[106,107] and show high biological activities for example in tumor inhibition.[108]

The rearrangement of the (-)-α-Santonin (**100**) derivative **108** to the guaianolide skeleton **109** resulted again in a mixture of double bond isomers which was rectified by selective epoxidation of the *endo*-isomer (Scheme 27).



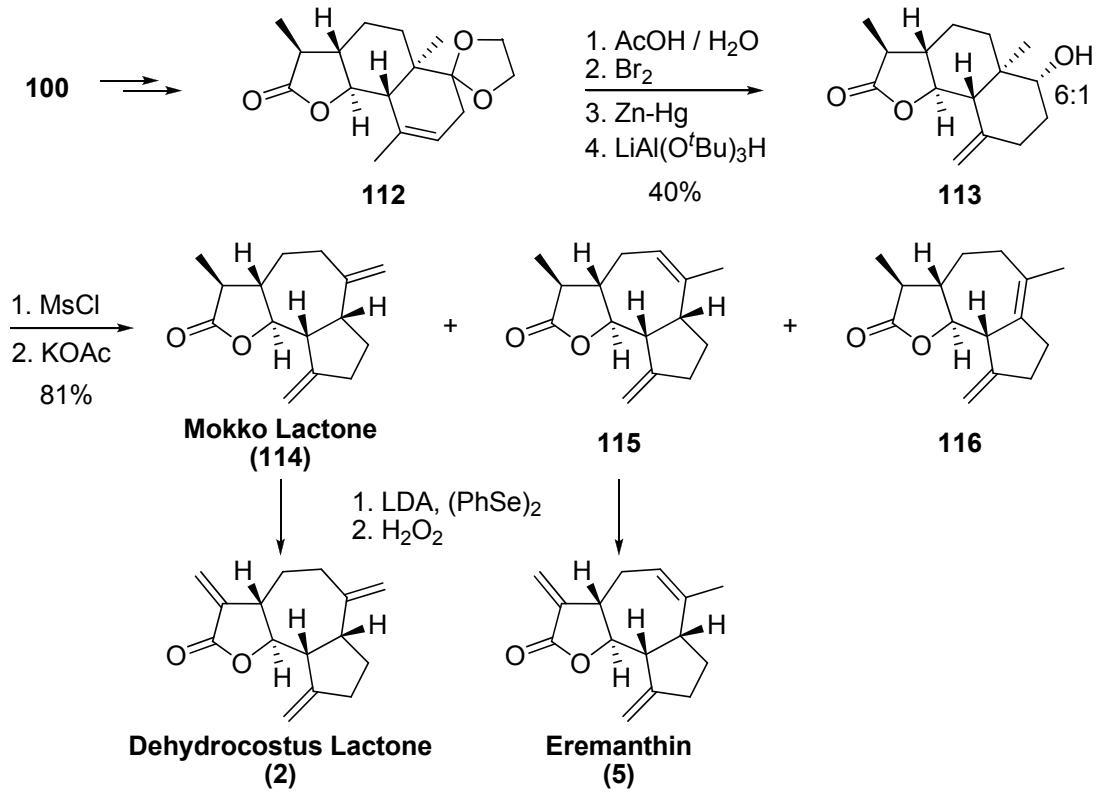
Scheme 27. Synthesis of (+)-Zaluzanin C/D (**111**).

Subsequent Mitsunobu-inversion of the secondary alcohol in **109** sets the right stereochemistry of the hydroxygroup in the cyclopentane ring of **110** and afforded after introduction of the *exo*-methylenic bond (+)-Zaluzanin C and D (**111**).

1.5.4 Mokko lactone, Dehydocostus Lactone and Eremanthin

Mokko Lactone (**114**) and Dehydrocostus Lactone (**2**) (both isolated from costus root (mokko)[109,110]) and Eremanthin (**5**) (isolated from the hartwood oils of *Eremanthus elaeagnus* and *Vanillosmopsis erytrhoppa*)[111-113] are also accessible via this route. A common feature of these three natural products is the lacking of the hydroxy functionality in the cyclopentane ring.

Starting again from (-)-α-Santonin (**100**) Ando and co-workers synthesized **112** (Scheme 28). After deprotection of the ketal and double bond isomerization the resulting ketone was reduced to the secondary alcohol **113**, which is needed for subsequent mesylation. Solvolysis directly affords Mokko Lacone (**114**) accompanied with its double bond isomers **115** and **116**. Desaturation of **114** and **115** releases Dehydrocostus Lactone (**2**) and Eremanthin (**5**), respectively



Scheme 28. Further Guaianolides starting from (-)-Santonin (**98**).

This strategy allowed *Ando et al.* to succeed in the total synthesis of over ten different guaianolides (Figure 4).[114]

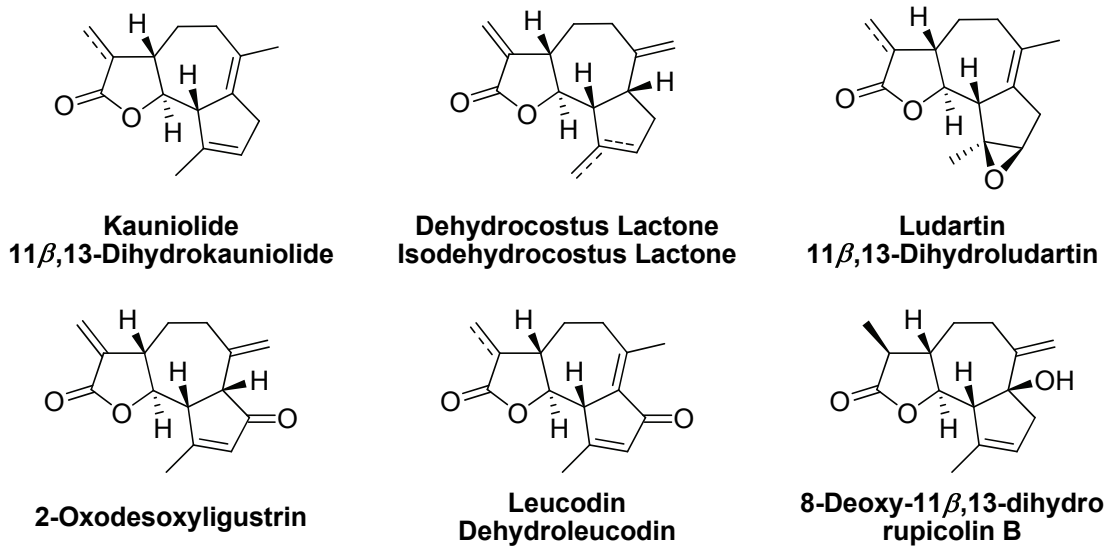
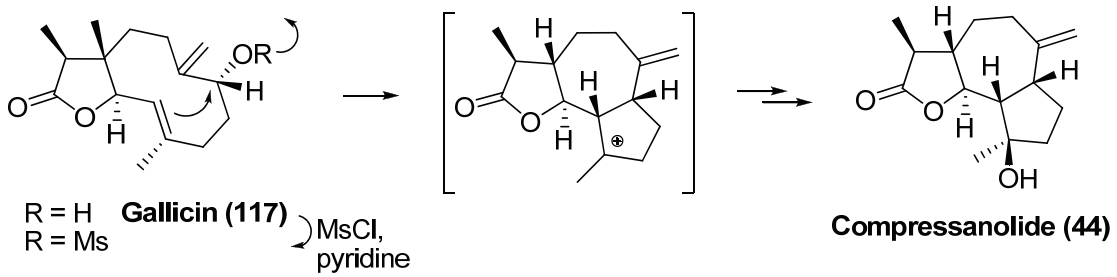


Figure 4. Some guaianolides prepared by Ando and co-worker.

Inspired by this route *Pedro et al.* were also able to present stereoselective hemi-syntheses for (+)-*11βH,13*-Dihydroestafiatin, (+)-*11βH,13*-Dihydroludartin, (-)-Compressanolide (**44**), and (-)-*11βH,13*-Dihydro-micheliolide starting from (-)-α-Santonin (**100**).[115]

1.5.5 Biomimetic synthesis of Absinthin

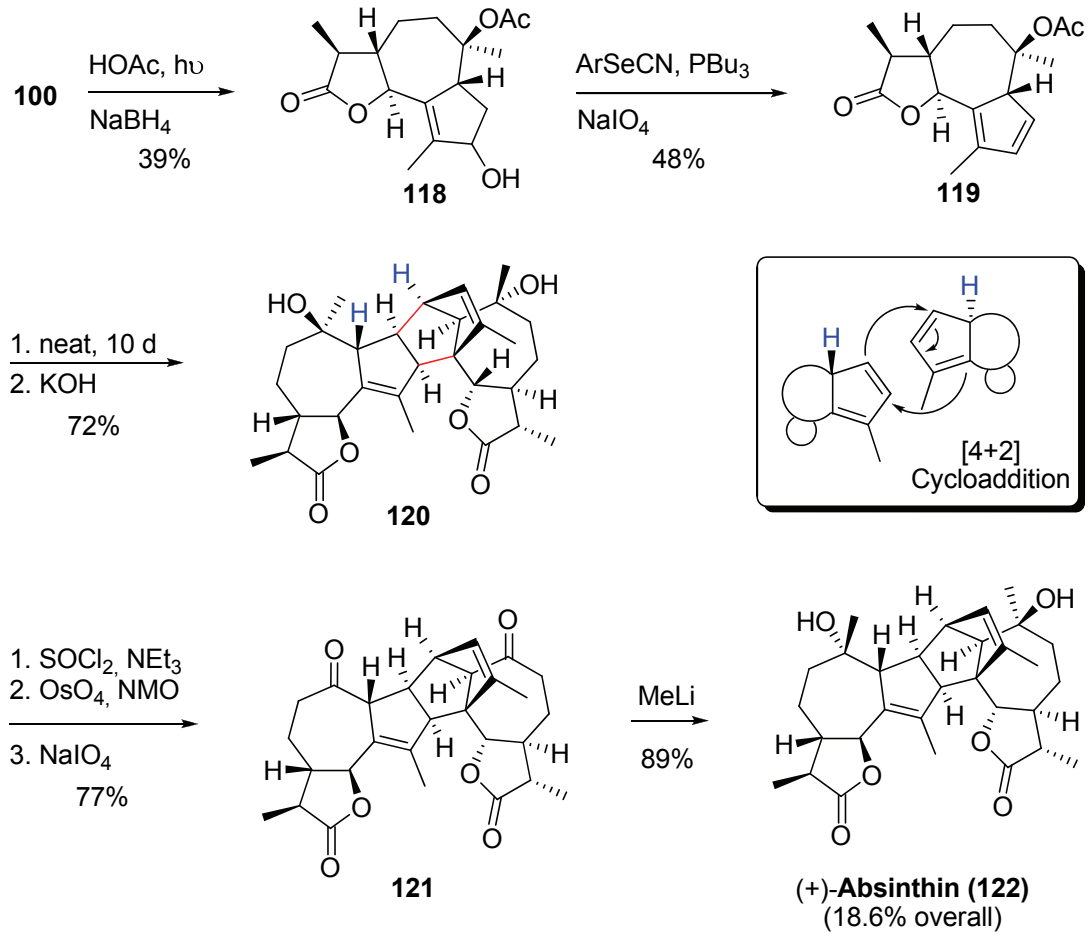
Several short biomimetic syntheses of several guaianolides starting from suitable modified natural germacranolides have also been reported in literature.[47,49,51,52] The main problems within these approaches are the insufficient availability of the staring materials or the frequently observed complex mixtures during the cyclization reactions in combination with poor yields. For example Gallicin (**117**) a germacranolide isolated from *Artemisia maritima gallica* ssp Willd can be mesylated and subsequent cyclization affords the guaianolide skeleton which can be further converted into Compressanolide (**44**) (Scheme 29).



Scheme 29. Biomimetic cyclization of germacranolides.

Isolated in 1953 by *Herout et al.*[116-118] as a main dimeric guaianolide from *Artemisia absinthium* L. the complex structure of (+)-Absinthin (**122**) was not determined before the 1980s.[119-122] The challenging structure and the biological activity of this compound inspired Zhang and co-workers to search for a synthetic approach towards this compound.[123]

Photochemical rearrangement of (-)-α-Santonin (**100**) provided access to the guaianolide skeleton and reduction yielded the alcohol **118** (Scheme 30). Subsequent Mitsunobu-arylselenation followed by oxidative elimination afforded the precursor diene **119**.



Scheme 30. Biomimetic dimerisation via [4+2] Cycloaddition.

The biomimetic dimerisation of the two identical Diels-Alder partners proceeded highly regio- and stereospecific towards **120**. This can be explained by minimizing the steric interactions during the approach of the reaction partners via the less hindered face (for the cyclopentadiene moieties). A head to head orientation (for the lactone moieties) also minimizes steric interactions between the 7-membered ring systems (inset box in Scheme 30). After basic cleavage of the acetyl-protecting groups the stereocenters of the resulting tertiary alcohol **120** had to be inverted. This was achieved by initial elimination and subsequent oxidative cleavage of the resulting *exo*-cyclic double bond to release diketone **121**. To complete this biomimetic total synthesis of (+)-Absinthin (**122**), stereoselective methylation of the carbonyl groups afforded the target compound in 18.6% overall yield.

1.6 Conclusions

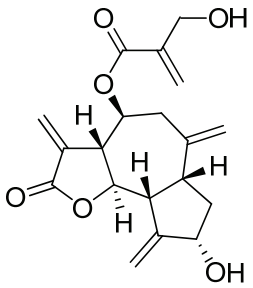
The search for new synthetic ways towards the guaianolides did not only result in new total synthesis of complex and biological active natural products, but also contributed to the development of a wide range of new and modern chemistry. The fundamental and methodological aspects of natural product synthesis have always proven to be of great importance beside the straight forward synthetic pathway towards the target structures. As there are more and more members of the guaianolide family discovered and extracted from different plants, the full evaluation of their biological activity is still of current interest. Therefore total synthesis has to find new, efficient and flexible ways to make these compounds and their derivatives available.

2. Aim of this work

This work seeks to explore a new synthetic strategy towards the total synthesis of two interesting members of the guaianolide family, namely Cynaropicrin (**123**) and Ixerin Y (**126**). A highly promising biological activity in combination with their complex structure makes these compounds challenging targets for total synthesis.

2.1 Cynaropicrin - the herb principle of artichoke

The artichoke (*Cynara scolymus* L.) was elected as the medical plant of the year 2003.[124] This 1.5-2 m tall perennial thistle is originated in southern Europe especially around Mediterranean (Figure 5).[125-129]



Cynaropicrin (123)

Figure 5. Pictures of *Cynara scolymus* L. and structure of Cynaropicrin (**123**).

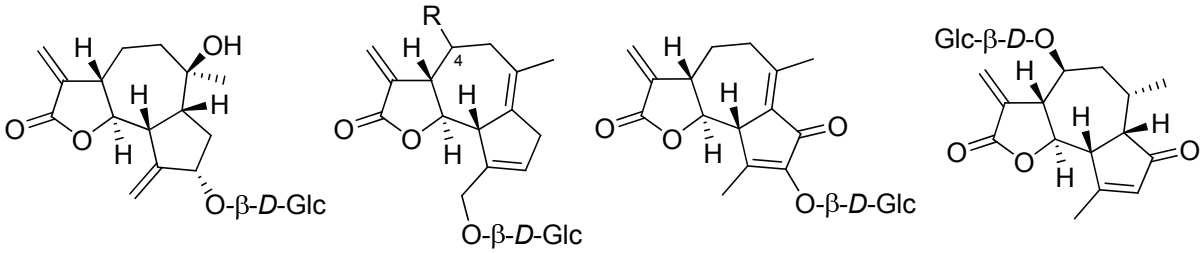
Dried or fresh leaves and stems of *Cynara* are used as a choleretic (to increase bile production) and to treat gallstones. Furthermore, drugs are prepared from the extracts for the treatment of dyslipidemias, arteriosclerosis and inflammatory bowel disorders.[130]
Responsible for the bitter taste of this vegetable is the guaianolide Cynaropicrin (**123**),[131,132] also identified as the active principle, which shows a broad variety of biological activities: Significant cytotoxicity against human tumor cell lines (ED_{50} = 0.23-1.72 µg/ml) was found by Choi and co-worker.[133] Further reports are provided in literature on the pro-apoptotic activity of Cynaropicrin (**123**) on leukocyte cancer cell lines[134] in combination with activity in acute and chronic inflammatory processes.[135-137] In addition to this, antibacterial effects are seen by irreversible inhibition of MurA, an enzyme responsible for the first step in cytoplasmatic biosynthesis of peptidoglycan precursors.[138] This enzyme is of certain interest for drug development projects, since the MurA-dependent metabolites are of vital importance for bacteria.[139-141]

2.2 Ixerin Y - a guaianolide sesquiterpene lactone glucoside

Various interesting natural products have been isolated from *Ixeris* plants (Figure 6), and sesquiterpene lactones as the Ixerins A-Z have been characterized (Figure 7).[142-146]

Figure 6. Pictures of *Ixeris denticulata f. pinnatiparita*.

A wide spectrum of biological activities, such as cytotoxicity[147] as well as having ant repellent[148] and antifeedant[149] properties is reported for some members of the Ixerin family. In addition to this, Ixerin Y (**126**) shows a promising inhibitory effect against the growth of human breast cancer cell lines (MCF7: IC_{50} = 6.36 µg/ml, MDA468: IC_{50} = 11.87 µg/ml).[57] Prominent members of the Ixerin guaianolide family are given in Figure 7.



Ixerin D (124) | **125** R = β-OH **Ixerin X**, **126** R = α-OH **Ixerin Y** | **Ixerin Z (127)** | **Ixerinoside (128)**

Figure 7. Prominent members of the Ixerin guaianolide family.

A common feature of the mentioned members of the Ixerins is the glycosidic linkage of a glucose moiety found at different positions on the hydroazulene core skeleton. Ixerin X (**125**) and Y (**126**) differ only in the configuration of the hydroxy functionality at the C4-position which is absent in Ixerin D (**124**) and Z (**127**).

Table 1. Sources of members of the Ixerin family.

Entry	Guaianolide	isolated from	Ref.
1	Ixerin D (**124**)	*Ixeris tamagawaensis*	[143]
2	Ixerin X (**125**)	*Ixeris Denticulata f. pinnatipartita* and *Ixeris sonchifolia resp.*	[57,150,151]
3	Ixerin Y (**126**)	*Ixeris Denticulata f. pinnatipartita* and *Ixeris sonchifolia resp.*	[57,150]
4	Ixerin Z **(127**)	*Ixeris Denticulata f. pinnatipartita* and *Ixeris sonchifolia resp.*	[150,152]
5	Ixerinoside (**128**)	*Ixeris sonchifolia*	[153]

The complex structure in combination with their broad spectrum of biological activity makes all these compounds to challenging targets for total synthesis.

2.3 Retrosynthetic analysis of the target compounds

All total synthetic approaches described so far (see introduction) find their first target in the construction of the guaiane core system. Once this skeleton is assembled, the *trans*-annulated lactone moiety is introduced in the synthesis. The stereochemistry is mostly substrate controlled via the hydroazulene core system and the target structures are finally reached by functional group transformations.

In contrast to this, the synthetic approach towards the two guaianolides described above seeks for a different route: The lactone moiety and its *trans*-substitution pattern is constructed first as seen in lactone aldehyde **129**, and the guaianolide skeleton is finalized by closing the hydroazulene substructure (Figure 8).

Although Cynaropicrin (**123**) and Ixerin Y (**126**) have been isolated from very different sources, there seems to exist quite an interesting structural relationship between these compounds: The basic framework of **123** and **126** differs only in the position of the double bonds within the guaiane skeleton as well as in the position of the hydroxy group on the allylic moiety in the cyclopentane ring.

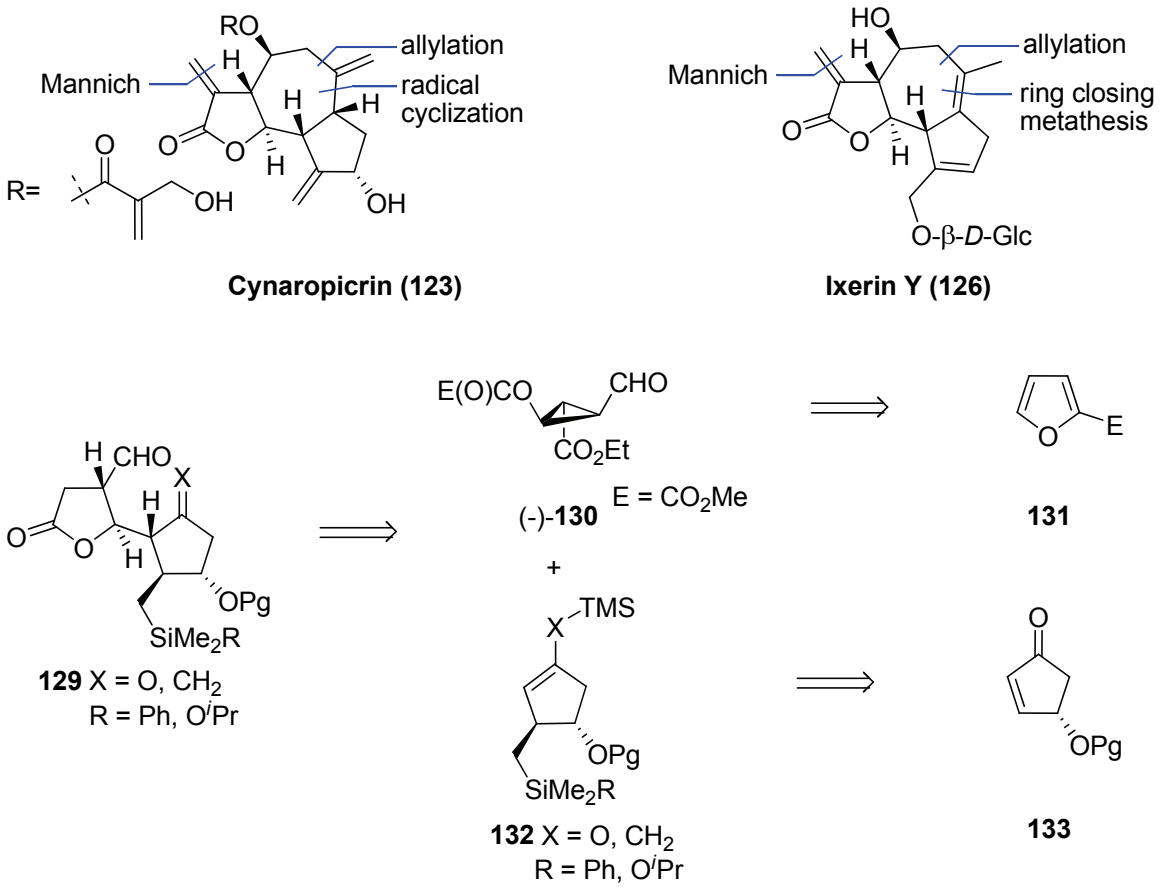


Figure 8. Retrosynthesis of Cynaropicrin (**123**) and Ixerin Y (**126**).

Because of this, a stereoselective synthesis of both natural products is envisioned to the common precursor **129** using either a radical cyclization or ring closing metathesis approach to form the central seven membered ring.

The lactone aldehyde intermediate **129** having already incorporated five stereocenters with respect to the target structures, was envisaged to be assembled from the cyclopropyl-carbaldehyde (-)-**130**, accesible from furan **131**, and the disubstituted allylsilane **132**. The construction of the latter is acchieved starting from the enantiomerically pure protected cyclopentenon **133**.

3. Synthesis of chiral allylsilanes

Allylsilanes have proven to be versatile tools in organic chemistry, especially for the mild and highly selective Hosomi-Sakurai allylation.[154-158] To construct the southern cyclopentane ring of the guaianolides, two chiral allylsilanes with all the desired substituents in place were prepared. Compounds **134** and **135** are envisioned as important key intermediates with three major features (Figure 9):

i) the allylsilane moiety allows the smooth addition onto the cyclopropylcarbaldehyde.
ii) the protected alcohol already possesses the right stereochemistry (with respect to Cynaropicrin (**123**)) and can be further functionalized.
iii) the bulky silyl group in the sidechain acts as a directing group during the addition reaction and can be transformed into a free hydroxy functionality later on.

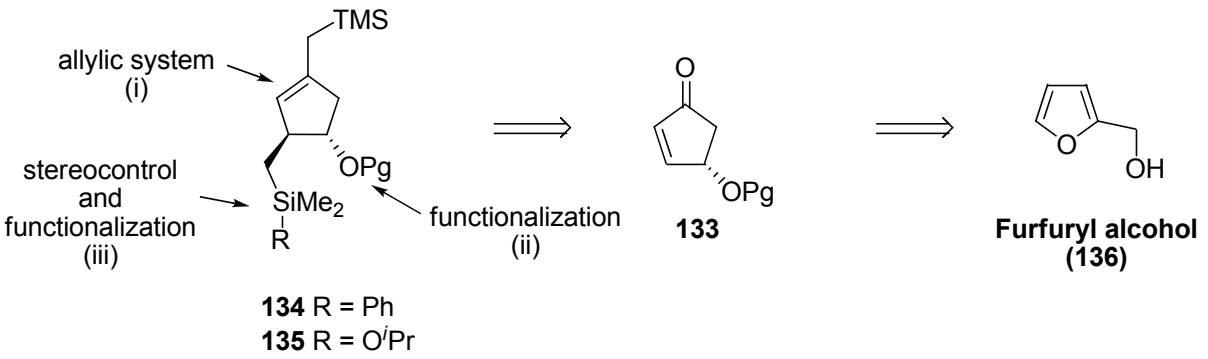


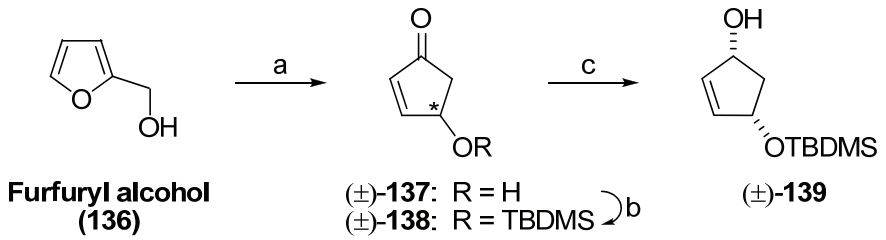
Figure 9. Retrosynthesis of chiral allylsilanes **134** and **135**, respectively.

To be able to introduce all of these features, the synthesis of the allylsilanes **134** and **135** is referred to the chiral protected cyclopentenone **133**, which is readily accessible in enantiomeric pure form, starting from inexpensive commercially available furfuryl alcohol (**136**).

3.1 Synthesis of the enantiomeric pure cyclopentenone

There are quite a number of methods known for the synthesis of optically active *cis*-2-cyclopenten-1,4-diol derivatives,[159-168] but many of these show certain inconveniences (e.g. cracking of dimer when starting from cyclopentadiene, instability of intermediates, loss of stereoselectivity during the synthesis).[169] To avoid these problems it was decided to follow a well established route reported by *Curran et al.* for large quantity preparation of optically active *cis*-2-cyclopenten-1,4-diols.[169,170]

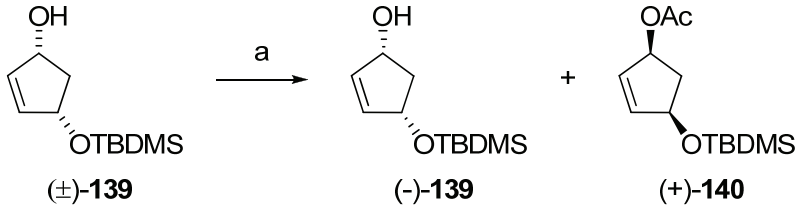
First, furfuryl alcohol (**136**) was rearranged to 4-hydroxycyclopent-2-enone (±)-**137** in moderate yield (Scheme 31).



Scheme 31. Synthesis of precursor for enzymatic resolution: 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 following TBDMS-protection of the free hydroxy group introduces a bulky substituent in (±)-**138**, which directs the subsequent reduction towards the *cis*-substituted (±)-**139** in good yield and selectivity.

The racemate of (±)-**139** was subjected to kinetic enzymatic resolution using porcine pancreas lipase (PPLE).[171] (-)-**139** and (+)-**140** were separated afterwards by simple chromatography on silica gel, and both compounds can be used in the further synthesis providing the important feature not to loose material within this early stage (Scheme 32).



Scheme 32. Enzymatic resolution: a) porcine pancreas lipase PPLE, vinylacetate (4.50 eq.), NEt_3 (0.68 eq.), TBME, rt, 48 h, (-)-**139** (95%, 92% *ee)*, (+)-**140** (80%, >99% *ee*).

The progress in the enzymatic resolution can easily be monitored via chiral GC analysis by determination of the *ee*-value for the starting material (-)-**139** (Figure 10).

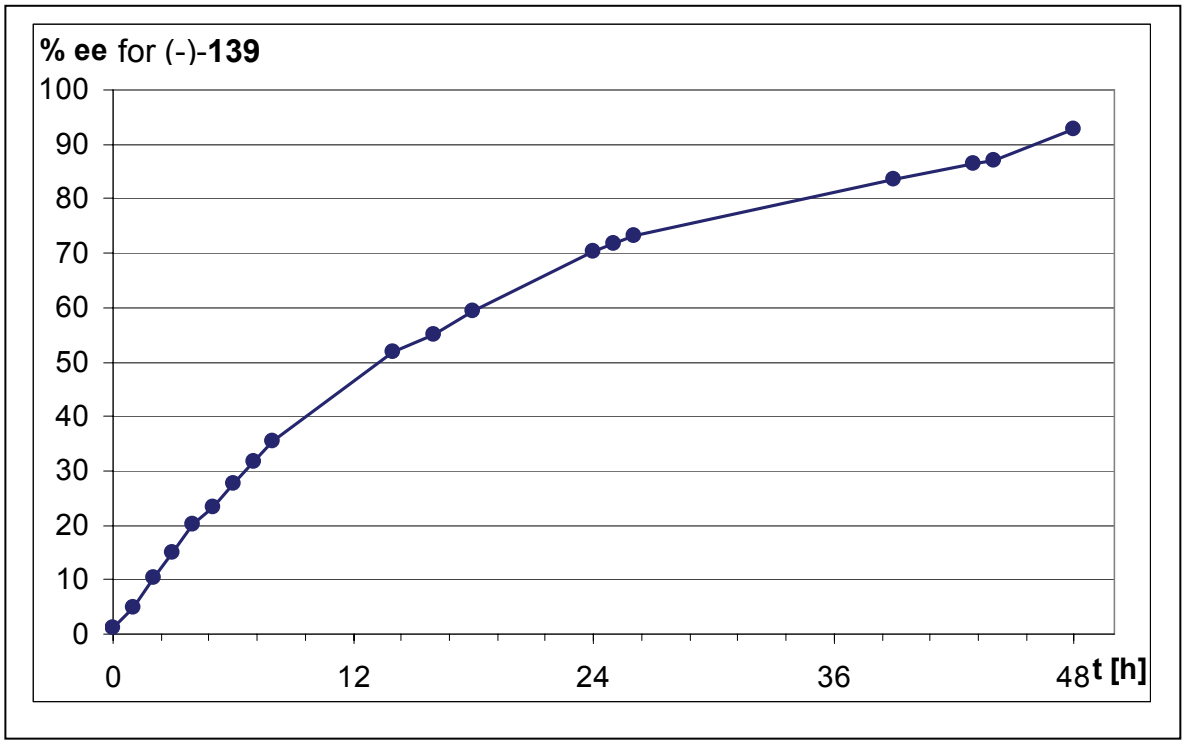
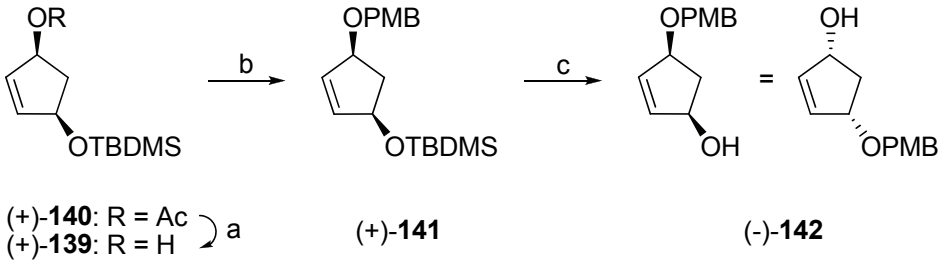


Figure 10. Kinetic resolution of (-)-**139** monitored by chiral GC.

In the first 12 h the reaction velocity was high, illustrated in the steep slope of the curve at the beginning (Figure 10). The maximum *ee* of 92% for (-)-**139** was reached after 48 h. A change of the high *ee*-value of >99% for the acetylated product (+)-**140** was not observed during this reaction. All attempts to recycle the used enzyme for further resolution reactions were not successful and only very low conversion was seen.

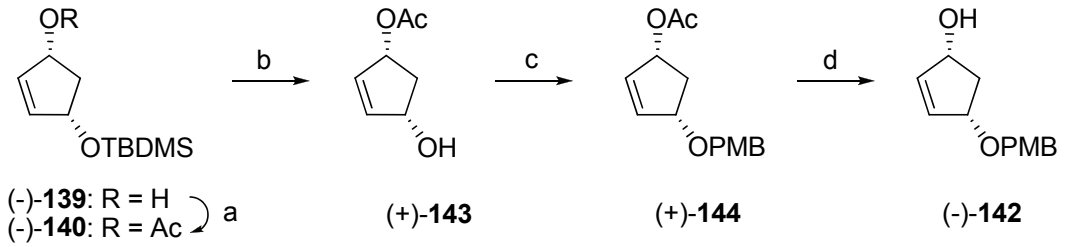
For the further synthesis, the acetyl-protection of (+)-**140** was removed by saponification using LiOH (Scheme 33).



Scheme 33. a) LiOH (1.20 eq.) THF:MeOH:H_2O (3:1:1), rt, 2 h, 96%; b) NaH (1.25 eq.), NaI (1.00 eq.), *p*-methoxybenzylbromide (1.30 eq.), THF, rt, 5 h, 86%; c) TBAF (1.00 eq.), NEt_3 (0.10 eq.), THF, rt, 24 h, 85%.

Because TBDMS- and benzyl-protection approaches already failed in previous attempts within similar syntheses of guaianolides carried out in our group,[172] the strategy within this work was changed to the protecting group *p*-methoxybenzyl (PMB) which is stable to all conditions needed in the further synthesis and is readily removed under mild oxidative conditions (preferably DDQ). Protection of (+)-**139** by *p*-methoxybenzylbromide afforded PMB-protected (+)-**141** in 86% yield and standard TBDMS removal by TBAF led to (-)-**142**.

(-)-**142** is also accessible by protecting group transformation starting from (-)-**139**. Reacting the free hydroxy functionality in (-)-**139** with acetic anhydride in pyridine afforded the fully protected compound (-)-**140** in excellent yield (Scheme 34).



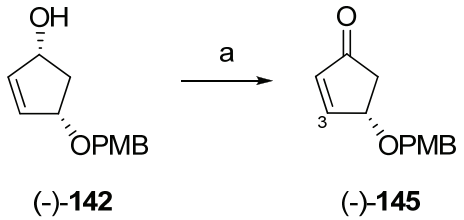
Scheme 34. a) pyridine (15.0 eq.), Ac_2O (4.5 eq.), rt, 6 h, 97%; b) TBAF (1.0 eq), NEt_3 (0.1 eq.), THF, rt, 2 h, 95%; c) *p*-methoxybenzyltrichloroacetimidate (1.67 eq.), $Cu(OTf)_2$ (5 mol%), CH_2Cl_2, 0 °C - rt, 24 h, 83%; d) LiOH (1.2 eq.), THF/MeOH/H_2O (3:1:1), rt, 2 h, 92%.

The removal of the TBDMS protection under standard conditions smoothly provided (+)-**143** as a colorless solid, which can be easily recrystallized from diethylether.

The introduction of the required PMB protecting group proved to be difficult on this substrate. First attempts using PMB-Br (similar to the synthesis of (+)-**141**, Scheme 33) failed due to racemization under these conditions. However, applying the trichloroacetimidate protocol under $Cu(OTf)_2$ catalysis as described by *Basu et al.*[173] afforded (+)-**144** in good yield and purity. Removal of the acetyl protection by standard saponification also provided (-)-**142** in 92% yield.

Altogether, both compounds resulting from the enzymatic resolution can be transformed into the same intermediate (-)-**142**, providing the important possibility to assemble large quantities of this material on this early stage of synthesis.

Final oxidation of (-)-**142** using PCC yielded the PMB-protected cyclopentenone (-)-**145** (Scheme 35).



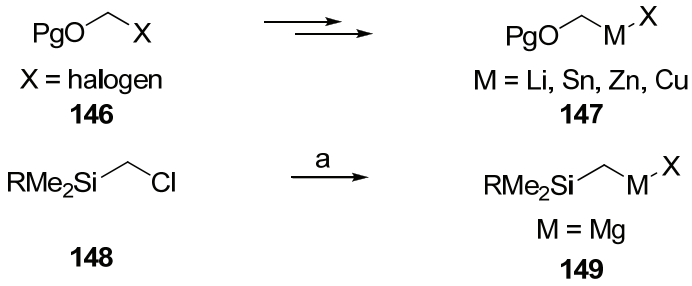
Scheme 35. Oxidation of (-)-**142** to key intermediate (-)-**145**: a) PCC (1.2 eq.), 4 Å MS, CH_2Cl_2, rt, 24 h, 86%.

With this synthesis the key intermediate (-)-**145** was accessible in 8-9 steps starting from commercially available furfuryl alcohol (**136**). Each step in the described sequence was a spot to spot reaction and could easily be monitored by TLC or GC. After optimization of the reaction conditions, up-scaling to 18 g batches in the enzymatic resolution was possible without loosing the enantiomeric purity of the resulting products.

3.2 Synthesis of the chiral allylsilanes

The PMB-protected cyclopentenone (-)-**145** was subjected to a highly selective 1,4-addition with appropriate cuprate reagents to introduce the functionalized carbon side chain at C3-position.

The desired hydroxy functionality is introduced in this step, masked as a bulky silyl group, offering certain advantages (Scheme 36): The desired cuprate reagents **147** with an n-electron donor atom (here oxygen) attached to the metalated carbon are not readily accessible from the corresponding halides **146** by usual procedures[174] and often involve multiple steps in their preparation (e.g. using tin-containing intermediates).[174,175]

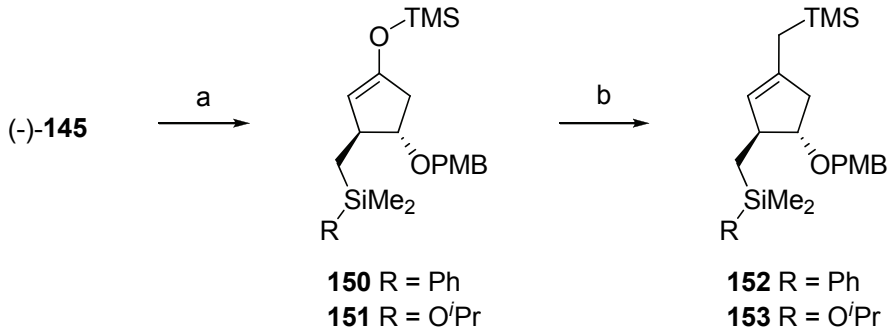


Scheme 36. Metal organyls used for 1,4-addition: a) Mg (3.0 eq.), THF, rt, 2 h.

Additionally, the introduction of a further hydroxy protecting group at this early stage of the synthesis was thought to be problematic in terms of restrictions in transformations and in protecting group differentiation.

To avoid these problems, commercially available chloromethylsilanes **148** (R = O^{i}Pr, Ph) were used for standard Grignard formation. *In situ* conversion to the appropriate cuprates provided the reagents for the 1,4-addition onto cyclopentenone (-)-**145**. The use of different substituents at the silicon atom (R = O^{i}Pr, Ph) opens the possibility to investigate different conversion protocols for the transformation of the masked hydroxy group into the corresponding free alcohol.

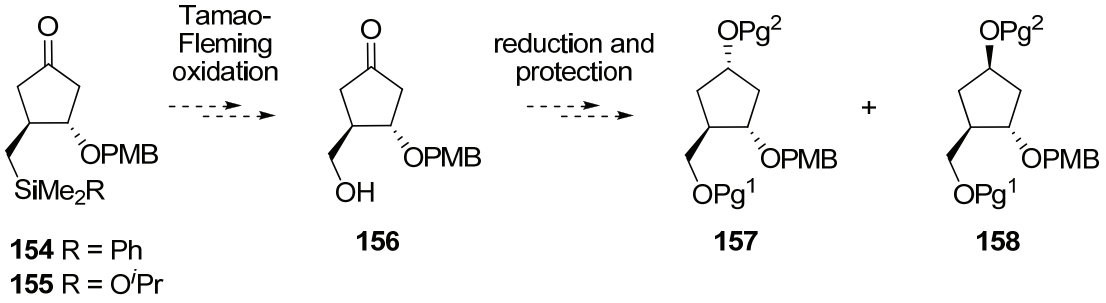
Because the bulky PMB-protecting group in (-)-**145** shields the lower half space, the cuprate addition proceeds highly diastereoselectively from the upper face resulting in the desired *anti*-substitution on the cyclopentane ring. The resulting enolates were trapped in the presence of TMS-Cl as the corresponding silylenolethers **150** and **151** (Scheme 37). These materials are very sensitive to heat and traces of acid.[176] 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.



Scheme 37. Synthesis of chiral allylsilanes: a) LiCl (0.3 eq.), CuI (0.15 eq.), TMSCl (4.0 eq.), R = Ph: $PhMe_2SiCH_2MgCl$ (1N in THF) (1.25 eq.), THF, -78 °C, 3 h, 99%, *dr* >99:1; R = O^{i}Pr: ^{i}PrOMe_2SiCH_2MgCl (1 N in THF) (1.15 eq.), THF, -78 °C, 3 h, 90%, *dr* >99:1; b) $Ni(acac)_2$ (0.1-1.0 eq.) Me_3SiCH_2MgCl (1 N in Et_2O) (1.5-2.0 eq.), Et_2O, rt, 5 d, R = Ph: 40%, R = O^{i}Pr: 34%.

For the final transformation of the silylenolethers into the corresponding allylsilanes **152** and **153** a modified procedure reported by *Kumada et al.* was used.[177] $Ni(acac)_2$ catalyzes the coupling of silylenolethers with the appropriate Grignard reagent to afford the desired allylsilanes **152-153** only in moderate yields (34-40%). This might be due to the highly substituted cyclopentane ring and the resulting steric strain preventing the cross coupling to the allylsilanes. Attempts to improve this reaction by gentle warming, elongated reaction times or increasing the catalyst loading as well as reagent excess did not lead to better results.

From the $Ni(acac)_2$ coupling reaction compounds **154** and **155** were also isolated as decomposition products of the corresponding silylenolether (Scheme 38).



Scheme 38. Possible use of by-products.

These *trans*-substituted cyclopentenones **154** and **155** are very interesting structures themselves, since sugar-like trisubstituted cyclopentanes **157** and **158** could become accessible within a short sequence, including Tamao-Fleming oxidation of the side chain and reduction of the resulting ketone **156**. These pseudo-anomeric structures have already proven to be important compounds as sugar mimics for pharmaceutical or biochemical purposes.[178]

4. Synthesis of the cyclopropylcarbaldehyde

Both enantiomers of the highly functionalized 1,2,3-trisubstituted cyclopropylcarbaldehyde **130** are readily accessible in enantiomeric pure form via a well established two step sequence starting from methyl-2-furoate (**131**).[6,74,179,180]

The stereochemical outcome of the sequence of cyclopropanation, ozonolysis to the cyclopropylcarbaldehyde **130** and subsequent allylation/retroaldol-lactonization depends on the stereochemistry of the bis(oxazoline)-ligand (BOX) **159** initially used (Figure 11 and Scheme 39).

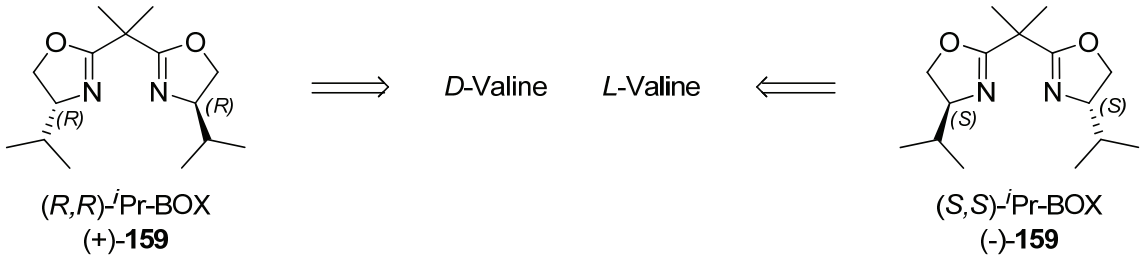
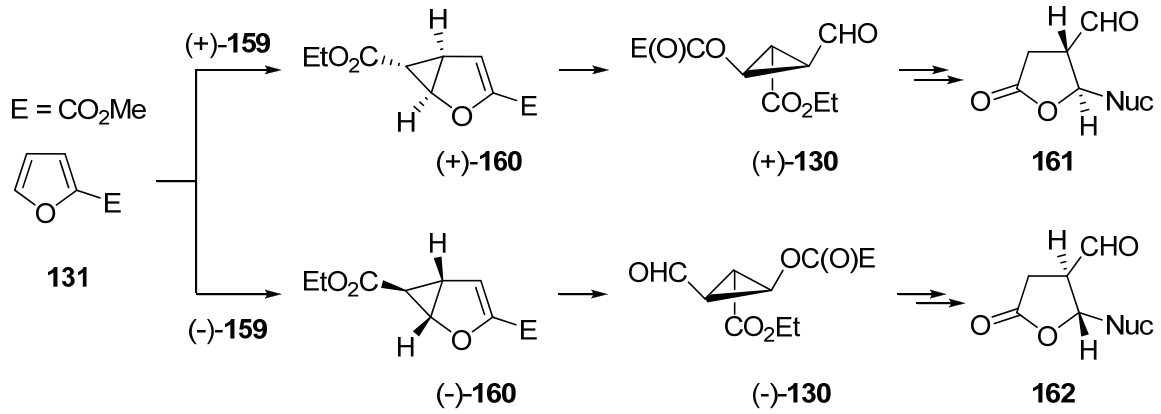


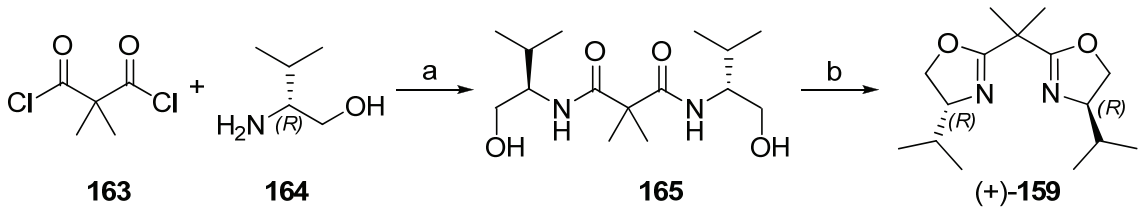
Figure 11. ^{i}Pr-BOX-ligands (+)/(-)-**159** used for asymmetric cyclopropanation.



Scheme 39. Stereochemical relationships of ^{i}Pr-BOX-ligands and stereochemistry of lactone aldehydes.

The (*R,R*)-^{i}Pr-BOX ligand (+)-**159** derived from *D*-valine leads to the desired substitution pattern on the lactone aldehyde **161** as found in the natural products, and subsequently the (*S,S*)-^{i}Pr-BOX ligand (-)-**159**, prepared from the less expensive natural *L*-valine, gives rise to the enantiomeric compound **162**.

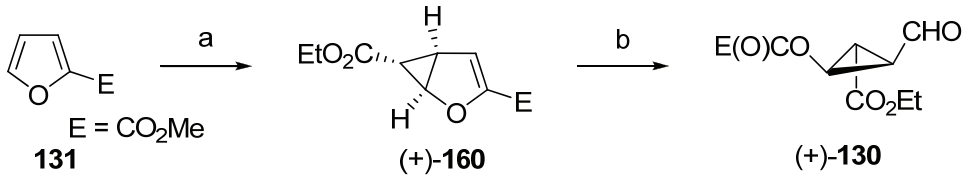
Both enantiomers of the chiral BOX-ligands **159** were prepared starting from *D*- or *L*-valinol **164**, derived from the corresponding amino acids by reduction with sodiumborohydride and iodine. Coupling of 2,2-dimethylpropane-dioyl-dichloride **163** and valinol **164** proceeded successfully to diamide **165** (Scheme 40). Subsequent tosylation and cyclization gives rise to the corresponding enantiomeric pure ligand (+)-**159**.[181]



163 **164** **165** **(+)-159**

Scheme 40. Synthesis of bis(4-isopropyloxazoline) ligand: a) valinol (2.0 eq.), NEt_3 (2.5 eq.), CH_2Cl_2, 0-rt °C, 70 min, 84%; b) DMAP (10 mol%), NEt_3 (4.0 eq.), TsCl (2.0 eq.), CH_2Cl_2, rt, 27 h, 83%.

BOX-ligand (+)-**159** was applied in a Cu(I)-mediated asymmetric regio- and diastereoselective cyclopropanation of methyl-2-furoate (**131**), resulting in (+)-**160** with high enantioselectivity of 85-90% *ee*, which was improved to >99% *ee* after recrystallization (Scheme 41).



131 **(+)-160** **(+)-130**

Scheme 41. Cyclopropanation and ozonolysis: a) (i) ethyl diazoacetate (2.67 eq.), $Cu(OTf)_2$ (0.66 mol%), (+)-**159** (0.84 mol%), $PhNHNH_2$ (0.70 mol%), CH_2Cl_2, 0 °C, 54%, 85-90% *ee*; (ii) recrystallization (CH_2Cl_2, pentane), >99% *ee*, 37%; b) (i) O_3, CH_2Cl_2, -78 °C; (ii) DMS (4.00 eq.), 22 h, -78 °C - rt, 90%.

The stereochemical outcome of this reaction can be explained applying the models suggested by Pfaltz[182] and Andersson[183] for the asymmetric cyclopropanation of alkenes:
The reactive complex **166** in this reaction is shown in Figure 12 (left). An approach of **131** (substituent CO_2Me oriented away from **166** to minimize steric interactions) from the right side is expected to be favored, since an attack from the left side shows strong repulsive steric interaction of the approaching olefin **131** and the ^{i}Pr group of the ligand (+)-**159** (Figure 12, right). An attack from the right side will also lead to a flipping of the ester group E in **166** to the left (counterclockwise), resulting in only small interactions with the hydrogen substituent H_a.

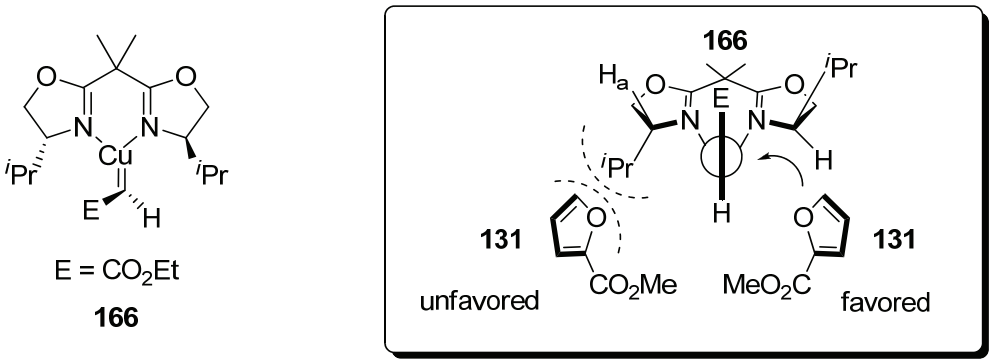


Figure 12. Reactive complex and model for asymmetric cyclopropanation.

In the subsequent cyclopropanation the less substituted and presumably more electron rich double bond of **131** is attacked.

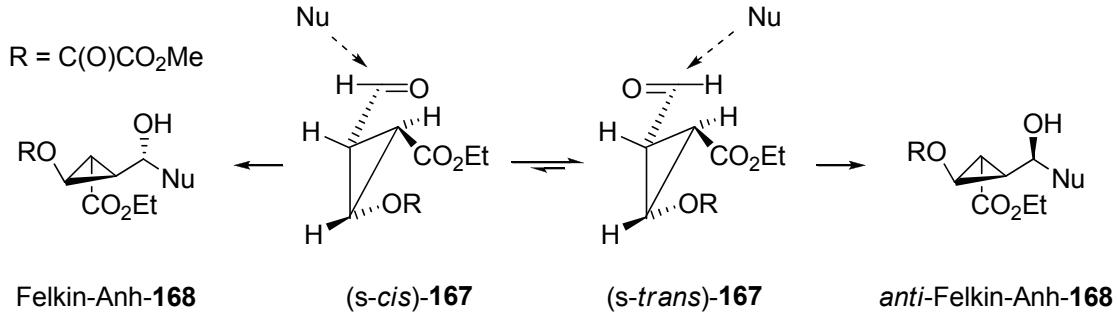
The formation of the corresponding *endo*-diastereomer was not observed and after optimization of the reaction conditions a scale-up to 50-100 g was possible, still affording high enantioselectivity, so that both enantiomers of **160** can be prepared in optical pure form and multigram quantities.

To access the cyclopropylcarbaldehyde, the double bond present in (+)-**160** was cleaved by ozonolysis followed by reductive work-up leading to (+)-**130** in 90% yield (Scheme 41). This material rendered solid upon treatment with diethylether and was stable for months while stored under a nitrogen atmosphere at -35 °C.

5. Formation of the *anti*-substituted lactone aldehyde

The next step was the addition of the chiral allylsilanes to the cyclopropylcarbaldehyde. In general, the stereocontrol of additions onto a cyclopropyl-substituted carbonyl compound **167** can be explained by analyzing the conformational preferences and applying the Felkin-Anh-model[184] in combination with the Curtin-Hammett-principle.[185]

The cyclopropane ring shows in analogy to an alkene double bond strong π-donating properties. These are only effective in the two bisected conformations, which are very similar to the Felkin-Anh conformations *s-cis*-**167** and *s-trans*-**167** of the cyclopropyl-substituted carbonyl compounds (Scheme 42).



Scheme 42. Nucleophilic attack on cyclopropyl-substituted carbonyl compounds.

From these possible conformations the latter is energetically more favored because the steric interactions of the aldehyde and the space demanding cyclopropane ring are minimized. A nucleophile attacking the more stable s-*trans*-**167** conformation would consequently have to approach over a bulky substituent leading to the *anti*-Felkin-Anh-**168** product. The experimentally observed Felkin-Anh-**168** product results from the s-*cis*-**167** conformation which is attacked by the nucleophile coming over a less hindered half space.

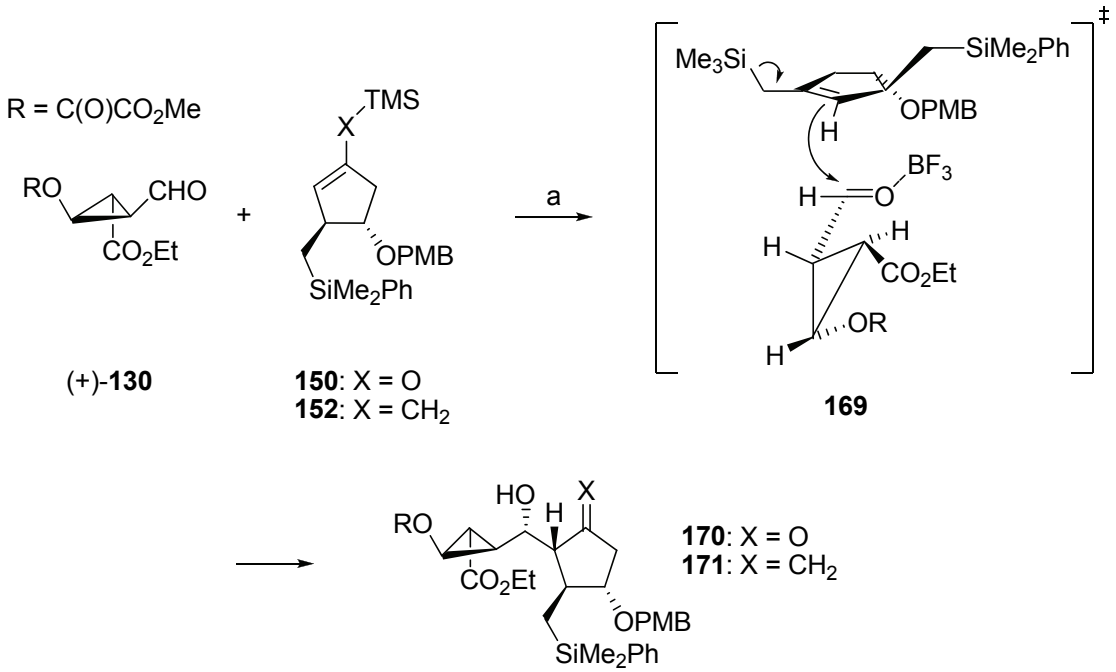
If the activation energies of the selectivity determining step are higher than the rotation barrier between the different conformers, the Curtin-Hammet principle can be applied. For this case not the preferred conformation of the substrate (here s-*trans*-**167**) is responsible for the product distribution, but the activation energy of the transition state determines the stereochemical outcome.

In the case described here, the rotation barrier for the transformation of s-*cis* to s-*trans* must be smaller than the activation barrier for the selective addition step and so the attack of bulky nucleophiles will occur on the less hindered path over the smaller substituent leading to the experimentally observed Felkin-Anh-**168** product.

The synthesized chiral silylenolethers **150**/**151** and allylsilanes **152**/**153** were now combined in a Lewis acid mediated Mukaiyama-aldol reaction or a Hosomi-Sakurai allylation with the cyclopropylcarbaldehyde (+)-**130**, respectively.

All attempts to add the silylenolether **151** and allylsilane **153** with the O^{i}Pr- substituent at the silicon atom in the side chain failed due to decomposition of the silyl precursor.

In contrast, the reactions using the Ph-substituted compounds **150** and **152** proceeded smoothly to the highly substituted intermediates **170** and **171** which were obtained as single diastereomers (Scheme 43). The Mukaiyama-aldol reaction of **150** (X = O) did not afford a clean product **170**, as the silylenolether could not be purified and therefore had to be used as a crude material.



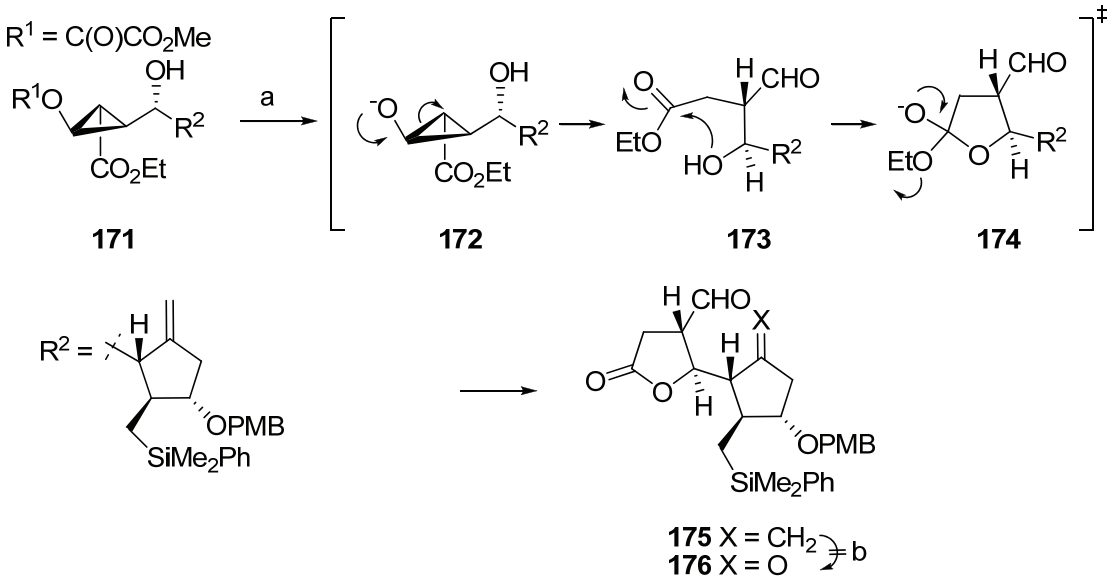
Scheme 43. Addition of chiral silylenolethers and allylsilanes to the cyclopropylcarbaldehyde: a) $BF_3{\cdot}OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 16 h, **170**: X = O: 95%, *dr* >99:1; **171**: X = CH_2: 95%, *dr* >99:1.

These highly functionalized materials can not be purified easily by distillation due to their high molecular mass or chromatography because they tend to decompose on silica gel. Simple extraction afforded the products in sufficient purity to proceed with the next step in the synthesis.

The stereochemical outcome of this reaction can be explained by the proposed transition state **169** (Scheme 43). In this case, the nucleophile attacks the *s-cis*-conformation of the carbonyl group in *anti*-orientation to its bulky substituent (CH_2SiMe_2Ph) leading to the *trans*-Felkin-Anh-products **170** and **171** (see discussion above).

In an attempt to combine **152** and (-)-**130** in the mismatched case, only a complex mixture of at least four compounds was observed in a very low yield, which indicates the importance of the double stereochemical differentiation with the chiral allylsilanes.

Upon treatment with $Ba(OH)_2$ in methanol only the Hosomi-Sakurai allylation product **171** (X = CH_2) rearranged to the lactone aldehyde **175** in 72% yield (Scheme 44). Attempts to use triethylamine or LiOH as base for this transformation failed. The reaction proceeds by saponification of the more labile oxalic ester, upon which a ring opening of the now unmasked donor-acceptor substituted cyclopropane **172** is triggered, followed by lactonization of **173** to give **175** as a single stereoisomer.



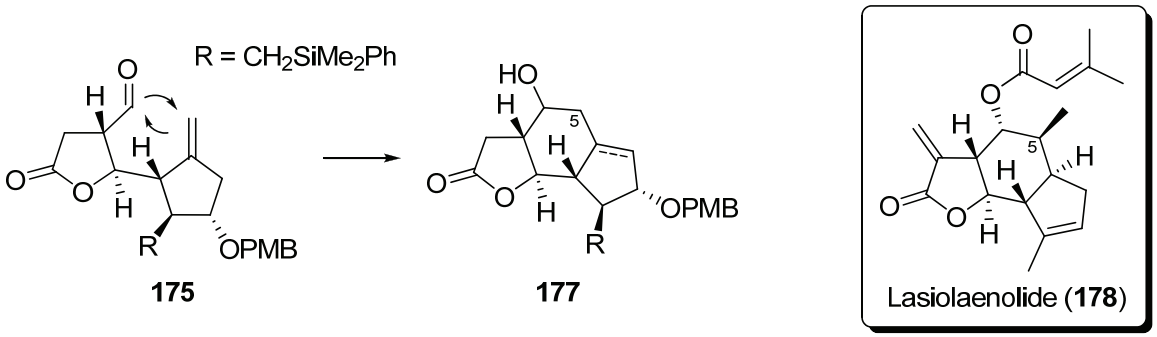
Scheme 44. Retroaldol-lactonization: a) $Ba(OH)_2 \cdot 8H_2O$ (0.55 eq.), MeOH, rt, 2 h, 72%, *dr* >99:1; b) i) O_3, CH_2Cl_2, -78 °C, 15 min; ii) DMS (4.0 eq.), -78 °C - rt, 24 h.

In contrast, the addition product **170** which resulted from the Mukaiyama-aldol reaction failed to rearrange into the ketone-aldehyde **176**. Therefore, an attempt was made to subject lactone aldehyde **175** to ozonolysis conditions to access the ketoaldehyde **176**, but only decomposition of the starting material was observed.

The lactone aldehyde **175** is an important key-intermediate in further investigations towards the total synthesis of guaianolide sesquiterpene lactones: The *trans*-stereochemistry at the lactone ring is already set and the cyclopentane ring is highly functionalized also having the stereochemistry at the connection point to the lactone ring and the protected hydroxy group set in the right way. The aldehyde group and the double bond present in the molecule are versatile functionalities, which allow many further transformations to construct the framework of the guaianolides and related natural products via certain ring closing reactions.

6. Investigations towards 5,6,5-ring systems

In addition to oxidative derivatisation, nature has also the possibility to rearrange the complex 5,7,5-carbon skeleton of the guaianolides. Probably by a Wagner-Meerwein-type rearrangement a 5,6,5-ring system is formed, as for example found in Lasiolaenolide (**178**) and its derivatives, isolated from various plants, such as *Lasiolaena santosii* (Scheme 45).[186]

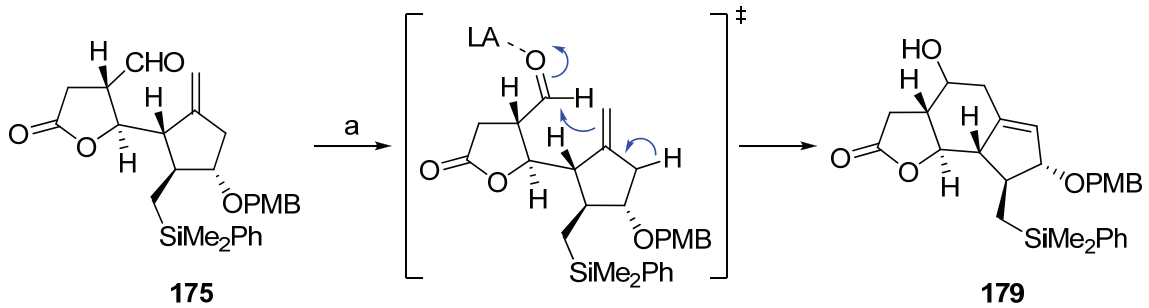


Scheme 45. Ring closing reactions to form rearranged guaianolides.

The lactone-aldehyde **175** should be a suitable precursor to construct the core **177** of this family of natural products. Connecting the carbonyl-carbon with the opposite double bond would lead to a 5,6,5-ring system. Although, the methyl group at the C5-position is lacking this transformation would provide a direct and interesting route to this skeleton.

6.1 Intramolecular carbonyl-ene reaction

The first approach to perform this ring closure was the utilization of an intramolecular carbonyl-ene reaction on aldehyde **175** which should directly lead to the 5,6,5-membered ring system **179** (Scheme 46).



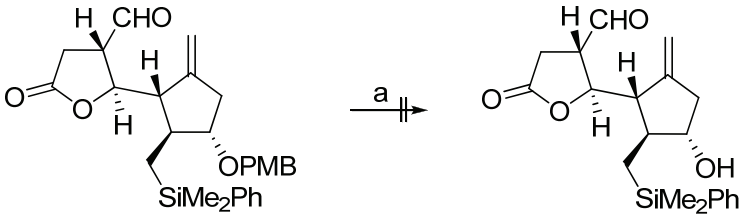
Scheme 46. Intramolecular carbonyl-en-reaction: a) see Table 2.

Although intramolecular carbonyl-ene reactions on less functionalized precursors have been reported,[187] treating lactone aldehyde **175** with different Lewis acids at different temperatures did not lead to the desired tricyclic structure **179** (Table 2). At low temperatures (-78 °C) no reaction was observed and at higher temperature (0 °C or rt) only decomposition of the starting material occurred.

Table 2. Intramolecular carbonyl-ene-reaction conditions.

Entry	Lewis Acid	Reaction conditions	Yield
1	$BF_3{\cdot}OEt_2$ (2.0 eq.)	-78 °C, 4 h	no reaction
2	$BF_3{\cdot}OEt_2$ (2.0 eq.)	rt, 4 h	decomposition
3	$BF_3{\cdot}OEt_2$ (2.0 eq.)	0 °C, 1 h	decomposition
4	$TiCl_4$ (2.0 eq.)	0 °C, 1 h	decomposition
5	$SnCl_4$ (2.0 eq.)	0 °C, 1 h	decomposition

The difficulties encountered in this transformation might be due to the high functionalization of **175** and moreover, the PMB protecting group might not be stable under these Lewis acidic conditions.



175 **180**

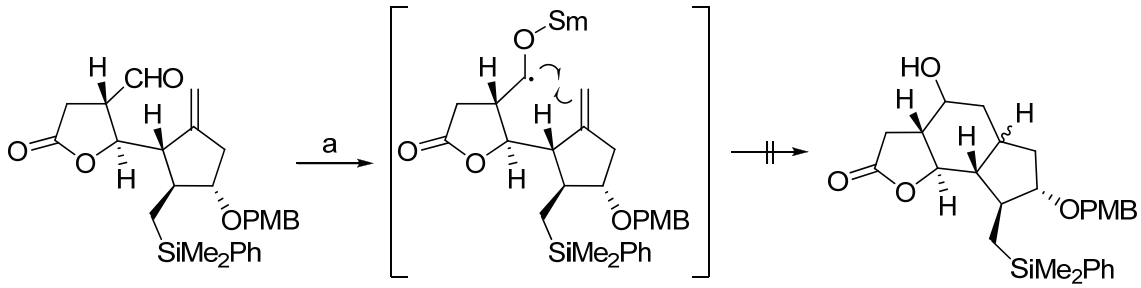
Scheme 47. PMB deprotection of **175**: a) DDQ (1.14 eq.), CH_2Cl_2/H_2O, rt, 2 h.

To remove the PMB protecting group, **175** was treated with DDQ (Scheme 47). This resulted in an inseparable mixture of unknown products and did not afford the desired free alcohol **180**.

6.2 SmI_2-promoted radical cyclization

Another potential reaction for the construction of the skeleton of type **177** is the SmI_2 promoted intramolecular radical cyclization of aldehydes into C=C-double bonds which already has found many applications in the total synthesis of various natural products.[188]

SmI_2 is a one-electron-transfer reagent, which should transform the lactone aldehyde **175** into the radical intermediate **181** (Scheme 48). Subsequent cyclization by incorporating the *exo*-double bond would led to the 5,6,5-membered ring system **182**. The 6-*endo* product should form with preference rather than the 5-*exo* product, since the *trans*-configuration at the lactone moiety introduces strain into the system. This should lead to the formation of the larger ring which is presumably thermodynamically more stable. Moreover, upon the 5-*exo* ring closure a primary radical rather than a tertiary radical as for the 6-*endo* ring closure would be formed.



175 **181** **182**

Scheme 48. SmI_2-promoted radical cyclization: a) SmI_2 (2.0 eq.), THF, 0 °C, 2 h.

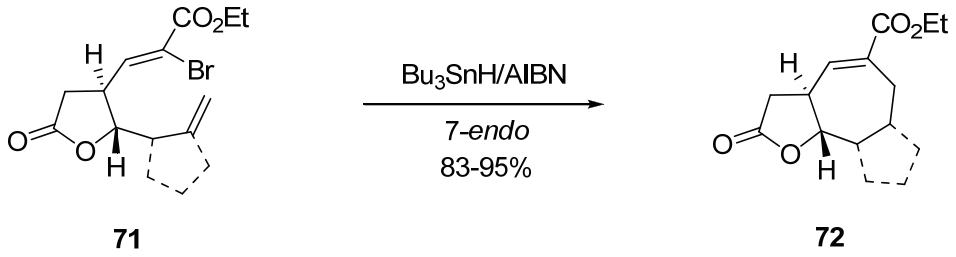
Unfortunately, applying the standard SmI_2 cyclization conditions on lactone aldehyde **175** did not afford the expected tricyclic structure and resulted in an inseparable mixture of undefinable products.

7. Investigations towards the guaianolide core skeleton

Since all previous attempts (carbonyl-ene reaction and SmI_2-radical cyclization) to build a tricyclic framework failed, the strategy was changed, focusing on the construction of the 5,7,5-membered ring system of the guaianolides. Different approaches to close the central 7-membered ring were explored including radical cyclization and ring closing metathesis.

7.1 Radical cyclization approach

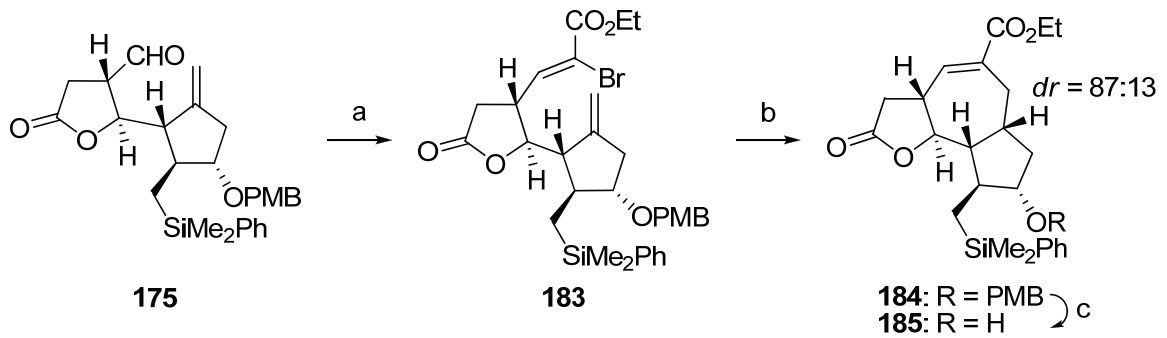
We were already able to show the transformation of simplified precursors **71** into bi- and tricyclic sesquiterpene lactone skeletons **72** via radical cyclizations (Scheme 49).[74]



71 **72**

Scheme 49. Synthesis of unsubstituted bi- and tricyclic sesquiterpene lactone scaffolds by radical cyclization.

This promising sequence was investigated on lactone aldehyde **175**. Alkenylation by a modified Horner-Wadsworth-Emmons (HWE) reaction gave rise to **183** in 72% yield and in an expected preference for the *Z*-isomer (*E*/*Z* = 17:83). Here it has to be noted that it proved to be more convenient and higher yielding to generate the 2-bromo-phosphonoacetate *in situ* to prevent the formation of unhalogenated HWE-product.



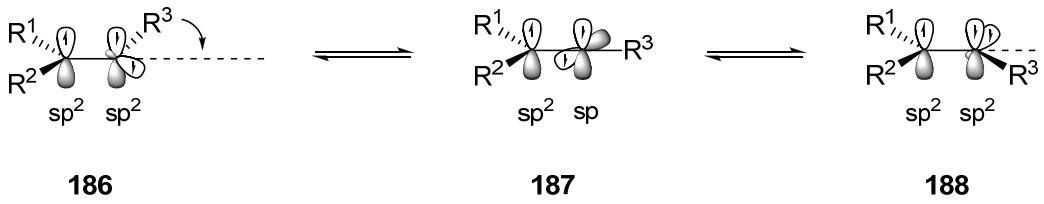
175 **183**

Scheme 50. Radical cyclizations towards the guaianolide skeleton: a) (i) NaH (1.05 eq.), triethylphosphonoacetate (1.05 eq.), Br_2 (1.11 eq.), THF, 0 °C, 1 h; (ii) NaH (1.05 eq.), **175**, THF, 0 °C to rt, 1 h, 72%, *E*/*Z* = 17:83; b) AIBN (0.2 eq.), Bu_3SnH (1.5 eq.), benzene, reflux, 2 h, 89%, *dr* = 87:13; c) DDQ (1.3 eq.), CH_2Cl_2, pH 7 buffer, rt, 4 h, 89%.

Under diluted radical generating conditions (AIBN, Bu_3SnH) an *E/Z*-mixture of **183** (17:83) reacted to the tricyclic guaianolide scaffold **184**. While comparing the remarkably high yield (89%) of this radical cyclization with the *E/Z*-ratio of the precursor it is clear, that both isomers can be cyclized.

Deprotection of the PMB-group on the finalized core skeleton under standard conditions using DDQ gave rise to **185** in 89% yield (Scheme 50), which can be subjected to further functionalization (e.g. oxidation, esterification, glycosylation).

Stork et al. have shown the synthetic value of vinyl radicals.[189,190] Based on this work it was recognized, that a fast inversion of the radical species between *E*- and the corresponding *Z*-isomer takes place. An explanation for this behavior is found in the analysis of the involved orbitals (Scheme 51).



186 **187** **188**

Scheme 51. Orbital inversion of vinyl radicals.

The orbital hybridization of **186** and **188** with a bent structure is best described as sp^2-hybrids: The unpaired electron is therefore found in a sp^2-orbital and an angle of approximately 60 ° against the elongated C-C bond is included.

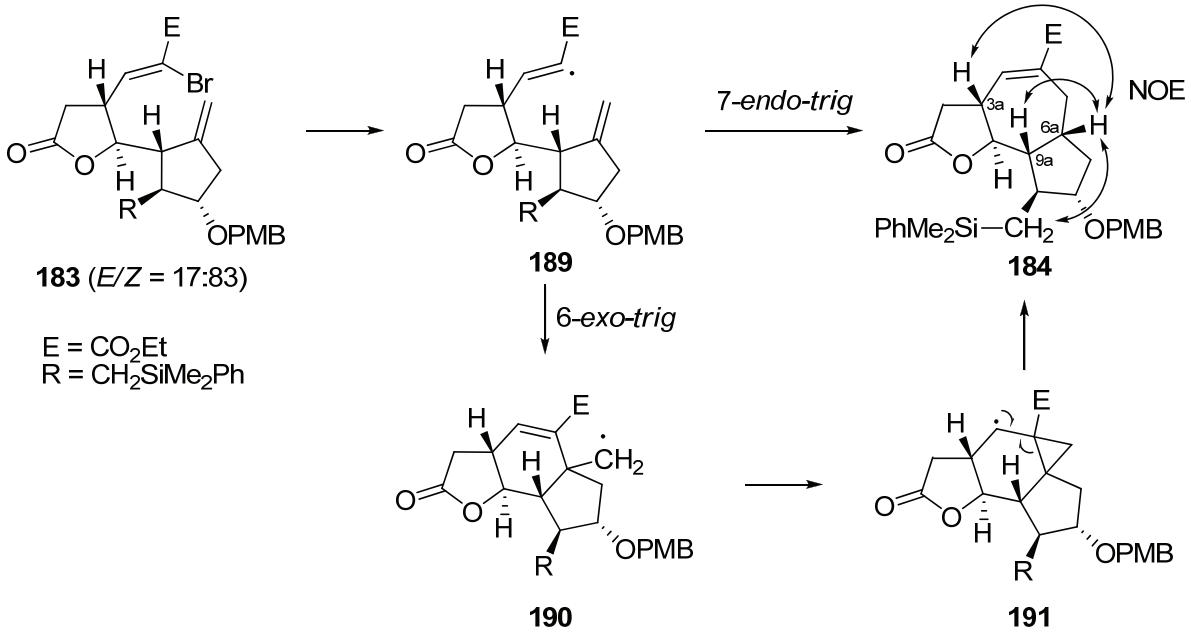
The transition state of the radical inversion is best represented with the linear structure **187** having a sp-hybridization and the unpaired electron located in a p-orbital perpendicular to the π-bond. The geometry of the radical center is highly influenced by the π-(C=C)-double bond and the σ-(C-R^3)-single bond and a nearly linear assembly is assumed. Indeed, this assumption was proven by EPR-spectroscopy (especially for R^3 = CO_2H or Ph)[191] and a low inversion barrier for the interconversion of *Z*- and *E*-isomers is seen, resulting in a fast inversion of the vinyl radical.[192,193] Therefore, both isomers can take part in the cyclization reaction to give rise to the observed high yield of 89% in this transformation.

The mechanism for the cyclization reaction of **183** to **184** appears obvious, but there are two pathways possible, both leading to the same final product (Scheme 52):

After initial radical formation, a reaction can take place directly with the opposite double bond present in **189** to form the observed product **184** via a 7-*endo-trig* cyclization.

Also, an initial 6-*exo-trig* cyclization of **189** towards **190** is conceivable, providing a primary radical which can subsequently form the cyclopropinylcarbinyl radical **191**. Rearrangement of this highly strained structure leads also to the isolated 7-*endo*-product **184**.

Although, radical trapping experiments in the presence of ethylacrylate as a possible scavenger were tried, the exact reaction mechanism remains unknown.



Scheme 52. Possible radical cyclization mechanisms towards **184**.

The stereochemistry of the final product **184** was then determined by NOE-experiments where a clear coupling between 6a-3a, 6a-9a and 6a-CH_2Si-protons is seen only for the major isomer. This is only possible in the *cis*-fused case, where these protons are found on the same side of the molecule. This preference (87:13) can be explained by a lower allover strain within the guaianolide core by a *cis*-fused cyclopentane ring system, where the final H-addition occurs from the top face of the molecule.

7.2 Ring closing metathesis approach

Ring closing metathesis (RCM) is a versatile tool in organic chemistry and has already proven to be suitable for the formation of also unusual ring sizes. Its application in the total synthesis of guaianolides was shown by *Ley et al.* in their investigations on the Thapsigargins (see Scheme 20).[75,77]

7.2.1 Hosomi-Sakurai allylation

For the application of RCM, a diene system is needed, which is constructed in the next step by an Hosomi-Sakurai allylation of the lactone aldehyde **175**.[155-158] This transformation is accompanied with the introduction of a new stereocenter in the northern sidechain, which is found in the final targets Cynaropicrin (**123**) and Ixerin X/Y (**125**/**126**) at the C4-position in the molecules (Figure 13).

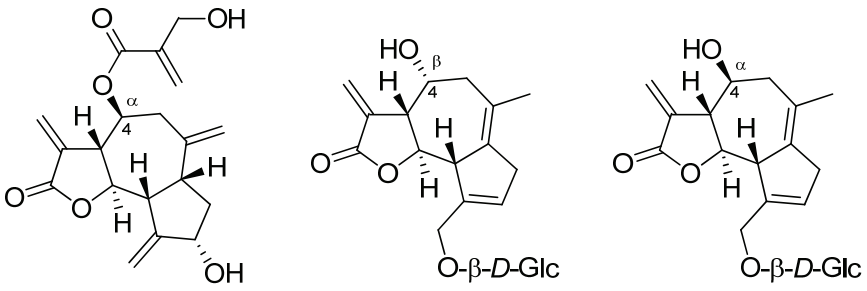
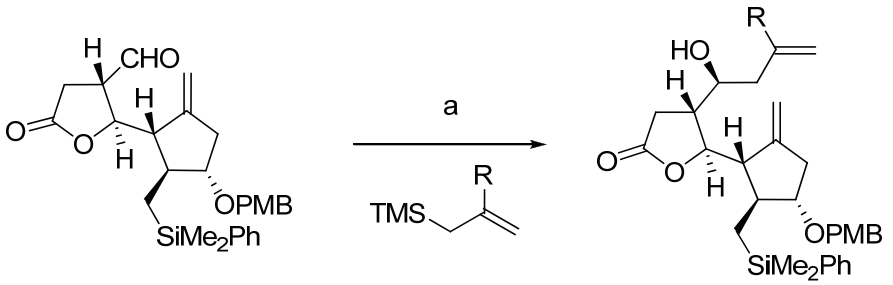


Figure 13. Stereochemistry of the natural products at the C4-position.

While Ixerin X (**125**) and Ixerin Y (**126**) differ only in the stereochemistry at this position, many guaianolides show only α-configuration for this hydroxy functionality. A control of this stereocenter is therefore essential and is achieved by substrate controlled Hosomi-Sakurai allylation of lactone aldehyde **175** with different acyclic allylsilanes **192**-**194** (Scheme 53).



175

192: R = H
193: R = Me
194: R = Br

195: R = H
196: R = Me
197: R = Br

Scheme 53. Hosomi-Sakurai allylation of **175**: a) Allylsilane (1.2-2.0 eq.), $BF_3{\cdot}OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 24 h, see Table 3.

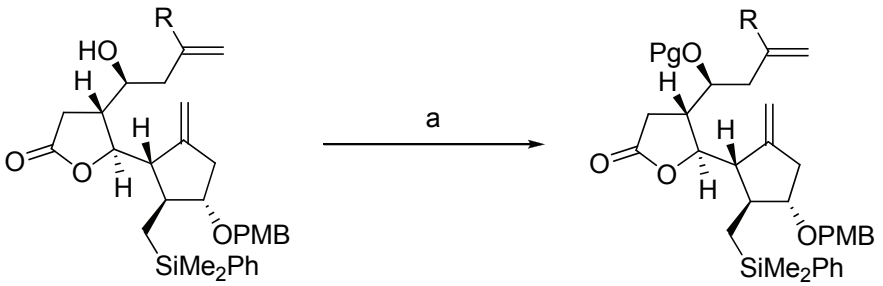
The allylated products were isolated in good yields, except for **197**, which might be due to the fact that an instable bromo substituted silane **194** was used. For the allylsilanes that carry a substituent at C2-position (X = CH_3, Br) a preference (up to 80:20) for the desired stereochemistry (Table 3, entry 2-3) with respect to Cynaropicrin (**123**) and Ixerin Y (**126**) is observed. In contrast, the unsubstituted allylsilane **192** (R = H) gave only a 50:50 mixture of diastereomers (Table 3, entry 1).

Table 3. Hosomi-Sakurai allylation.

Entry	Product	R	Yield [%]	*dr* [a]
1	**195**	H	73	50:50
2	**196**	CH_3	72	80:20
3	**197**	Br	35 [b]	78:22

[a] determined by ^{1}H NMR; [b] 10 h, -78 °C, 41% aldehyde **175** recovered.

As we have learned from our earlier experiments on similar unsubstituted structures,[194] the new free hydroxy functionality is known to disturb the subsequent ring closing metathesis.
To overcome this known problem, different protecting groups were installed in the next step to afford the RCM precursor dienes **198** (Scheme 54 and Table 4).



195: R = H
196: R = Me
197: R = Br

198a-d

Scheme 54. Protection of the free hydroxy group to form RCM precursors **198a-d**: a) see Table 4.

Although being quite bulky, the TES-protection on this position led to good results in previous investigations on less substituted substrates.[194] Therefore it was assumed that this silyl protection might be suitable for **196** as well, which was achieved using TES-Cl in 68% yield (Table 4, entry 1).

As a key step in the further synthesis the Tamao-Fleming oxidation of the silyl side chain was planned for which acidic conditions (HOAc, HBF_4) will be needed (Scheme 64). Therefore, the necessity for an acid and fluorine stable protection arises. Acetyl-protection is known to be suitable for these conditions. Treatment of **195-197** with acetic anhydride yielded the corresponding protected RCM precursors in 80-99% yield. (Table 4, entry 2,3,4).

A separation of the formed diastereomers is not possible at this stage of the synthesis and the mixture was used for the subsequent RCM reaction.

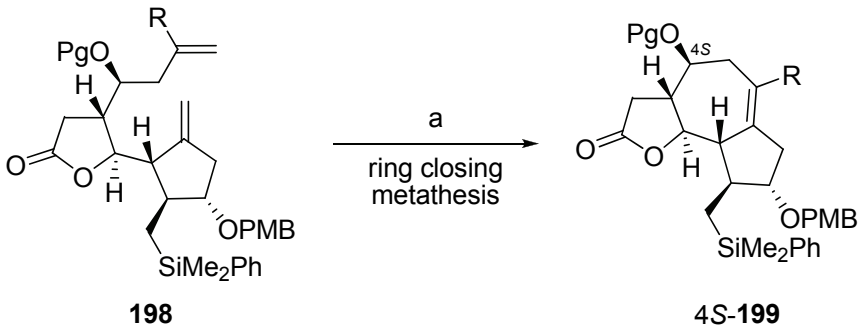
Table 4. Protection of RCM precursors.

Entry	Product	R	Pg	Reaction conditions	Yield [%] [a]	*dr* [b]
1	**198a**	CH_3	$SiEt_3$	TESCl (1.5 eq.), NEt_3 (2.0 eq.), CH_2Cl_2, rt, 48 h	68	80:20
2	**198b**	H	Ac	Ac_2O (1.5 eq.), DMAP (0.1 eq.), NEt_3 (1.5 eq.), CH_2Cl_2, rt, 24 h	80	50:50
3	**198c**	CH_3	Ac	Ac_2O (1.5 eq.), DMAP (0.1 eq.), NEt_3 (1.5 eq.), CH_2Cl_2, rt, 24 h	99	80:20
4	**198d**	Br	Ac	Ac_2O (2.0 eq.), DMAP (0.1 eq.), NEt_3 (2.0 eq.), CH_2Cl_2, rt, 16 h	86	75:25

[a] isolated yield; [b] determined by ^{1}H NMR.

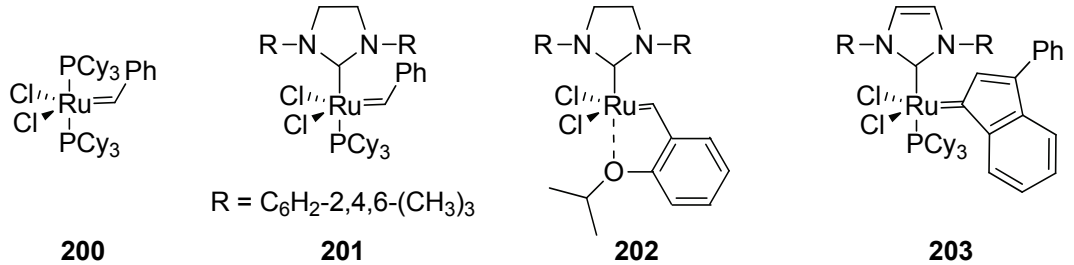
7.2.2 Ring closing metathesis

With the protected dienes in hand, the guaianolide ring system was formed in the next step (Scheme 55). The formation of a highly substituted double bond in combination with the formation of a *trans*-annulated 7-membered ring system is still a challenging task. Therefore different catalysts (Figure 14) were screened while applying the already established inert gas sparging technique to remove the evolving ethylene from the reaction mixture.[194]



198 4*S*-**199**

Scheme 55. Ring closing metathesis: a) catalyst (3x5 mol% every 2 h), abs. toluene, inert gas (Ar or N_2) sparging, 95 °C, 6 h.



200 Grubbs 1st gen 1995

201 Grubbs 2nd gen 1999

202 Hoveyda 2nd gen 2000

203 catMETium® IMesPCy degussa.

Figure 14. Ring closing metathesis catalysts.

The results of the RCM experiments are summarized in Table 5. Comparing the isolated yields, it becomes clear that Grubbs 1st gen catalyst **200** and Hoveyda-Grubbs 2nd gen catalyst **202** are not suitable for this ring closing reaction. In contrast, Grubbs 2nd gen **201** and catMETium®[195] **203** completed the guaianolide skeleton in very good yield (77-94%) while a change in the diastereomeric ratio during the reaction is not observed.

15 mol% of catalyst had to be employed to achieve good conversions, attempts to decrease the catalyst loading were not successful.

The RCM product **199c** (R = CH_3, Pg = TES, Table 5, entry 6) could not be separated from still remaining starting material **198a**. Therefore, the sily-protecting group was removed by TBAF *in situ* after the reaction to afford the free alcohol as a more polar final product, which was now separable by chromatography.

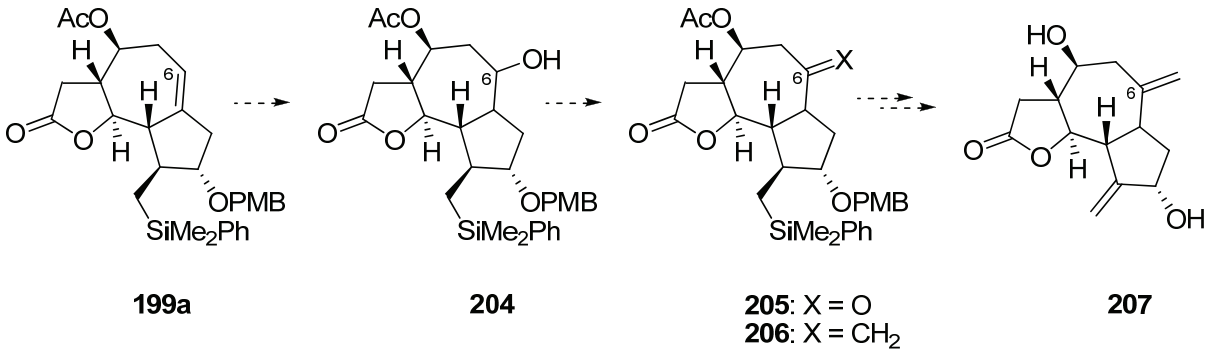
Table 5. Ring closing metathesis.

Entry	R	Pg	Product	Catalyst	Yield [a]
1	H	Ac	**199a**	Grubbs 2nd gen **201**	82% (75% 4*S*, 90% 4*R*)
2	CH_3	Ac	**199b**	Grubbs 1st gen **200**	7%[b]
3	CH_3	Ac	**199b**	Grubbs 2nd gen **201**	94% (93% 4*S*)
4	CH_3	Ac	**199b**	Hoveyda-Grubbs 2nd gen **202**	43% [c]
5	CH_3	Ac	**199b**	catMETium® **203**	78% (82% 4*S*)
6	CH_3	TES	**199c**	Grubbs 2nd gen **201**	77% [d]

[a] isolated yield, *dr* did not change during reaction; [b] 87% starting material isolated; [c] 57% starting material isolated; [d] isolated yield of free alcohol after TBAF deprotection, *dr* = 80:20.

A big advantage of the acetyl-protection is found in the fact that the RCM reaction can easily be monitored by TLC as the precursors **198b/c** and the corresponding products **199a/b** show different R_f-values. A further important feature of the acetyl protected RCM products is the possibility to separate the diastereomers, resulting from the initial Hosomi-Sakurai allylation (Scheme 53). This provides access to diastereomeric pure materials which is essential for the further synthesis.

Compound **199a**, lacking the methyl group at the C6-position could provide a direct entry towards the Cynaropicrin skeleton **207** (Scheme 56). Hydroboration of the trisubstituted double bond should introduce a hydroxy group on the less substituted C6-position in **204**, which could be further oxidized to the corresponding ketone **205**.

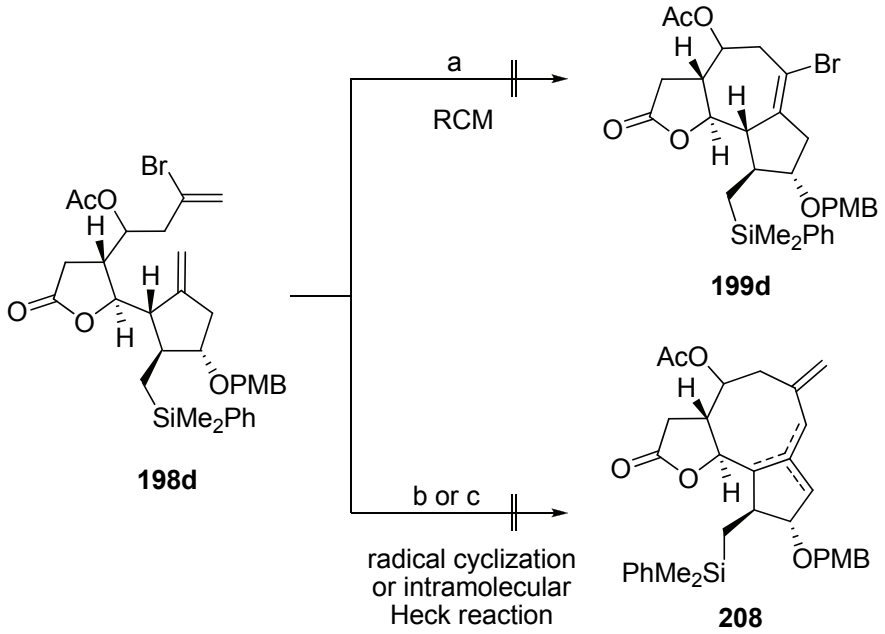


199a **204** **205**: X = O **206**: X = CH_2 **207**

Scheme 56. Proposed strategy towards the Cynaropicrin skeleton **207**.

A Wittig reaction as reported in the Vanderwalle synthesis of (±)-Compressanolide (**44**) (Scheme 9)[3,62] or in Rigby´s synthesis of (±)-Estafiatin (**4**) (Scheme 13)[69] would introduce the *exo*-methylenic double bond in **206** at the C6-position and further transformations in the cyclopentane ring could afford the Cynaropicrin skeleton **207**. This promising synthetic sequence remains to be explored.

The bromo-substituted precursor diene **198d** opens the possibility to generate the guaianolide skeleton **199d** via RCM reaction (Scheme 57, top). The incorporated vinylbromide at the 7-membered ring system would allow further transformations and functionalization (e.g. palladium coupling) at this position.



Scheme 57. Ring closing attempts on **198d**: a) Grubbs 2nd gen **201** (3x5 mol%), abs. toluene, N_2-sparging, 95 °C, 6 h; b) Bu_3SnH (1.5 eq.), AIBN, toluene, reflux, 1 h; c) $Pd(PPh_3)_4$ (20 mol%), K_2CO_3 (5.0 eq.), CH_3CN, reflux, 18 h.

In contrast to the good results obtained above (Table 5), all attempts to successfully achieve a RCM reaction on the bromo-substituted diene precursor **198d** failed, and only starting material was recovered.

Because of the vinylic-bromide present in **198d**, this compound is suitable for other ring closing strategies (Scheme 57, bottom): Unfortunately, intramolecular radical cyclization using the standard Bu_3SnH/AIBN protocol, as well as the application of standard intramolecular Heck-reaction conditions resulted only in decomposition or dehalogenation of the starting material and no ring closing to tricyclic systems like **208** was observed.

7.3 Synthesis of a 3x3 scaffold library

To explore the scope and limitations of this approach towards the skeleton of the guaianolides, a small combinatorial library around the backbone motif **209** was constructed (Figure 15). Utilizing a short five step sequence, a set of interesting scaffolds found in several classes of natural products is accessible starting from cyclopropylcarbaldehyde (-)-**130** and various allylsilanes **211**. Also hybrid structures, which combine typical structural features of guaianolides and their derivatives within the same molecule, are accessible and provide a highly diverse oriented synthesis of natural product related core structures.

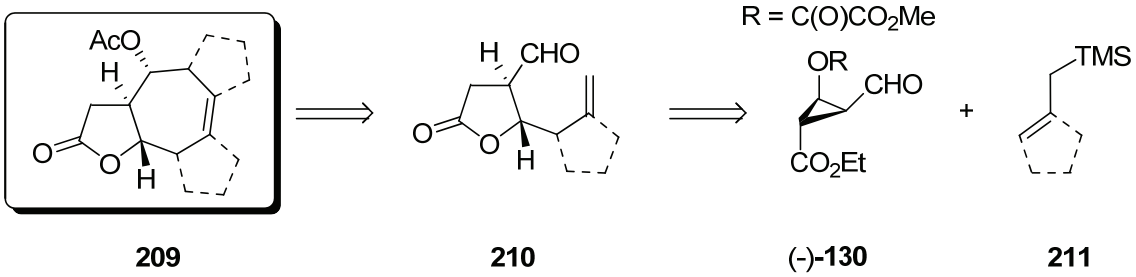


Figure 15. Design and retrosynthesis of a scaffold library.

The allylsilanes used for the allylation reactions are given in Figure 16: If not commercially available, the reactants are accessible within one or two steps.

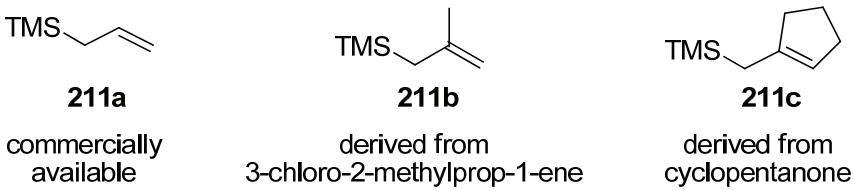
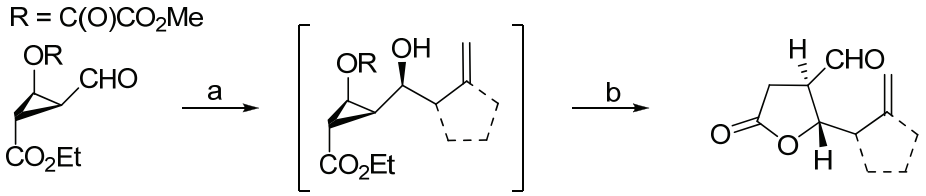


Figure 16. Allylsilanes **211** used for synthesis.

Reaction of linear and cyclic allylsilanes **211a-c** with cyclopropylcarbaldehyde (-)-**130** resulted in the allylated products **212a-c** (Scheme 58) with high diastereoselectivity. These materials proved to be sensitive to heat and traces of acid. Therefore, it was not possible to purify these compounds by chromatography or distillation, but nevertheless, after simple extraction the material was sufficiently pure for the lactonization step without further purification.

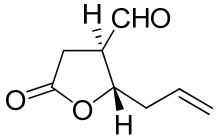
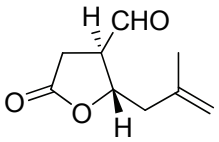
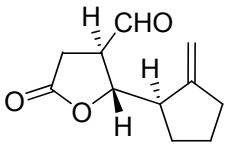


(-)-**130** **212a-c** **210a-c**

Scheme 58. Synthesis of lactone aldehydes **210**: a) allylsilane (1.1 eq.), $BF_3{\cdot}OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 18 h; b) $Ba(OH)_2{\cdot}8H_2O$ (0.55 eq.), MeOH, 0 °C, 5 h.

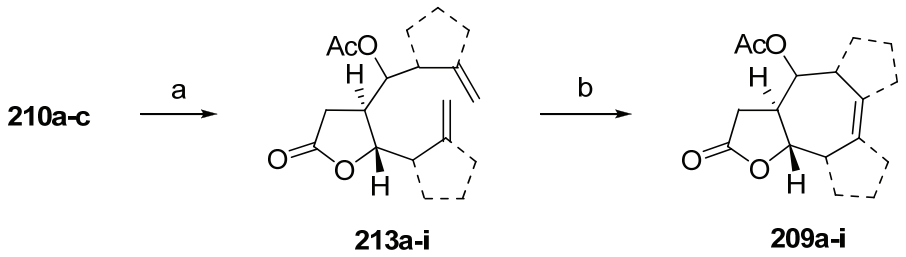
Base induced retro-aldol lactonization gave directly rise to the lactone aldehydes **210a-c** in moderate yields, but with excellent selectivity (Scheme 58, Table 6). The stereoselectivity in the nucleophilic additions to cyclopropyl substituted aldehydes and the lactone aldehydes has been discussed in detail before (see Scheme 42).

Table 6. Synthesis of lactone aldehydes.

Entry	Allylsilane	Product	Yield [%] [a]	*dr* [b]
1	**211a**	 **210a**	51	95:5
2	**211b**	 **210b**	50	96:4
3	**211c**	 **210c**	45	95:5:0:0

[a] isolated yield over 2 steps; [b] determined by ^{1}H NMR.

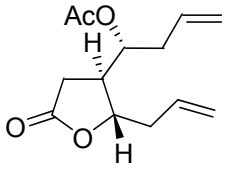
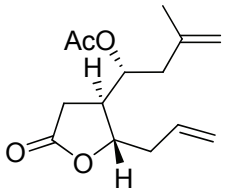
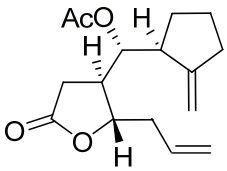
On the lactone aldehydes **210a-c** the same allylsilanes **211a-c** (Figure 16) were used in a second Hosomi-Sakurai allylation (Scheme 59). Subsequent acetyl-protection of the crude products afforded the protected precursor dienes **213a-i** for the ring closing metathesis key step (Table 7). The allylation introduces new stereocenters in the northern sidearm and a separation of the resulting diastereomers was not possible at this stage of the synthesis.



Scheme 59. Completion of the library: a) (i) allylsilane (1.50 eq.), $BF_3{\cdot}OEt_2$ (1.15 eq.), CH_2Cl_2, -78 °C, 18 h; (ii) Ac_2O (1.50 eq.), DMAP (10 mol%), NEt_3 (1.75 eq.), CH_2Cl_2, rt, 18 h; b) 3x5 mol% Grubbs 2nd gen catalyst **201**, toluene, N_2-sparging, 95 °C, 6 h.

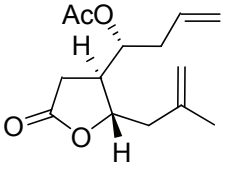
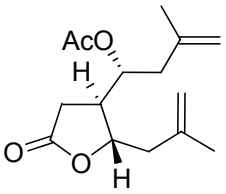
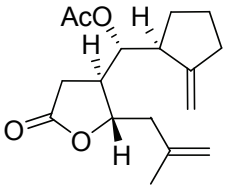
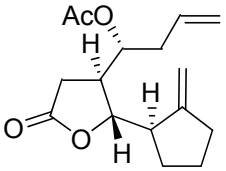
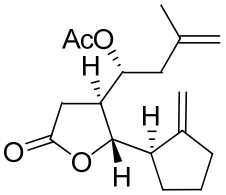
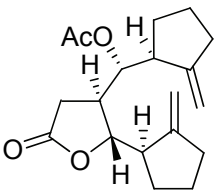
The central 7-membered ring was constructed by applying ring closing metathesis. Since Grubbs 2nd generation catalyst **201** already proved to be most efficient for this kind of transformation,[187] 3x5 mol% were used in the optimized procedure in combination with the N_2-sparging technique.[194] The results for the RCM reaction are summarized in Table 8.

Table 7. Synthesis of precursors **213a-i** for ring closing metathesis.

Entry	Aldehyde	Allylsilane	Product [a]	Yield [%] [b]	*dr* [c]
1	**210a**	**211a**	 **213a**	67	73:27
2	**210a**	**211b**	 **213b**	49	67:33
3	**210a**	**211c**	 **213c**	53	82:18:0:0

continued

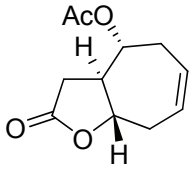
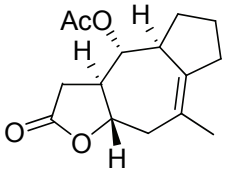
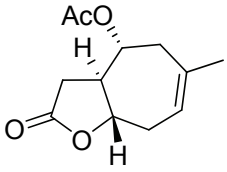
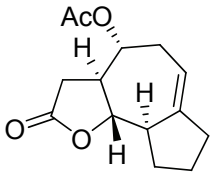
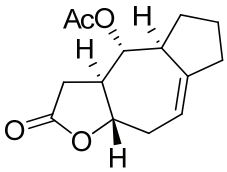
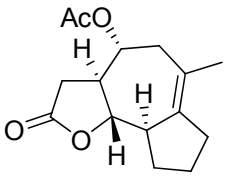
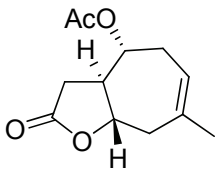
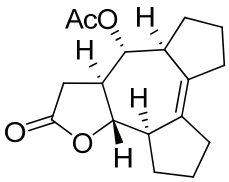
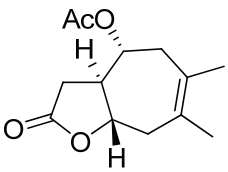
Table 7. *continued.*

Entry	Aldehyde	Allylsilane	Product [a]	Yield [%] [b]	*dr* [c]
4	**210b**	**211a**	 **213d**	73	77:23
5	**210b**	**211b**	 **213e**	57	70:30
6	**210b**	**211c**	 **213f**	59	79:21:0:0
7	**210c**	**211a**	 **213g**	57	80:20
8	**210c**	**211b**	 **213h**	47	70:30
9	**210c**	**211c**	 **213i**	53	>99:1:0:0

[a] major isomer shown; [b] isolated yield over two steps; [c] determined by ^{1}H NMR.

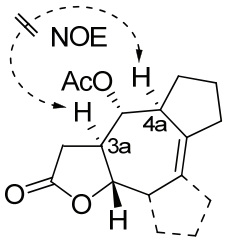
All precursors **213** cyclized to the desired RCM-products **209** except **213a**, leading to an inseparable mixture of unknown, partially polymeric products during the course of the reaction. In this case, the only disubstituted double bond would be formed within this set of compounds, resulting in a reactive alkene **209a**, which might be able to undergo further metathesis steps such as ring opening polymerization (ROMP). In all successful cases, the diastereomeric ratio before and after cyclization remained the same. Only for **213f** the major diastereomer seems to react with high preference, since only one isomer of **209f** was isolated from the reaction mixture.

Table 8. Results of ring closing metathesis.

Entry	Product [a]	Yield [%] (*dr*) [b]	Entry	Product [a]	Yield [%] (*dr*) [b]
1	 **209a**	- (-)	6	 **209f**	78 (>99:1)
2	 **209b**	96 (68:32)	7	 **209g**	87 (79:21)
3	 **209c**	76 (84:16)	8	 **209h**	96 (72:28)
4	 **209d**	93 (80:20)	9	 **209i**	48 (>99:1)
5	 **209e**	91 (75:25)			

[a] major isomer shown; [b] isolated yield, *dr* determined by ^{1}H NMR.

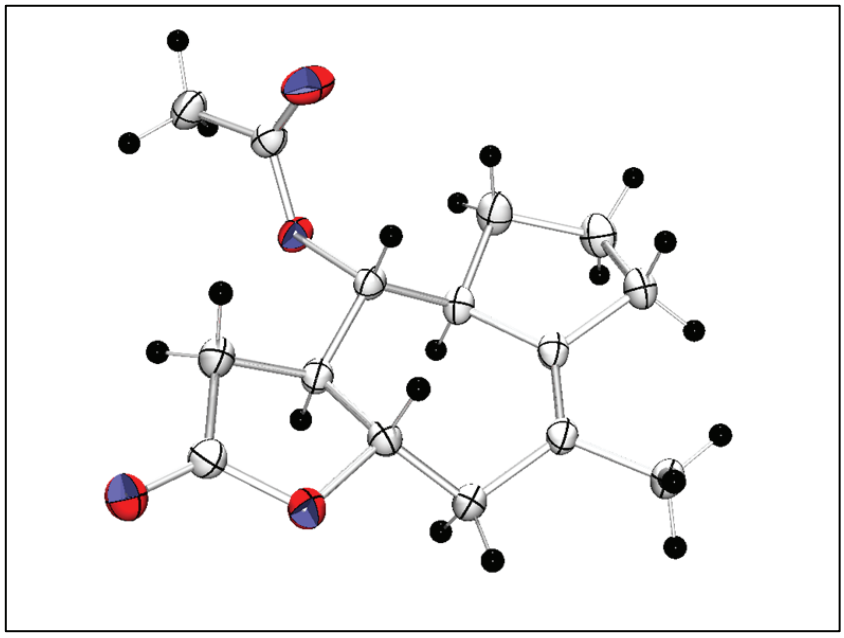
The yield of the ring closing reaction is constantly high (76-96%), with the exception of **209i**, which was isolated in a yield of only 48% probably due to steric reasons. Compound **209i** is of special interest, since it can be seen as a hybrid structure, combining the northern and the southern cyclopentane ring present in various guaianolides within one molecule (Figure 20). Investigating the stereochemistry of **209c**, **209f** and **209i** at the 4a-position at the northern cyclopentane ring proved to be difficult: The NOE experiments did not allow a clear interpretation, because the complex multiplet structures of the protons 3a (chosen as point of reference) and 4a (Figure 17) are found to be very close in their chemical shift and their NMR-signals overlap with other complex multiplets of diastereotropic protons.

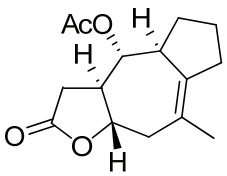


209c,f,i

Figure 17. Unsuccessful NOE experiments to determine the stereochemistry at the 4a-position.

The RCM-products **209f** and **209i** were isolated as single diastereomers (Table 8) and both crystallized from diethylether in colorless needles which were suitable for X-ray experiments.

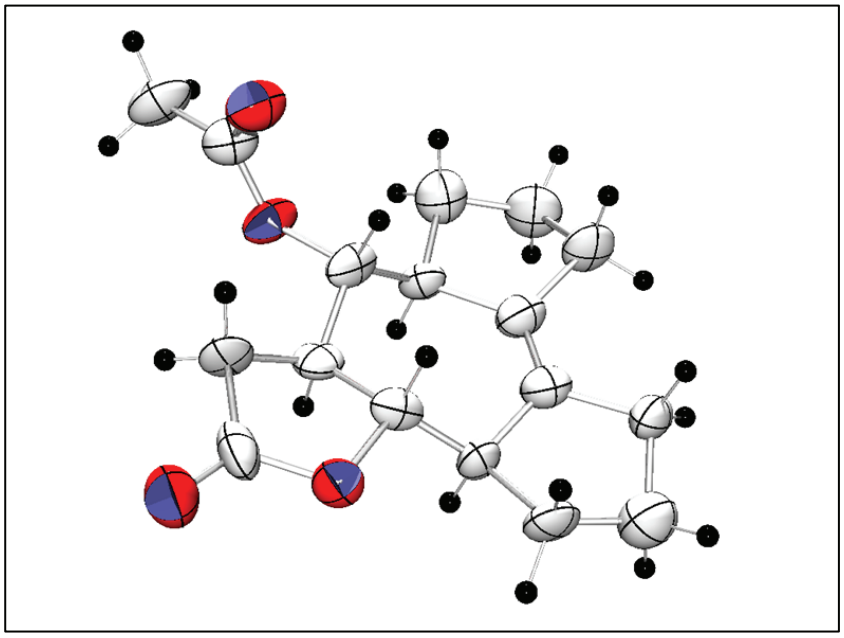


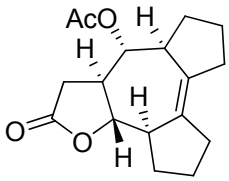


209f

Figure 18. X-ray structure of **209f**.

The X-ray structures of **209f** (Figure 18) and **209i** (Figure 19) clearly show the all *trans*-configuration of the central 7-membered ring system and prove the stereochemistry at the 4a-positions. Unfortunately, **209c** did not render crystalline, but because of the very close structural relation, it can be assumed that here the same configuration at the 4a-position is present as the major product.





209i

Figure 19. X-ray structure of **209i**.

The bicyclic structures **209b,d,e** represent very interesting derivatives of the xanthanolide backbone. Xanthatin (**214**) (Figure 20) is a very prominent member of this class of natural products and shows promising antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA)-strains.[196] The more linear 5,7,5-ring systems of **209c,f** is envisioned to be a skeleton similar to pseudo-guaianolides as for example Britanin (**215**), a compound isolated from *Inula britannica wild*[197] and *Inula caspica*.[198] The tricyclic structures **209g,h** display interesting derivatives of the guaianolide scaffold, providing the possibility for the synthesis of further natural product analogues.

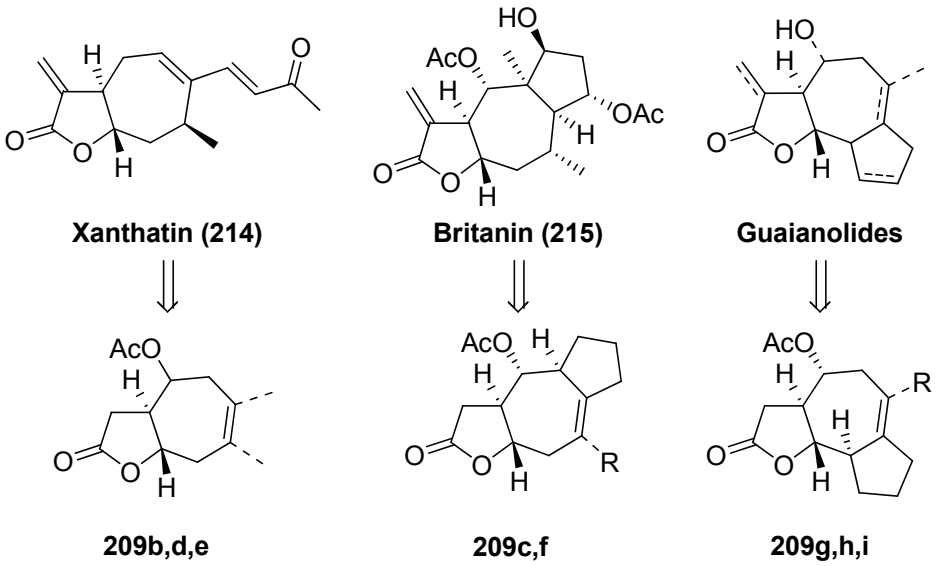


Figure 20. Biological active xanthanolides and pseudoguaianolides.

In summary, a small library consisting of eight new core structures was synthesized, including interesting structural motifs of various γ-butyrolactone containing natural products.

The allylation with commercially available or easily accessible allylsilanes introduces diversity at two points during this synthesis:

- allylation of the cyclopropylcarbaldehyde **130** results in the possibility of controlling the ring size and/or substitution pattern in the southern part of the molecules.
- allylation of the lactone aldehyde provides the chance to control also the ring size and/or substitution of the northern part.

Finally, a third point of diversity can be introduced by acylation of the hydroxy group at the C4-position: It is known, that different ester groups (e.g. derived from angelic acid, butyric acid, (*S*)-2-methylbutyric acid, senecioic acid) are present at this particular position in many natural products of the guaianolide family.[75,77]

8. Towards Cynaropicrin and Ixerin Y

The ring closing metathesis reaction finalized the synthesis of the guaianolide skeleton and afforded already highly functionalized compounds that seem to be suitable for further conversion towards the target molecules.

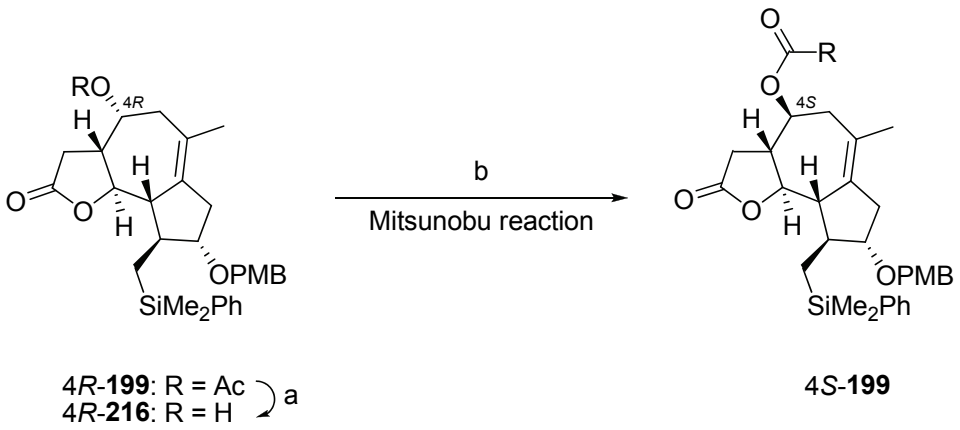
8.1 Inversion of the C4-stereocenter

Since the Hosomi-Sakurai allylation of the lactone aldehyde **175** (Scheme 53) proceeded only in moderate selectivity (80:20), it is of great interest to find a way to transform the minor diastereomer into an intermediate that is useful for the further synthesis of Cynaropicrin (**123**) or Ixerin Y (**126**). This can be achieved by an inversion of the stereocenter on the C-4 position of the minor isomer 4*R*-**199** resulting from the RCM reaction.

8.1.1 Mitsunobu reaction

A standard procedure for this inversion is the Mitsunobu reaction, providing a powerful tool for the transformation of stereogenic centers in natural product synthesis.

In a first step, the acetyl-protection in the minor isomer 4*R*-**199** was removed to release the free secondary alcohol 4*R*-**216** in 75% yield (Scheme 60). Following the standard protocol for the inversion of secondary alcohols, 4*R*-**216** was treated with excess diethylazodicarboxylate (DEAD), triphenylphosphine and various acids (Table 9).



Scheme 60. Mitsunobu reaction to invert the C4-stereocenter: a) K_2CO_3 (0.55 eq.), MeOH, 0 °C-rt, 24 h, 75%; b) R-CO_2H (4.4 eq.), DEAD (5.0 eq.), PPh_3 (5.0 eq.), THF, rt, 24 h.

Table 9. Mitsunobu reaction.

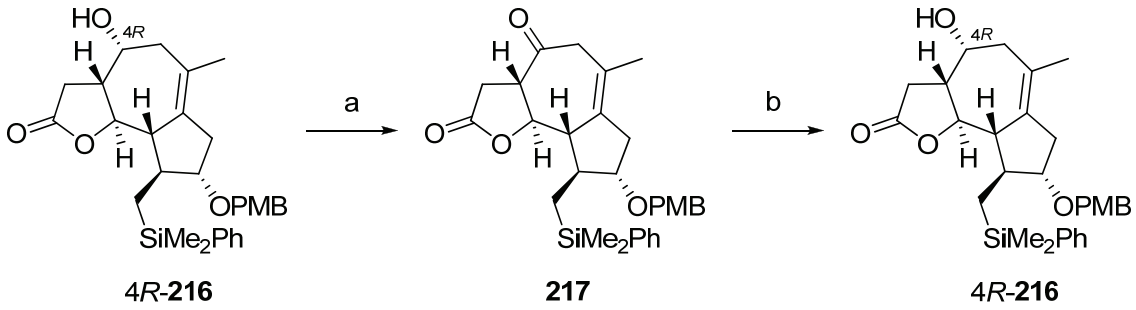
Entry	acid	pK_a	Yield [%]
1	acetic acid	4.75	- [a]
2	benzoic acid	4.20	- [a]
3	*p*-nitro-benzoic acid	3.44	- [a]

[a] no conversion.

First, acetic acid was used in the Mitsunobu reaction, since this could directly afford the major acetyl protected isomer 4*S*-**199** (R = CH_3) isolated from the RCM reaction (Scheme 55). Since this attempt failed, stronger acids were used, but here also only starting material was recovered after work-up (Table 9).

8.1.2 Oxidation/Reduction approach

Because the Mitsunobu approach failed, an attempt was made to achieve the inversion on the C4-position by an oxidation/reduction sequence (Scheme 61). The free hydroxy group in 4*R*-**216** was oxidized by PCC to the ketone **217** in 75% yield.



4*R*-**216** **217** 4*R*-**216**

Scheme 61. Oxidation/Reduction approach: a) PCC (1.5 eq.), 4 Å MS, CH_2Cl_2, rt, 5 h, 75%; b) $CeCl_3$ (1.3 eq.), $NaBH_4$ (1.3 eq.), MeOH, -5 °C, 30 min, 82%.

The subsequent Luche-reduction[199] using $NaBH_4/CeCl_3$ was predicted to be substrate controlled by an attack from the less hindered face of the molecule. Indeed, only one diastereomer was isolated in 82% yield from this reaction, unfortunately showing the same configuration at C4-position as the starting material 4*R*-**216**. Therefore, an inversion is also not possible via this route.

8.2 Investigations on epoxidations

In some guaianolides such as Arglabin (**1**) or the closely related Arborescin (**107**), an epoxide at the 7-membered ring junction at 6-6a-position is present showing α-configuration leading to a *trans*-annulation of the cyclopentane ring system (Figure 21).

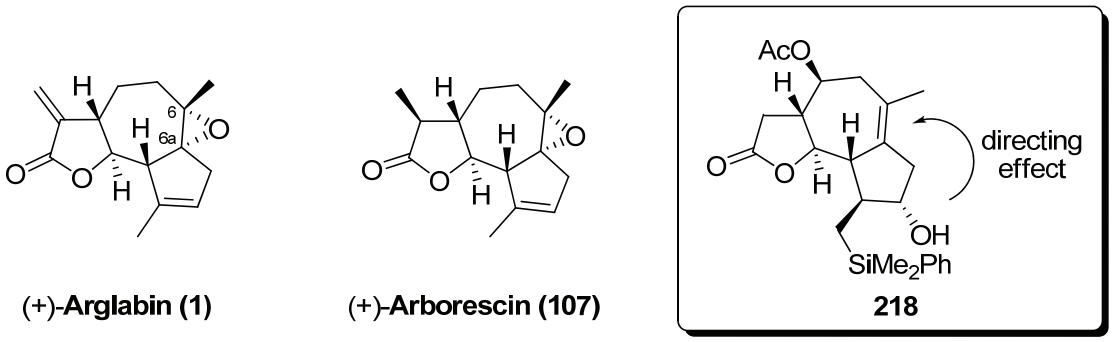
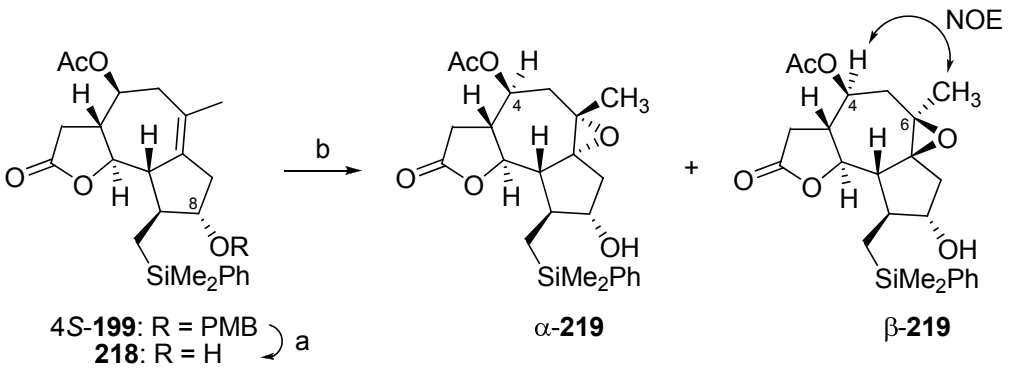


Figure 21. Epoxides in various guaianolides and proposed directing effect in **218**.

In earlier studies on similar structures, it was recognized that there is a preference for epoxidation from the undesired β-face of the molecule.[172,200] To overcome this problem, a homoallylic alcohol substituent as shown in **218** (Figure 21) is envisioned to direct the epoxidizing agent (such as *m*CPBA) to approach from the α-face.[201] Furthermore, the bulky $SiMe_2Ph$-group pointing to the top face of the molecule can presumable shield the upper half space allowing the attack only from the less hindered down face as seen in Ando´s synthesis of (+)-Arborescin (**107**), Scheme 26).

To generate the desired homoallylic alcohol moiety, the PMB protection in 4*S*-**199** was removed in 90% yield, using DDQ in order to release the free hydroxy group at the C8-position in **218** (Scheme 62).



Scheme 62. Deprotection and epoxidation: a) DDQ (1.2 eq), CH_2Cl_2/H_2O, rt, 2 h, 90%; b) *m*CPBA (1.7 eq), CH_2Cl_2, 0 °C-rt, 24 h, 96%, α-**219**:β-**219** = 20:80.

Reaction of **218** with *m*CPBA at ambient temperature afforded an inseparable mixture of α-**219** and β-**219** epoxide in a ratio of 1:4, respectively. The stereochemistry of the resulting products was determined by NOE-experiments and a clear crosspeak between the protons of the CH_3-group on the C6- and the proton on C4-position of the major isomer β-**219** is detected (Scheme 62, right). This indicates the close distance of these protons, which is only possible for the undesired β-**219**. The high preference for the *cis*-fused ringsystem is indicating that there is no directing effect based on the homoallylic alcohol system or the shielding by the $SiMe_2Ph$.

An alternative epoxidizing agent known to be suitable for acyclic homoallylic alcohols is provided with $V(O)(acac)_2$/*tert*-butylhydroperoxide systems, but remains to be tested on this substrate.[202]

8.3 Tamao-Fleming oxidation

In addition to retro-aldol lactonization and ring closing metathesis, a further essential key step in the projected syntheses of Cynaropicrin (**123**) and Ixerin Y (**126**) is the transformation of the silyl side chain into a primary alcohol. Procedures for this conversion of high synthetic value were developed in parallel by the groups of K. Tamao[203,204] and I. Fleming.[205,206]

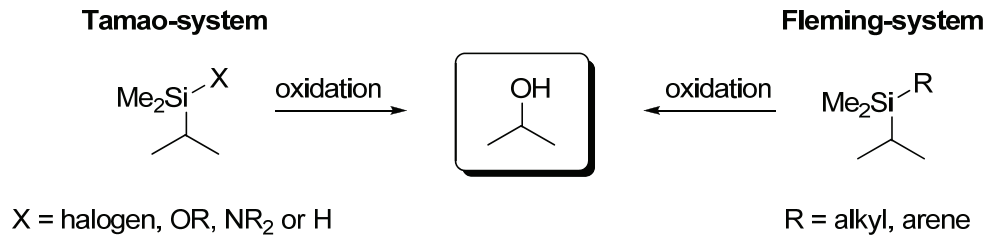


Figure 22. Comparison of the Tamao and Fleming system.

The difference in their systems is found in the substitution pattern at the silicon atom: Tamao and his co-workers used a silyl group that already carries a nucleofugal group such as a halogen, oxygen or nitrogen substituent (Figure 22, left). Considering the fact that these groups are already reactive functionalities, they are usually not suitable to be carried through many steps within the synthesis and have to be converted immediately after their introduction.[207] In contrast to this, the group of Fleming used silyl groups, fully substituted

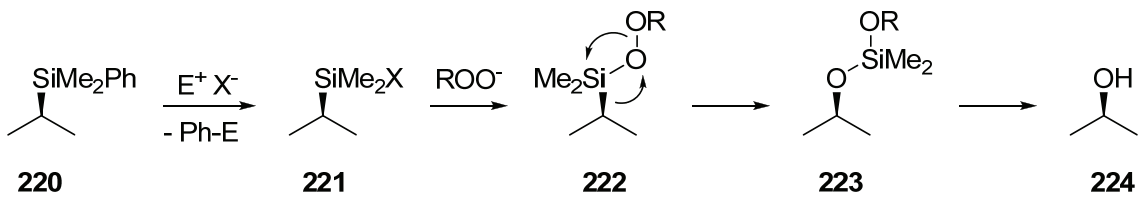
by carbon ligands, which are much more robust and can be converted into the corresponding alcohols by oxidation at any appropriate stage (Figure 22, right).[205,208]

This can turn for example the phenyldimethylsilyl group into a masked alcohol, marking the position of a future hydroxy functionality. The $PhMe_2Si$-group is sterically bulky and relatively unreactive under most conditions commonly used in organic synthesis. It possesses no lone pairs to coordinate with Lewis acids and with four tetrahedrally arranged substituents it shows a very low dipole moment without having the possibility of hydrogen bond formation.

To conclude, the Fleming system, utilizing a $PhMe_2Si$ group, behaves chemicaly opposite to a free or protected OH-group (small, electronegative, Lewis base and/or a Brønsted acid, contributes a substantial dipole moment to the polarity, forms strong H-bonds). Furthermore, its electronic influence on adjacent groups is rather electron donating than electron withdrawing.

The $PhMe_2Si$ group is easily introduced into a molecule either as an electrophile (phenyldimethylsilylchloride ($PhMe_2SiCl$)) or as a nucleophilic reagents (e.g. bis(phenyl-dimethylsilyl)cuprate ($Cu(PhMe_2Si)_2$), $PhMe_2SiCH_2MgCl$). Due to its robustness and the different ways of introduction, the phenyldimethylsilyl-group has already found several applications in synthetic work.[209-212]

The mechanism of the Fleming oxidation is illustrated in Scheme 63: In a first step the phenyl substitutent in **220** has to be exchanged by aromatic electrophilic substitution using electrophiles such as a proton, mercuric ion or bromine to form the more reactive intermediate **221**, comparable to the Tamao system (see Figure 22, left).

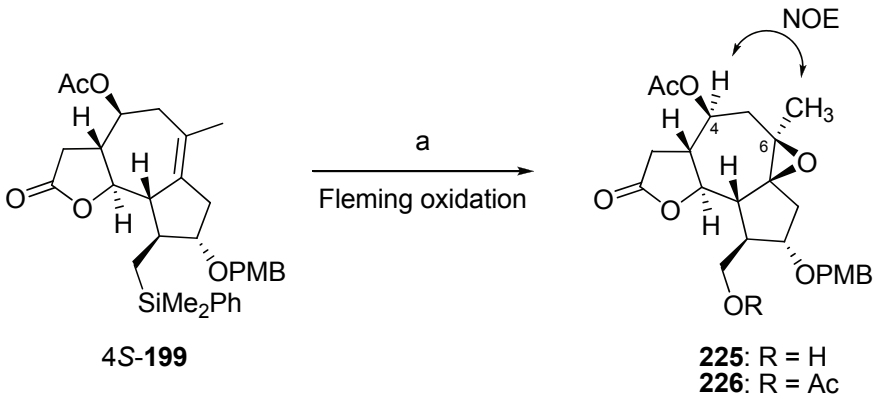


Scheme 63. Fleming oxidation of phenyldimethylsilyl group.

After displacement by peracid, the peroxocompound **222** rearranges to **223** and subsequent protic work-up releases the desired alcohol **224** with retention of configuration.

Many different protocols for the Fleming oxidation are reported in literature, but performing the whole sequence as a one-pot reaction[213] is most desirable and even procedures catalytic in mercury are reported.[205]

The first attempts to apply the standard Fleming conditions (HBF_4, *m*CPBA or KBr/peracetic acid) on substrate 4*S*-**199** failed to afford the free alcohol and only decomposition of the starting material was observed, which might be due to the strong acidic conditions needed (Scheme 64, Table 10, entry 1-2).



4*S*-**199**

225: R = H
226: R = Ac

Scheme 64. Fleming oxidation of 4*S*-**199**: a) see Table 10.

Using an acetic anhydride/H_2SO_4/H_2O_2 mixture yielded **225** in moderate yield along with some acetyl protected material **226**. This might be due to the excess of acetic anhydride used. The best results for this transformation were obtained by the application of $Hg(OAc)_2$/peracetic acid as an oxidizing system (Table 10, entry 4).

Table 10. Results of the Fleming oxidation of 4*S*-**199**.

Entry	Reaction conditions	Yield [%][a]
1	HBF_4, *m*CPBA	-
2	KBr, HO_2Ac, NaOAc, HOAc	-
3	Ac_2O, H_2SO_4, H_2O_2, HOAc, $Hg(OAc)_2$ (1.6 eq.)	46[b]
4	HO_2Ac, $Hg(OAc)_2$ (1.25 eq.)	70
5	HO_2Ac, $Hg(OAc)_2$ (0.3 eq.), $Pd(OAc)_2$ (0.1 eq.)	-[c]

[a] isolated yield, [b] additionaly acetyl-protected product **226** isolated in 10% yield, [c] product **225** was formed initially, but decomposed over time.

The use of stoichiometric mercury is necessary, since the protodemercuration of arylmercuric salts, which is important for the regeneration of the mercury ions, is slower than the protodesilylation of arylsilanes.[214] Furthermore, arylmercuric salts are known to be unreactive towards oxidizing agents and can therefore not be recovered by oxidation.[215]

An environmental and economical goal is to find suitable conditions to render this process catalytic in mercury: $Pd(OAc)_2$ is known to help to recover $Hg(OAc)_2$ from the corresponding arylmercury compounds[216] and the resulting arylpalladium species are readily oxidized by peracids.[217] For this reason, *Fleming et al.* developed a catalytic one-pot procedure,[205] and the proposed catalytic cycle is illustrated in Figure 23.

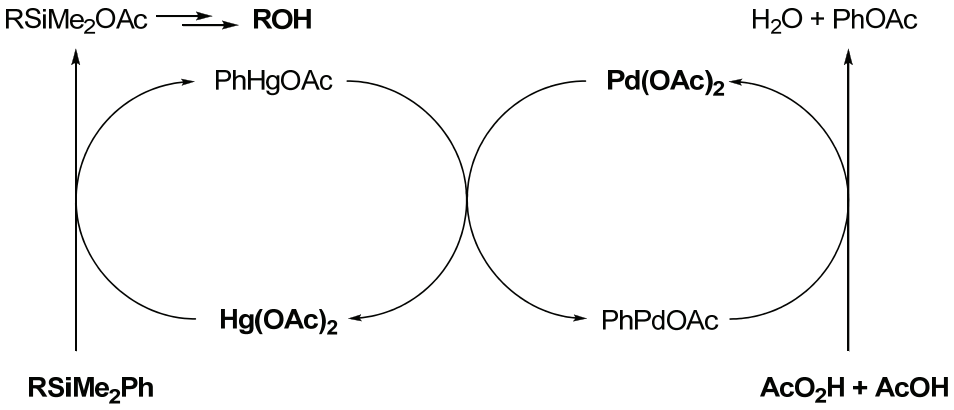
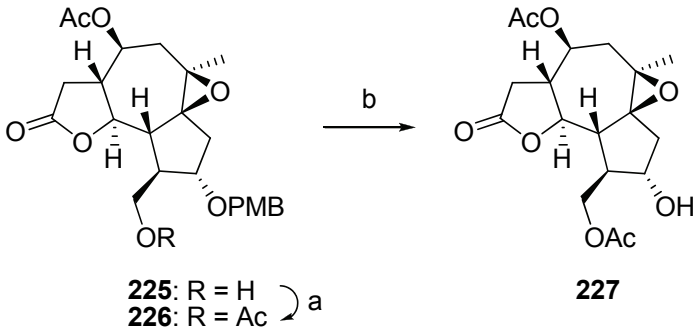


Figure 23. Catalytic cycle for mercurydesilylation.

Mercurydesilylation of $RSiMe_2Ph$ substitutes the phenyl ring at the silicon by acetate, which is then oxidized and rearranged to the desired free alcohol. Within this process $Hg(OAc)_2$ is transformed into the corresponding arylmercury compound PhHgOAc, from which the phenyl ring is then transmetalated into the palladium acetate. This recovers the $Hg(OAc)_2$, which enters the catalytic cycle again. Subsequent oxidation to $Pd(OAc)_2$ by peracetic acid releases PhOAc and finishes the catalytic cycle.

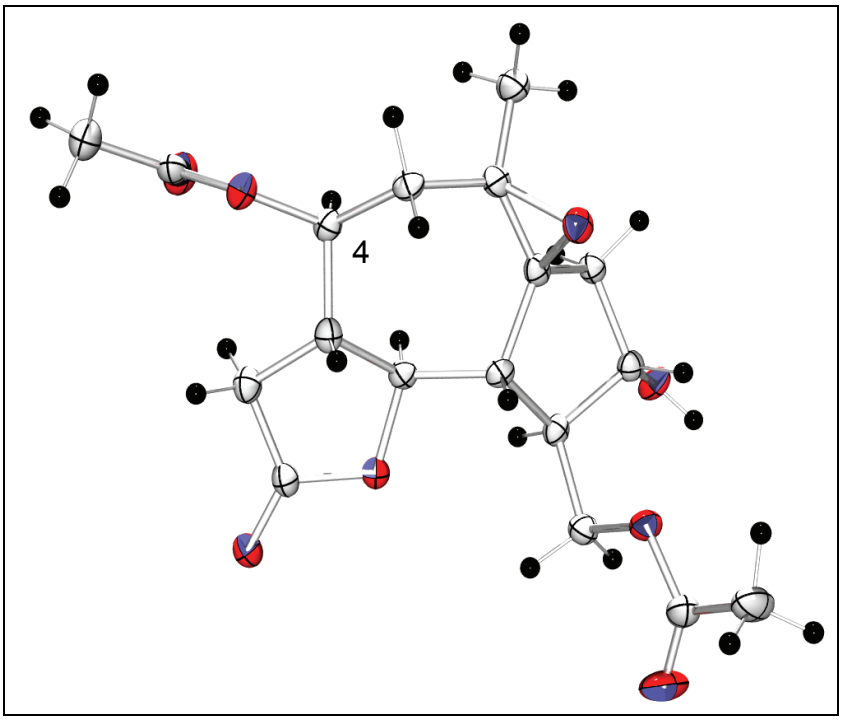
These reaction conditions catalytic in mercury and palladium were applied onto 4*S*-**199** and resulted in an initial formation of the desired product **225** as determined by TLC on comparison with an authentic sample of **225**. After complete consumption of the starting material, the product started to decompose and no material could be isolated from this reaction (Table 10, entry 5).

As mentioned before (Scheme 62) the double bond present in **199** can be epoxidized, and during the Fleming oxidation also an epoxidation at the 6-6a-positions is observed. The stereochemistry of the resulting epoxide was determined by NOE-experiments and a clear cross signal for the CH_3 group on C6- and the proton at C4-position was detected, which is only possible if both are located on the same side of the molecule (Scheme 64).



Scheme 65. Protecting group transformation: a) Ac_2O (2.0 eq.), NEt_3 (2.0 eq.), DMAP (10 mol%), CH_2Cl_2, rt, 16 h, 99%; b) DDQ (1.5 eq.), CH_2Cl_2/H_2O, rt, 5 h, 90%.

The proof for all stereocenters present was obtained with the X-ray structure of **227** (Figure 24), which was accessible by acetyl-protection of the free primary alcohol **225** and subsequent PMB deprotection following the standard DDQ protocol to afford the free secondary alcohol **227** in 90% yield (Scheme 65).



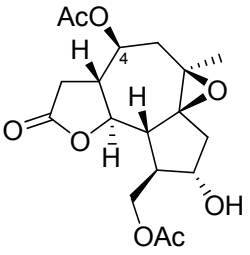


Figure 24. X-ray structure of **227**.

The crystal structure of **227** reveals the all-*trans*-configuration along the hydroazulene core skeleton as found in the final natural products. The acetoxy-substituent on C-4 is oriented to the same side as the proton on the 3a-position. Also the stereochemistry of the epoxide on the 6-6a-position is shown to be β-oriented, resulting in a *cis*-fused cyclopentane ring system.

The additional epoxidation reaction observed during the Fleming oxidation does not have to be seen as a disadvantage, although no such functionality is found at this position in Cynaropicrin (**123**) and Ixerin Y (**126**): This epoxide might act as a protecting group for the double bond during the elimination reactions investigated later on (Figure 26).

8.4 Oxidation at the C8-position

A common feature often found in various guaianolides is a keto-functionality at the C8-position in the molecule as for example seen in the structures of the Chinensiolides A-C **228**-**230** (Figure 25). These compounds were isolated from *Ixeris chinensis* Nakai (Compositae),[218-220] also known as Siyekucai, a plant which is used in Chinese folk medicine for the treatment of bronchitis, pneumonia, pharyngitis, dysentery and poisonous indigestions.

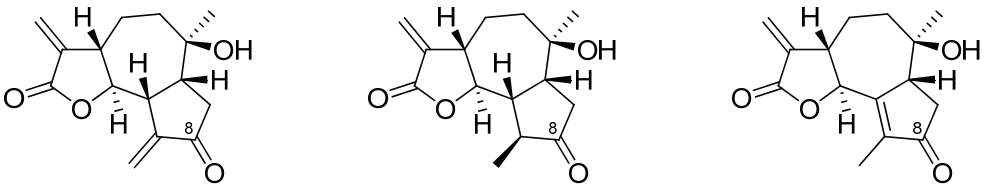
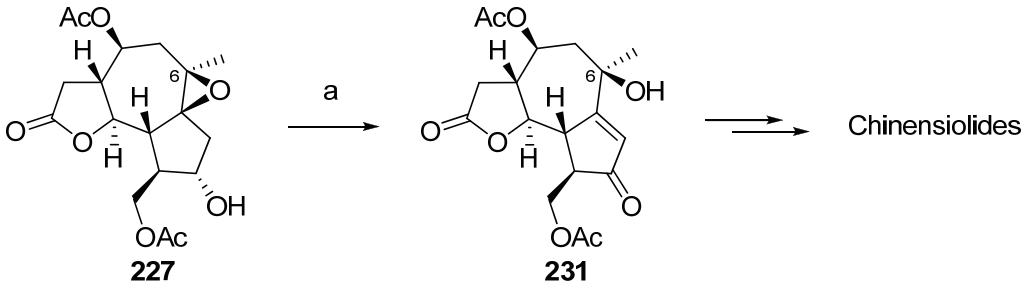


Figure 25. Guaianolides isolated from siyekucai (*Ixeris chinensis*).

A possible way to introduce this keto-functionality at this position is the oxidation of the secondary alcohol present in **227**. The application of the standard PCC protocol oxidized the hydroxy group to the desired keto-functionality in **231** (Scheme 66).



Scheme 66. Oxidation of the secondary alcohol: a) PCC (1.3 eq.), 4 Å MS, CH_2Cl_2, 5 h, rt, 80%.

This reaction is accompanied by the opening of the epoxide, generating the tertiary allyl alcohol **231** in 80% yield. The stereochemistry at the C6-position is defined by the starting

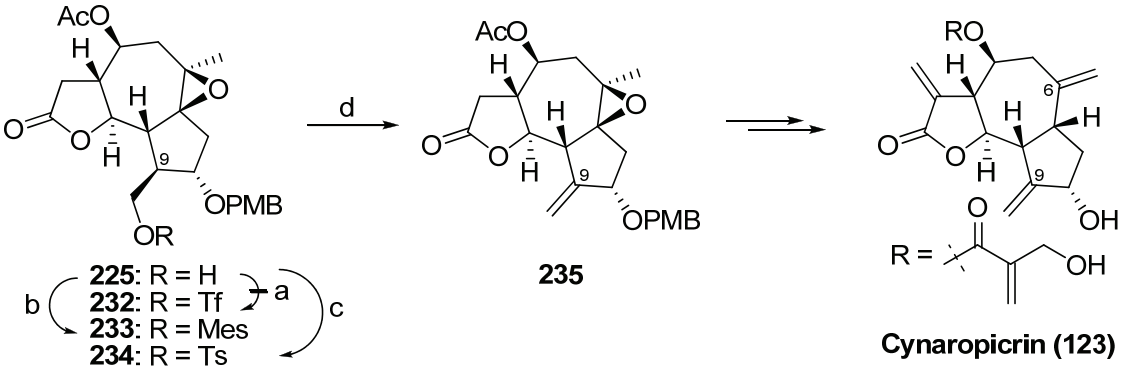
epoxide and is in the same configuration as found in the natural products **228**-**230**. The resulting material is only barely soluble in most organic solvents, except acetonitrile.
Hydrogenation of the now introduced double bond in **231** and elimination within the still acetyl-protected side chain can set the stage for the synthesis of interesting members of the chinensiolide family. Since nearly all stereocenters are already set in **231** with respect to the natural products, functional group transformation in the cyclopentane ring and subsequent α-methylenation could lead to the final natural products.

8.5 Elimination reactions

The next essential step towards the target molecules Cynaropicrin (**123**) and Ixerin Y (**126**) is the introduction of a double bond at the cyclopentane ring. With the various hydroxy functionalities set in place regioselective elimination should introduce the desired C=C-double bonds at the appropriate positions.

8.5.1 Elimination reactions towards Cynaropicrin

An *exo*-methylene double bond is found in the Cynaropicrin core skeleton **123** at the C9-position. To introduce this functionality the primary hydroxy group in the side chain of **225** was transformed into a suitable leaving group (Scheme 67).



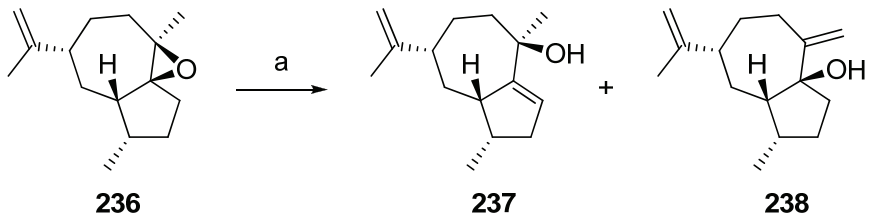
Scheme 67. Elimination towards Cynaropicrin: a) Tf_2O (1.2 eq.), pyridine (4.0 eq.), CH_2Cl_2, 0 °C, 24 h; b) MesCl (3.0 eq.), NEt_3 (4.0 eq.), CH_2Cl_2, 0 °C, 2 h, 92%; c) TsCl (4.0 eq.), pyridine (8.0 eq.), CH_2Cl_2, rt, 24 h, 66%; d) NaI (2.0 eq.), DBU (4.0 eq.), 35-100 °C, 5 h, 55%.

Attempts to achieve elimination by using the Tf_2O/pyridine system to generate the triflate **232** failed and resulted in complete decomposition. To investigate milder reaction conditions, the mesylate **233** was formed successfully in a yield of 92%.

In contrast to this, tosylation resulted only in a moderate yield (66%) of **234**, which might be due to steric reasons. The application of standard elimination conditions (NaI, DBU) on both compounds **233** and **234**, respectively, transformed only the tosylated precursor into the corresponding *exo*-methylenic compound **235**.

The chemical shifts (^{1}H and ^{13}C NMR) of the so introduced C=C-double bond were compared with these of a sample of originally isolated Cynaropicrin (**123**)[221] and matched the reported values exactly.

What remains to be tested is the selective epoxide opening in **235** to introduce the second *exo*-methylenic group at the C6-position, which is needed for the final natural product **123**.



236 **237** **238**

Scheme 68. Epoxide opening on substrates similar to **235**: a) Lithium dicyclohexylamide, cyclohexylmagnesium bromide, DME, **237**: 23%, **238**: 74%.

There are quite a number of methods reported in literature to selectively perform this transformation on very similar substrates with high regioselectivity. An example for the regioselective opening of epoxide **236** is given in Scheme 68, where a high preference for the desired structure **238** is found.[222,223]

Final desoxygenation following the Barton-McCombie protocol, which is also known to be suitable for tertiary alcohols,[224-229] would remove the hydroxy group. Due to ring strain the desired thermodynamically more stable *cis*-fused cyclopentane ring system as found in **123** should form. This assumption is also confirmed by the results obtained for the radical cyclizations (Scheme 52) where also a high preference for the *cis*-annulation is observed.

8.5.2 Elimination reactions towards Ixerin Y

The elimination towards Cynaropicrin (**123**) can only result in one regioisomer (elimination of a primary alcohol, Scheme 67). In contrast to this is the elimination of a secondary alcohol **239** towards Ixerin Y (**126**) accompanied by two problems (see Figure 26):

i) unfavoured *syn*-elimination due to the *trans*-substitution pattern in the cyclopentane ring affording the Ixerin Y (**126**) scaffold.

ii) preference for a formation of a conjugated system with already present C=C-double bond towards **240**.

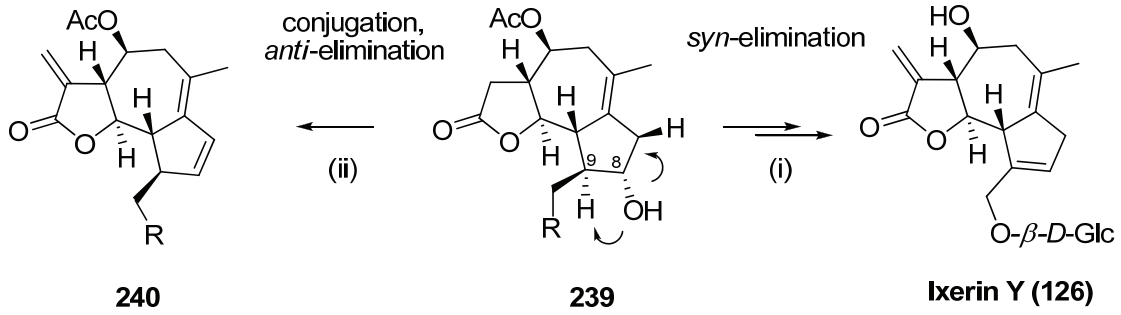
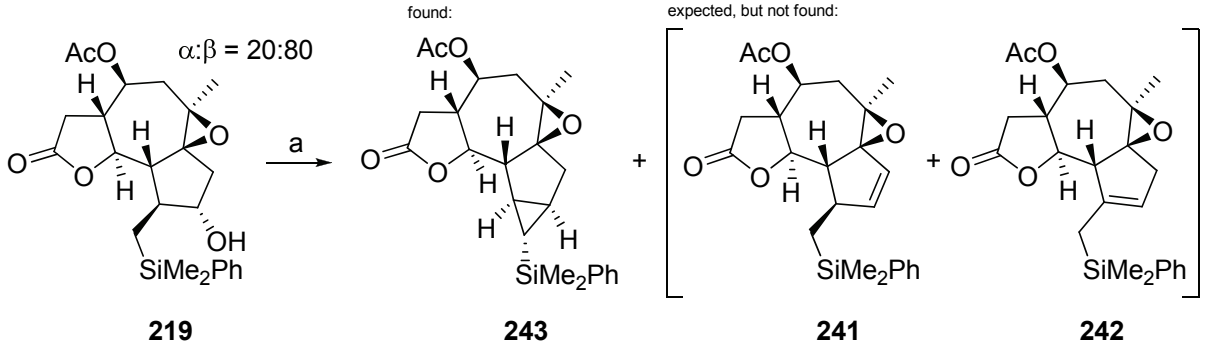


Figure 26. Problems within the elimination towards Ixerin Y (**126**).

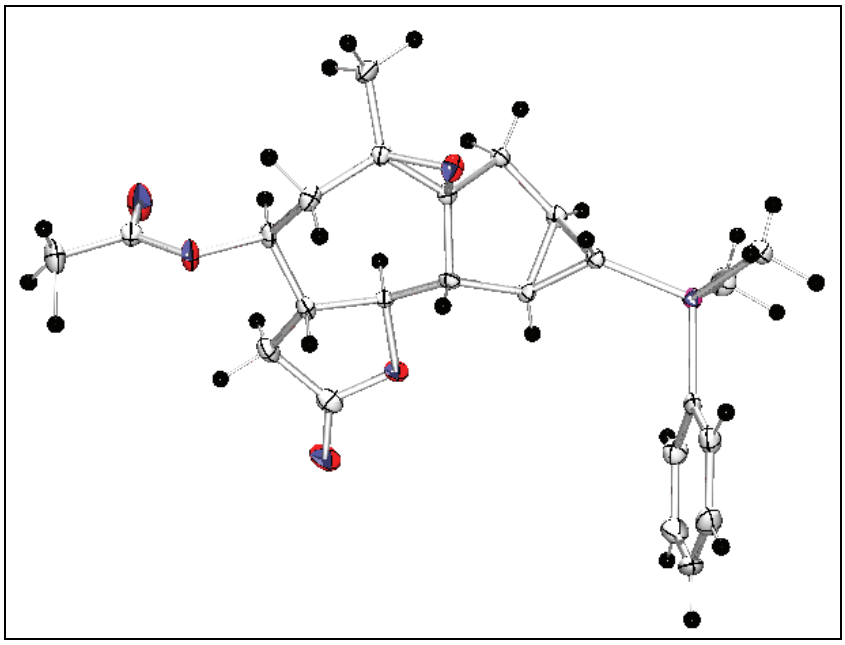
As mentioned before (Scheme 64), the problem of forming a conjugated system with the C=C-double bond at the 6-6a-position disappears when this functionality is "protected" as an epoxide.

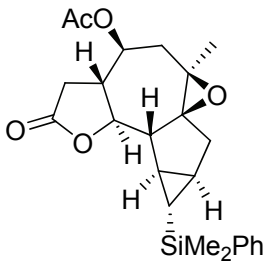
The first attempt to introduce the desired double bond in the cyclopentane ring was made on a 20:80 mixture of α-/β-**219** (Scheme 69). The Tf_2O/pyridine system, known to undergo *cis*-elimination, has proven to be suitable for this transformation on similar substrates and should afford preferentially **242** rather than **241**.[172]



Scheme 69. Elimination on **219** (α:β = 20:80): a) Tf_2O (2.0 eq), pyridine (6.0 eq), CH_2Cl_2, 0 °C-rt, 24 h, 13%.

Treating **219** with Tf_2O and pyridine at 0 °C afforded a mixture of various products. The cyclopropanated product **243** was isolated as the only characterizable compound and was set for crystallization. This afforded a single crystal that was suitable for X-ray crystallography (Figure 27).



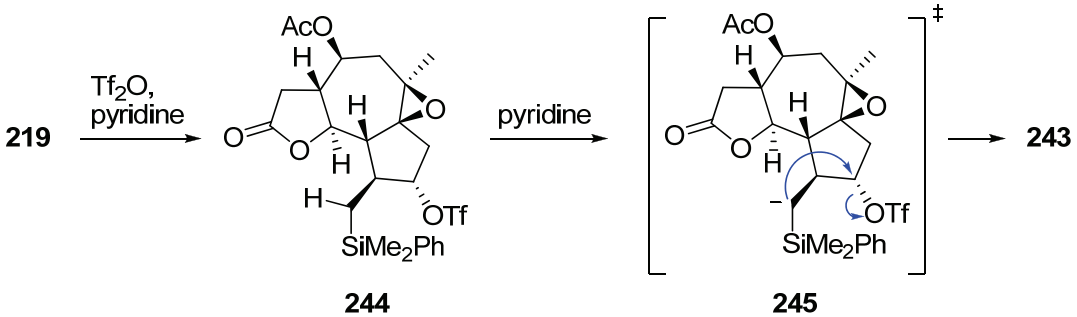


243

Figure 27. X-ray structure of **243**.

As seen in the X-ray structure of **243** (Figure 27) no elimination has taken place, but instead a 1´-silyl-cyclopropane ring has formed pointing to the β-face of the molecule. Furthermore, the structure shows the bulky phenyldimethylsilyl-group being positioned on the sterically more favored *exo*-position which is oriented away from the rest of the molecule.

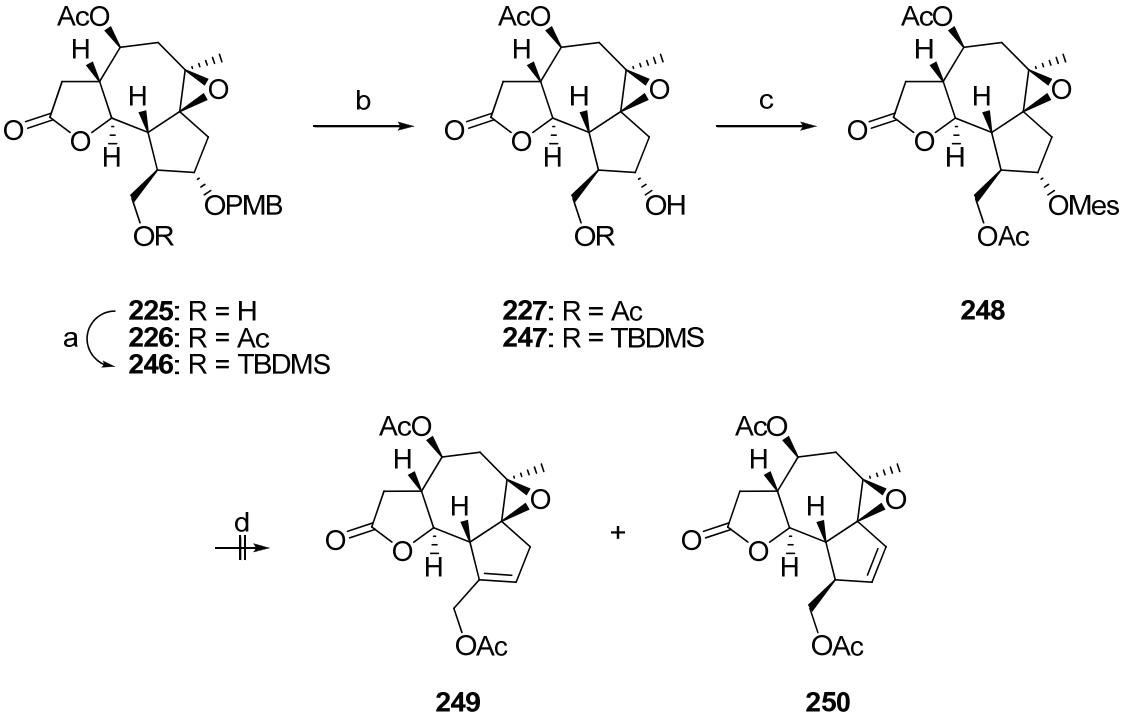
Similar reactions are reported by *Schaumann et al.*, who used appropriate tosylates and strong bases for the formation of 1-silyl-substituted cyclopropanes.[230] A possible mechanism for this reaction is proposed in Scheme 70:



Scheme 70. Proposed mechanism for the formation of **243**.

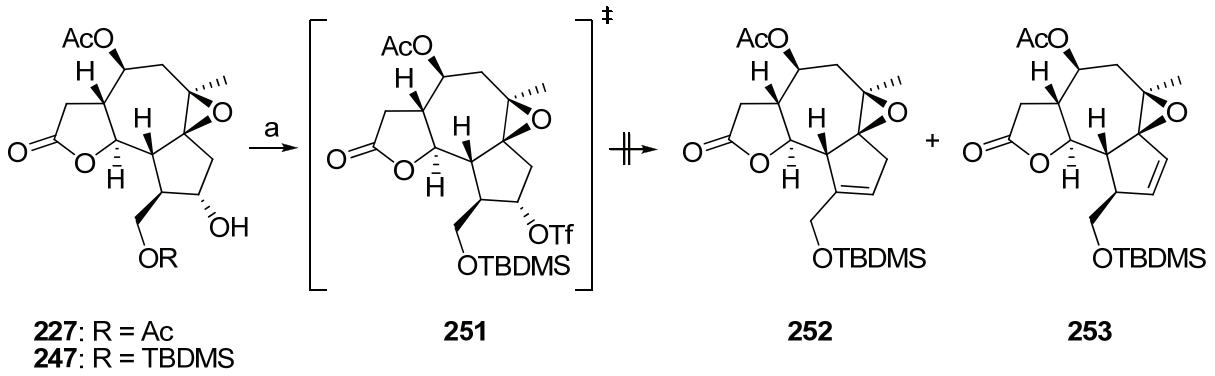
The secondary alcohol **219** reacts with Tf_2O to form the corresponding triflate **244**. Excess of pyridine deprotonates in α-position to the silicon atom (α-effect of Si) and an attack of the corresponding anion **245** from the top face substitutes the triflate to generate **243**.

A further attempt on the elimination reactions towards Ixerin Y (**126**) was made on substrates, where the phenyldimethylsilyl-group was converted to the corresponding alcohol.
The primary alcohol in the sidechain of **225** was acetyl- or TBDMS-protected and the PMB protection was removed by DDQ to afford the free secondary alcohols **227** and **247** in good overall yield (Scheme 71).



Scheme 71. Protecting group transformations: a) TBDMSCl (3.0 eq), NEt_3 (3.5 eq.), DMAP (10 mol%), CH_2Cl_2 rt, 24 h, 80%; b) R = Ac: DDQ (1.5 eq.), CH_2Cl_2/H_2O, rt, 5 h, 90%; R = TBDMS: DDQ (1.25 eq.), CH_2Cl_2/pH7 buffer, rt, 3 h, 88%; c) MesCl (3.0 eq.), NEt_3 (4.0 eq.), CH_2Cl_2, 0 °C, 1 h, 94%; d) NaI (2.0 eq.), DBU (4.0 eq.), 100 °C, 5 h.

On the acetyl protected **227** the free hydroxy group was transformed into the corresponding mesylate **248** to generate a good leaving group, but the application of elimination conditions (NaI/DBU) did not lead to the eliminated products **249** or **250**.
Changing the strategy, **227** and **247** were subjected to the Tf_2O/pyridine elimination protocol, but for the acetyl protected precursor **227** only decomposition was observed (Scheme 72).

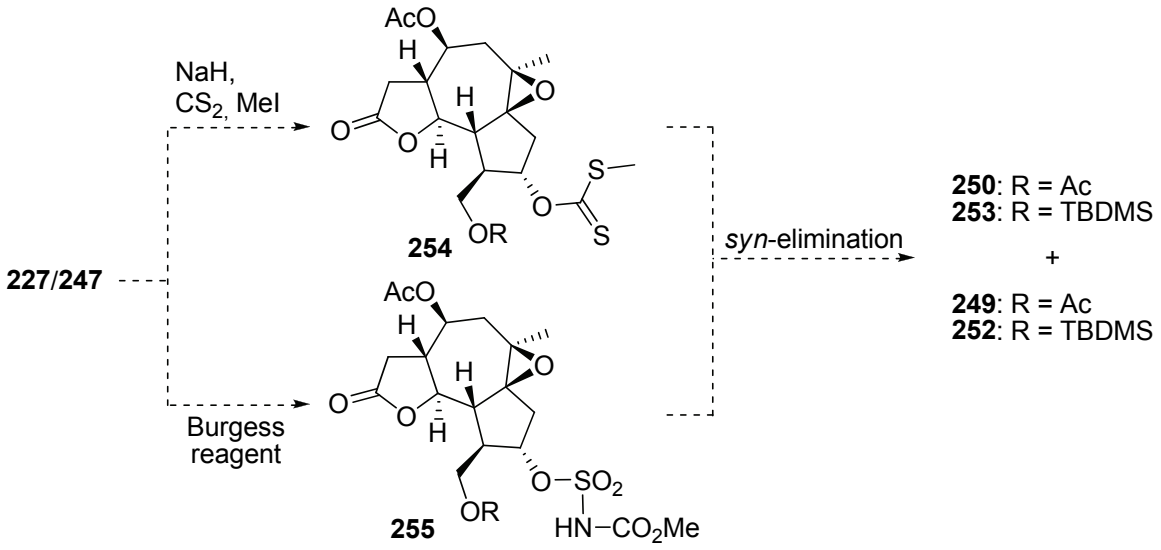


Scheme 72. Elimination towards Ixerin Y (**126**): a) Tf_2O (2.0 eq.), pyridine (5.0 eq.), CH_2Cl_2, -10 °C-rt, 16 h.

The same elimination conditions applied on the TBDMS protected precursor **247** afforded a highly unstable material (presumably the corresponding triflate **251**), which decomposed upon concentration during isolation, but did not release the products **252** or **253**, respectively, even on elevated temperatures.

Although similar elimination reactions on related structures proofed successful, an analogues transformation on the substrates described here was not achieved.

Alternatives to perform this *syn*-elimination is seen in the application of the Chugaev-conditions,[231,232] were the free hydroxy group in **227** or **247** is transformed into the corresponding xanthogenates **254** (Scheme 73, top), to undergo subsequent elimination. Also Burgess reagent[233] (see Estafiatin (**4**) synthesis by Vandewalle (Scheme 10)) should transform **227**/**247** under mild conditions into **255** (Scheme 73, bottom). Selective *syn*-elimination should than also lead to the desired products. These reactions remain to be tested on these substrates.



Scheme 73. Chugaev-reaction and application of Burgess-reagent.

9. Stereoselective Synthesis of small molecule HAT Inhibitors

The complex of DNA and certain proteins is called chromatin and is basically organized in three levels: DNA wrapping around nucleosomes ("beads on a string structure"), 30 nm condensed chromatin fiber (consisting of nucleosome array in their most compact form) and higher level DNA packing into the metaphase chromosome (Figure 28).

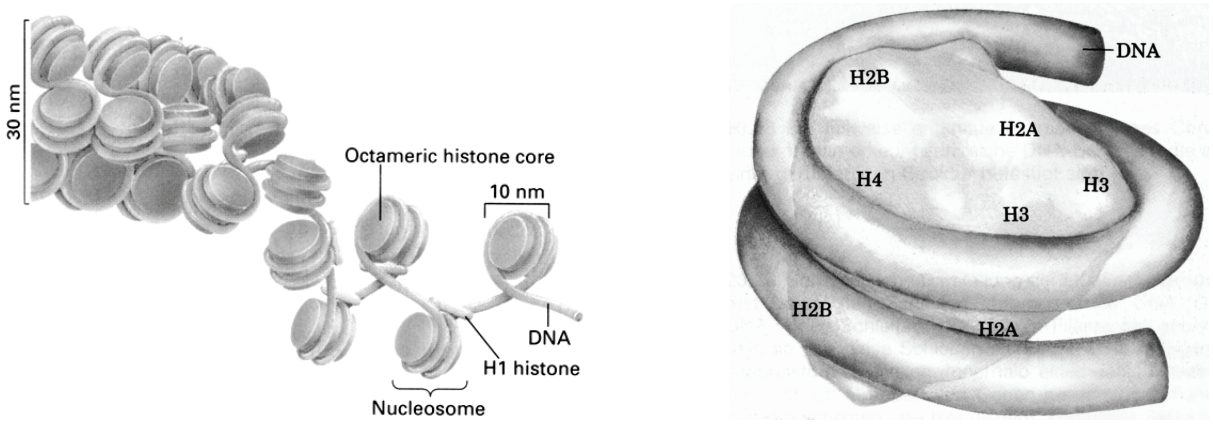


Figure 28. DNA packing and nucleosome structure.

Although other chromosomal proteins have important roles too, the fundamental building blocks of eukaryotic chromatin are the histone proteins and the nucleosomes they form with DNA. The core of the nucleosomes consists of highly conserved histone proteins (two copies of H2A, H2B, H3 and H4) forming a disc shaped molecule. The H1 protein is bound to the outside, closing the complex and interacting with other nucleosomes.

The basic histone-proteins consist of a DNA-interacting globular region and approximately 20-40 more flexible termini, which extend from the globular domains. The N-termini show positively charged lysine groups, important for interaction with charged phosphates in DNA or neighboring nucleosomes. Furthermore, the chromatin is subject to a vast array of posttranslational modifications, where especially the lysine-residues are known to undergo reversible acetylation, thereby regulating access to the underlying DNA. These modifications contribute to the so called "Histone-Code"-hypothesis, referring to the assumption that the modification of the histone tails creates a substitution pattern, which is recognizable for certain regulatory proteins.[234] These can create a connection between histone modification and cellular processes like activation or repression of transcription.[234-237]

A control of histon-acetyltransferases (HATs) and histon-deacetylases (HDACs) is thus of great importance for investigations of the „Histon-Code“ but offers also interesting novel targets for pharmaceutical industry.[238-241]

In their ongoing investigations on histon-modifying enzymes *Giannis et al.*[242] reported the design, synthesis and biological evaluation of a selective small-molecule inhibitor (±)-**256** for the histone acetyltransferase Gcn5.
Based on the assumption that acetyl-CoA has to bind to Gcn5 first to make the binding pocket accessible, a ternary complex consisting of HAT-enzyme, acetyl-CoA and the histone protein is formed (Figure 29, A).[243-245]

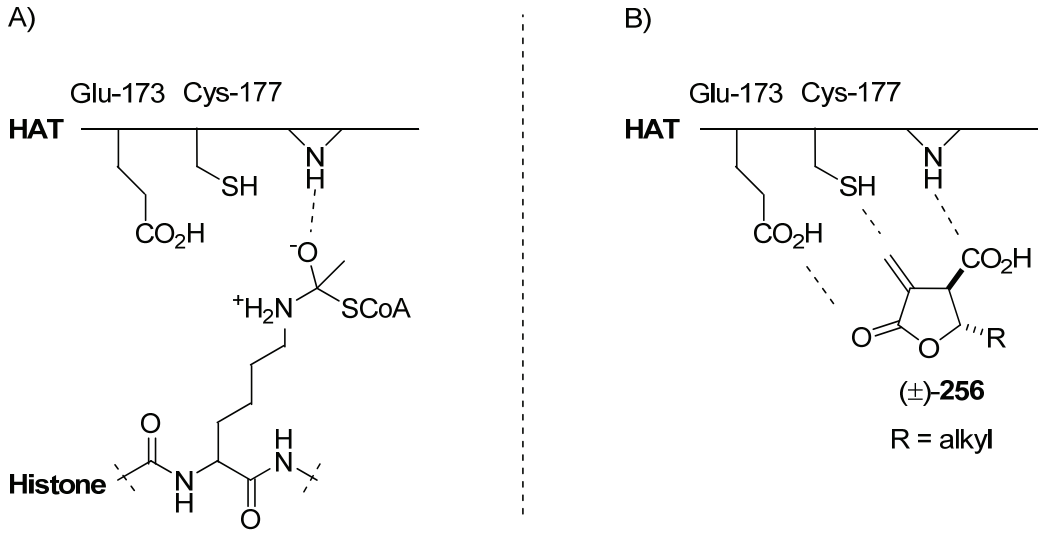
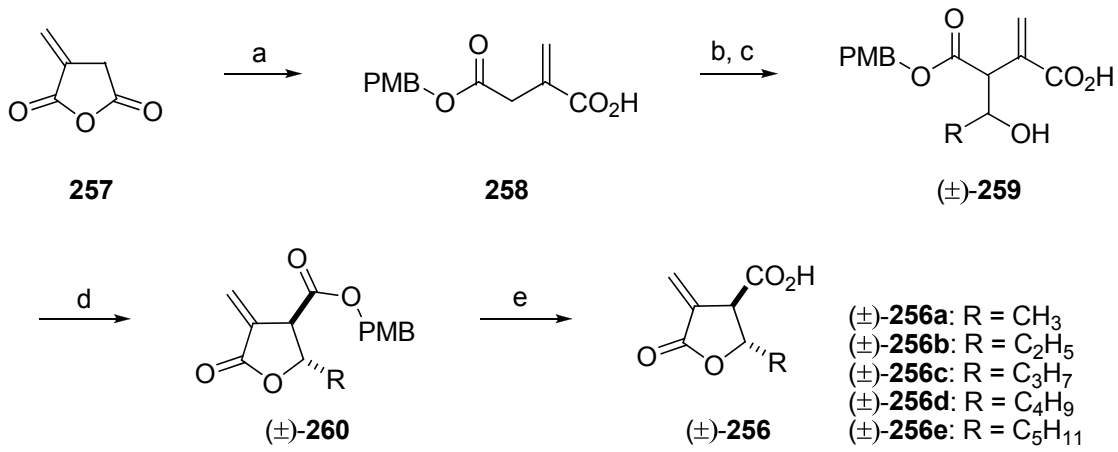


Figure 29. Comparison of binding of natural substrate and small-molecule inhibitor (±)-**256**.[242]

The highly conserved glutamic acid Glu-173 is assumed to activate the lysine side chain of the approaching histone protein and facilitates the attack of the neighboring thioester of acetyl-CoA (Figure 29, A). A hydrogen bond to the backbone amide of Cys-177 stabilizes the corresponding intermediate and decomposition releases Glu-173, acetylated histone and CoASH.

Based on this mechanism, Giannis and co-worker envisioned the γ-butyrolactone (±)-**256** as a promising HAT inhibitor (Figure 29, B). Their short, but racemic synthesis towards (±)-**256** started from itaconic anhydride **257** (Scheme 74).[242]



Scheme 74. Racemic synthesis of γ-butyrolactones (±)-**256** by Giannis and co-workers: a) *p*-methoxybenzyl-alcohol, hexane, toluene, 60 °C, 36 h, 88%; b) LiHMDS, THF, -78 °C, 1 h; c) RCHO, THF, -78 °C, 12 h; d) $CHCl_3$, EtOH, rt, 72 h 42-47% over 3 steps; e) phenol, HOAc, 60 °C, 3 h, 90-96%.[242]

Regioselective ring opening of **257** at the non-conjugated side by *p*-methoxybenzylalcohol gave rise to PMB protected **258**. Subsequent aldol reaction with various aliphatic aldehydes afforded racemic (±)-**259**, which closed the *trans*-substituted γ-butyrolactone ring to form (±)-**260**. PMB deprotection with acetic acid in liquid phenol afforded the final products (±)-**256a-e** in good yields, although in racemic form.

Giannis et al. tested these butyrolactones in an *in vitro* HAT assay against Gcn5 and CBP where (±)-**256c-e** showed inhibition of CBP ((±)-**256c**: 0.5 mM, (±)-**256d** and (±)-**256e:** 1.7-2 mM). In contrast to this, only (±)-**256c** inhibited the HAT Gcn5 with an IC_{50} = 100 mM. Because the binding of histone H3 by Gcn5 (or PCAF) in presents of acetyl-CoA is approximately 100 mM, compound (±)-**256c** showed comparable affinity to Gcn5 as the natural substrate H3.

These results make compound (±)-**256c** a promising starting point for further investigations on these structures towards the evaluation of the "Histone-Code" while targeting Gcn5.

In addition to this, also other groups are interested in these compounds: The γ-butyrolactone (+)-**256c** was isolated by *Matsuura et al.*[246] as a toxin produced by *Lasiodiplodia theobromae*, one of the main pathogens responsible for fruit decay, which provides serious economical impact on the agricultural industry. The relative stereochemistry of the five-membered lactones of type **256** was investigated by *Thiele et al.*[247] It was shown that residual dipolar couplings (RDCs) in NMR can be used for the determination of the relative configuration even when conventional approaches (e.g. NOE, angular restraints from ^3J-coupling constants, cross-correlated relaxation) fail due to high substitution or distance of the stereogenic centers.

For further investigations on the inhibition of HATs it is essential to determine the biological active enantiomer of (±)-**256c**.

Therefore, a highly stereoselective synthesis of these compounds has to be developed, not only to control relative, but also absolute stereochemistry of the lactone ring. In a retrosynthetic view the butyrolactone **256c** was referred to the lactone aldehydes (+)- and (-)-**210a** with both stereocenters already set (Figure 30).

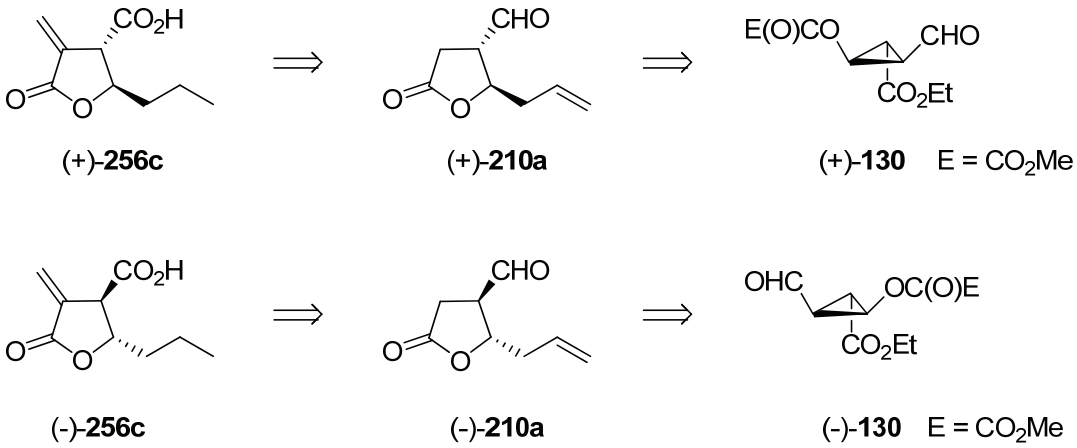
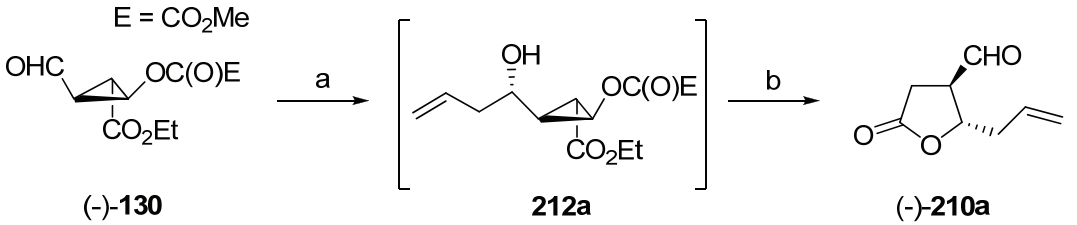


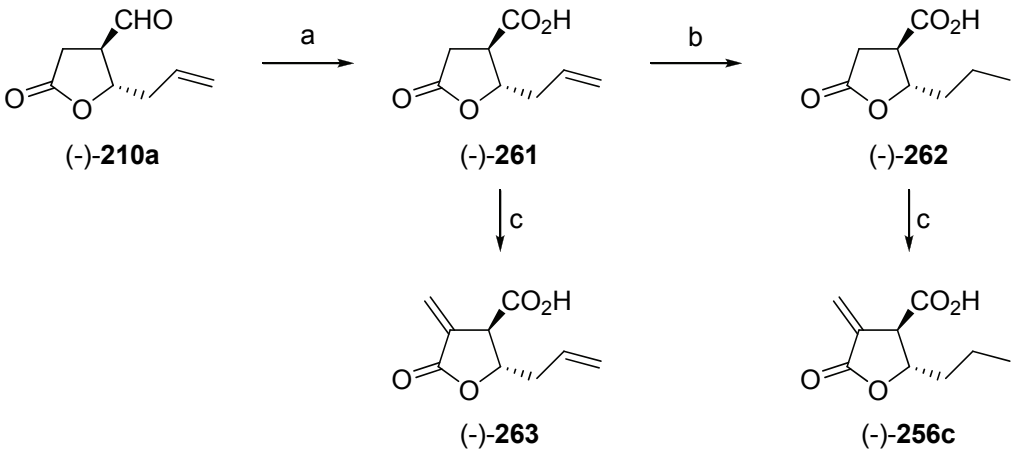
Figure 30. Retrosynthesis of (+)- and (-)-**256c**.

Allylation of the cyclopropylcarbaldehyde (-)-**130** with commercially available trimethyl-allylsilane **211a** (Figure 16) and subsequent retroaldol-lactonization afforded the lactone aldehyde (-)-**210a** in moderate yield of 51%, but highly selective (for discussion see Scheme 39 and Scheme 42). Following this route, both enantiomers of aldehyde **210a** were synthesized (Scheme 75).



Scheme 75. Stereoselective synthesis of lactone aldehyde **210a**: a) **211a** (1.1 eq.), $BF_3 \cdot OEt_2$ (1.1 eq.), CH_2Cl_2, -78 °C, 18 h; b) $Ba(OH)_2 \cdot 8H_2O$ (0.55 eq.), MeOH, 0 °C, 5 h, 51%, *dr* = 95:5.

Since hydrogenation of the double bond in (-)-**210a** failed, the aldehyde was first oxidized to the corresponding carboxylic acid (-)-**261** and subsequent hydrogenation afforded the aliphatic sidechain of (-)-**262** in 96-98% yield (Scheme 76).



Scheme 76. Stereoselective synthesis of (-)-**256c**: a) KH_2PO_4 (0.6 eq.), $NaClO_2$ (1.6 eq.), H_2O_2 (1.6 eq.), 0 °C-rt, CH_3CN 16 h, 79-81%; b) Pd/C (1.0 mol%), ethylacetate, H_2, rt, 24 h, 96-98%; c) (i) methoxymagnesium-methylcarbonate (2 N in DMF, 37.5 eq.), 135 °C, 3 d; ii) HCHO, *N*-methylaniline, acetic acid, rt, 3.5 h, 53-63%.

The lacking *exo*-methylene group was introduced in a two step sequence following a slightly modified procedure described by *Greene et al.*:[248] First Stiles´s-reagent (methoxy-magnesiummethylcarbonate) was used to carboxylate (-)-**261** and (-)-**262.** A Mannich-type reaction under decarboxylation was then triggered and afforded in moderate yields the desired *exo*-methylene products (-)-**263** and (-)-**256c**.

Following this route, four compounds in both enantiomeric forms have been prepared. All spectroscopic data of (-)-**256c** and (+)-**256c** perfectly matched the literature values as reported by *Giannis et al.*[242] The optical purity of **256c** and **263** was determined by chiral HPLC (Figure 31) indicating the high stereoselectivity of this synthesis.

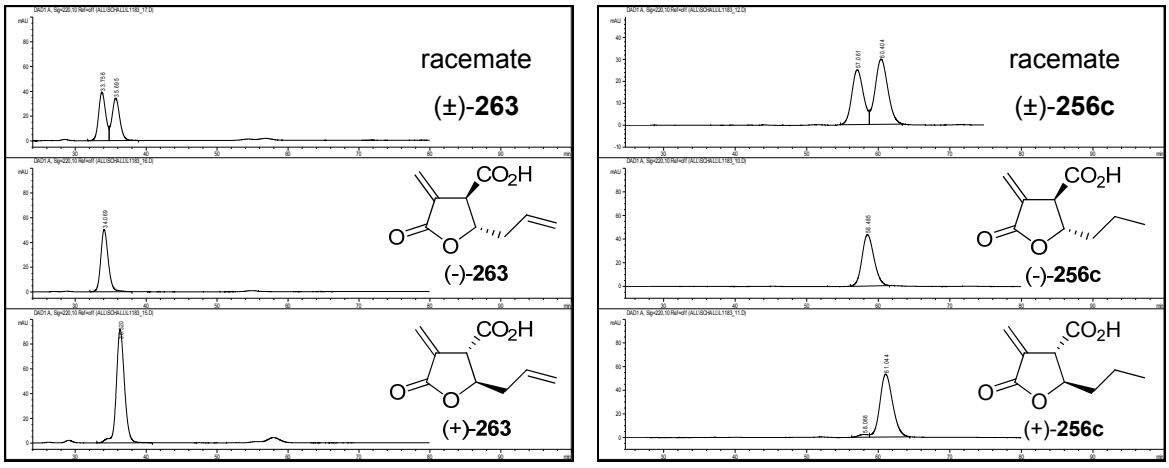


Figure 31. Chiral HPLC analysis for synthesized lactones.

Although, a complete baseline separation of the racemate was not possible (Figure 31, top), the chiral HPLC report of **256c** and **263** proves the enantiomerical purity of the synthesized compounds.

First attempts to evaluate the biological activity of all prepared compounds as described by *Giannis et al.* did not show the reported results, but further investigations in this field are being continued.

The described synthetic route can be extended towards the scaffold **264**, which offers certain points for derivatization (Figure 32). The initial use of various allylsilanes (such as seen in Figure 16) allows the control of ring size and substitution pattern of the southern sidearm. Elongation of the northern carboxylic acid sidechain (e.g. by Arndt-Eistert elongation) may also be of certain interest to generate derivatives.

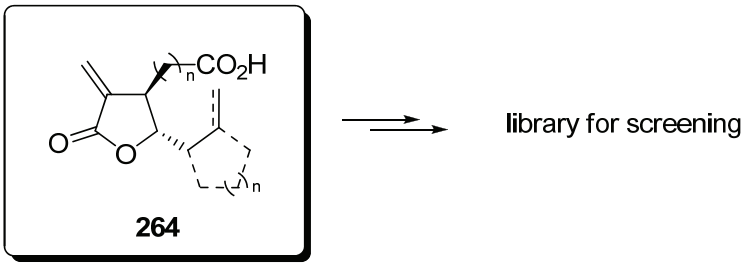


Figure 32. Possible derivatization on skeleton **264**.

In summary, a flexible and divers oriented stereoselective synthesis towards the scaffold **264** was shown. The design and synthesis of a library for the screening on HAT-enzymes is possible, since there are many points for derivatisation present. The construction of a small molecule library and its biological evaluation could afford important results, which contribute knowledge in the field of the “Histone-Code”-hypothesis.

10. Summary

Natural products have long presented chemists with golden opportunities for discovery. The synthesis of various members of the guaianolide family was reviewed to introduce this class of compounds as sources of inspiration for the development of unique synthetic strategies.
The aim of this work was to seek for the first synthetic route towards Cynaropicrin (**123**) and Ixerin Y (**126**), two prominent guaianolides with promising widespread biological activity (Figure 33).

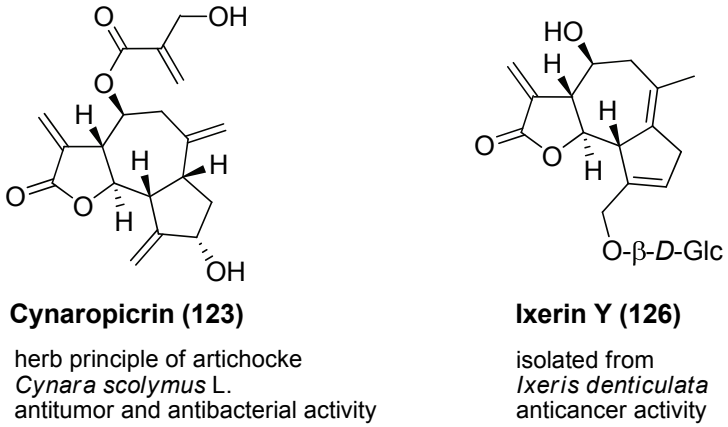
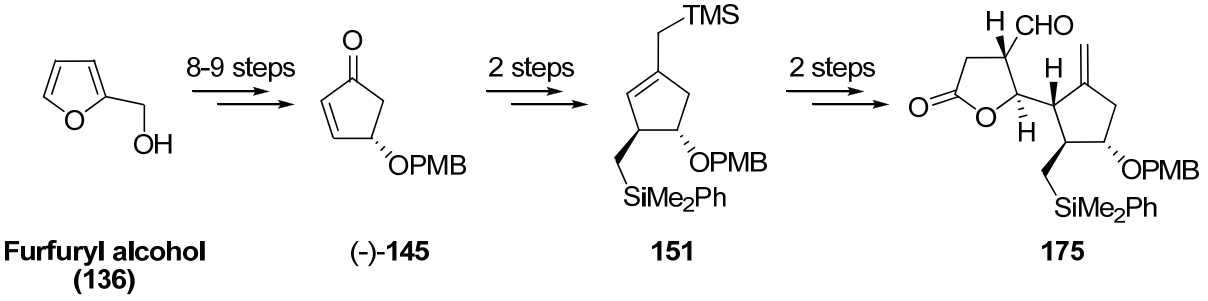


Figure 33. Structure of Cynaropicrin (**123**) and Ixerin Y (**126**).

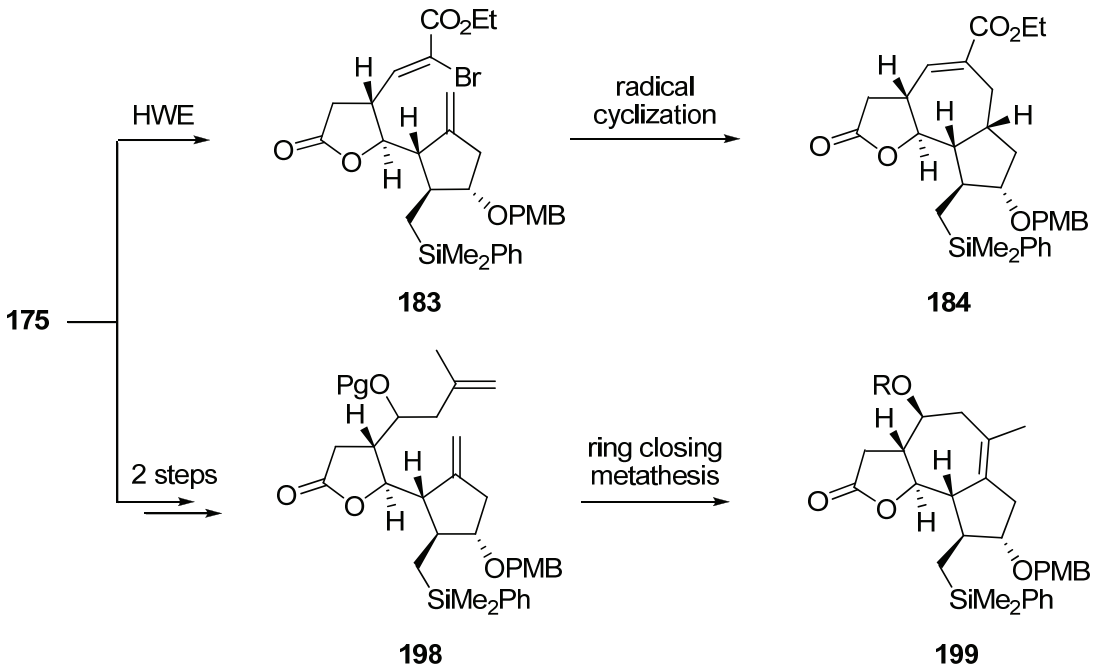
Within 8-9 steps starting from furfuryl alcohol (**136**) the enantiomerical pure PMB-protected cyclopentenone (-)-**145** was prepared utilizing kinetic enzymatic resolution as a key step (Scheme 77).



Scheme 77. Synthesis of the chiral allylsilane **151** and the lactone aldehyde **175** as central key intermediates.

Two additional steps provided the chiral allylsilane **151** which was further transformed into the lactone aldehyde **175**, a key intermediate of the further synthesis with many stereocenters set in right configuration.

175 was subjected to a modified HWE reaction releasing the brominated precursor **183** which afforded the guaianolide skeleton **184** by radical cyclization (Scheme 78, top).



Scheme 78. Completion of the guaianolide skeletons.

Stereoselective allylation of **175** and subsequent protection afforded dienes **198**. Ring closing metathesis completed the 5,7,5-skeleton **199** and provided a powerful and flexible entry towards the core of the guaianolides (Scheme 78, bottom).

Further transformations on the skeleton **199** were demonstrated (Figure 34): Epoxidation of the double bond in the 7-membered ring, as well as deprotection and oxidation of various hydroxy groups was shown. Tamao-Fleming oxidation of the silyl-side chain released a primary alcohol, which was subjected to elimination reactions to introduce a C=C-double bonds at this position.

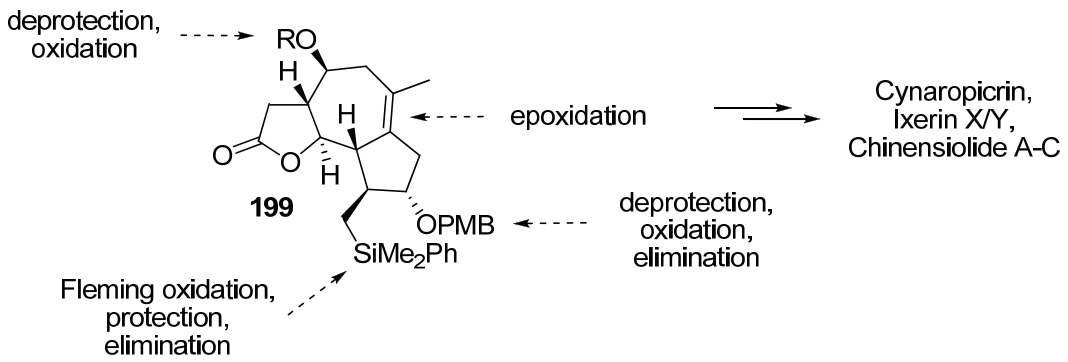
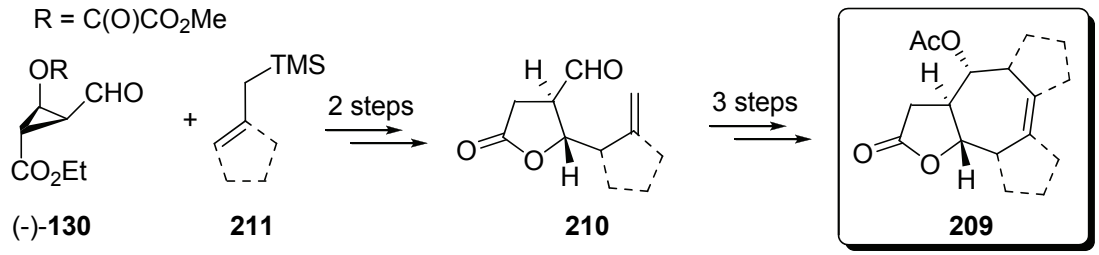


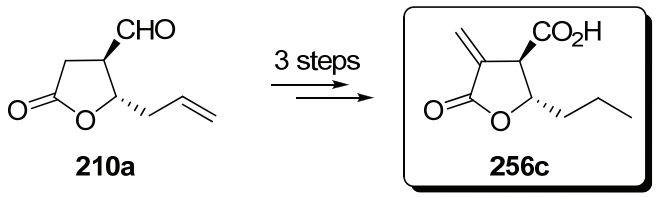
Figure 34. Functional group transformations on **199**.

To investigate the scope and limitations of this synthetic strategy a small library consisting of eight natural product-like scaffolds was synthesized (Scheme 79).



Scheme 79. Synthesis of a 3x3 scaffold library.

In addition to this, a second library of potential small molecule histone acetyl transferase inhibitors was synthesized (Scheme 80). Starting from enantiomeric pure lactone aldehyde intermediate **210a** a set of eight compounds around the scaffold **256c** was prepared in high stereoselectivity.



Scheme 80. Stereoselective synthesis of small molecule HAT inhibitors.

11. Experimental Part

11.1 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.

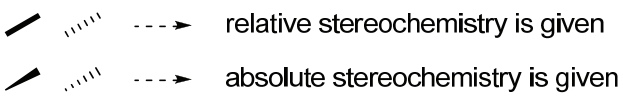
Solvents: Abs. solvents were prepared according to usual lab procedures or taken from the MB-SPS solvent purification system. Ethylacetate, hexanes (40-60 °C) and dichloromethane were purified by distillation before use. Further solvents and reagents were of p.a. quality.

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.

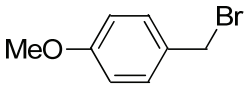
11.2 Abbreviations

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

Indication of relative and absolute stereochemistry:



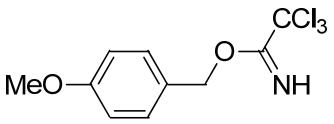
11.3 Synthesis of chiral allylsilanes



_p_-methoxybenzylbromid[249]

HBr (47% in H_2O, 19.19 g, 12.8 ml, 111 mmol, 1.75 eq.) was added to *p*-methoxybenzylalcohol (8.80 g, 7.93 ml, 63.7 mmol, 1.0 eq.) at rt. The reaction mixture was stirred for 24 h. Et_2O (100 ml) was added and the layers were separated. The aqueous layer was again extracted with Et_2O (2x50 ml). The combined org. layers were carefully washed with sat. $NaHCO_3$ (2x15 ml), dried (Na_2SO_4) and concentrated in vacuo. 11.38 g (56.6 mmol, 89%) of the crude product was obtained and was used without further purification.

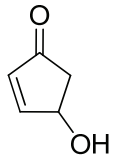
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 4.52 (s, 2H, CH_2), 6.80-6.90 (m, 2H, *o*-H), 7.30-7.40 (m, 2H, *m*-H).



_p_-methoxybenzyl-2,2,2-trichloroacetimidate[250]

Under a N_2-atmosphere a solution of *p*-methoxybenzylalcohol (5.20 g, 4.68 ml, 37.6 mmol, 1.0 eq.) in abs. Et_2O (25 ml) was added to a suspension of NaH (60% in paraffin oil, 151 mg, 3.76 mmol, 0.1 eq.) in abs. Et_2O (25 ml). After stirring for 30 min at rt, the reaction mixture was cooled to 0 °C and CCl_3CN (5.43 g, 3.77 ml, 37.6 mmol, 1.0 eq.) was added slowly. The reaction mixture was allowed to warm to rt and stirred for 4 h. The mixture was concentrated in vacuo without heating and hexanes (50 ml + 160 µl MeOH) was added. The resulting mixture was filtered over celite and the solution was concentrated to afford 9.44 g (33.4 mmol, 89%) product as a yellowish oil. The crude product was stored under a N_2-atmosphere in the fridge and was used without further purification.

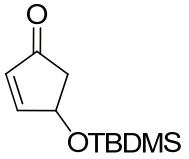
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 5.25 (s, 2H, CH_2), 6.90-6.97 (m, 2H, *o*-H), 7.35-7.45 (m, 2H, *m*-H), 8.35 (bs, 1H, NH).



(±)-4-hydroxycyclopent-2-enone ((±)-137)

Furfuryl alcohol **136** (62 g, 632 mmol, 1.0 eq.) was dissolved in H_2O (1.5 l). K_2HPO_4 (3.15 g) was added and the pH was adjusted to 4.1 using H_3PO_4 (0.25 N). The reaction mixture was refluxed for 40 h and than cooled to rt. The liquid was decanted from the brown slurry and the aqueous layer was extracted with toluene (3x200 ml). The aqueous layer was than concentrated to 100 ml and extracted with ethylacetate (5x150 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated affording 24.6 g (251 mmol, 40%) crude product as a slightly brown oil, which was used without further purification.

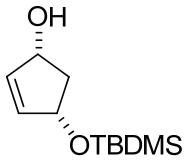
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (dd, *J* = 18.5, 6.0 Hz, 1H, 5-H), 2.75 (dd, *J* = 18.5, 3.2 Hz, 1H, 5-H), 3.6 (bs, 1H, OH), 5.0 (m, 1H, 4-H), 6.20 (d, *J* = 5.6 Hz, 1H, 2-H), 7.61 (dd, *J* = 5.6, 4.8 Hz, 1H, 3-H).



(±)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone ((±)-138)

Under a nitrogen atmosphere (±)-4-hydroxycyclopent-2-enone (±)-**137** (21.96 g, 224.0 mmol, 1.0 eq.) was dissolved in abs. THF (75 ml). NEt_3 (34.00 g, 47.2 ml, 336 mmol, 1.50 eq.) and DMAP (1.37 g, 11.2 mmol, 5 mol%) were added and the mixture cooled to 0 °C. TBDMSCl (38.8 g, 257 mmol, 1.15 eq. dissolved in 50 ml abs. THF) was added over 20 min and the mixture was allowed to warm to rt over night. After cooling to 0 °C the reaction mixture was diluted with Et_2O (50 ml) and slowly H_2O (100 ml) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2x100 ml). The combined organic layers were washed with brine (100 ml) and H_2O (100 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 5:1) afforded 42.14 g (198 mmol, 89%) product as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 6H, $SiMe_2$), 0.88 (s, 9H, Si^{t}Bu), 2.25 (dd, *J* = 18.2, 6.0 Hz, 1H, 5-H), 2.72 (dd, *J* = 2.3, 18.2 Hz, 1H, 5-H), 4.9 (m, 1H, 4-H), 6.20 (d, *J* = 5.7 Hz, 1H, 3-H), 7.48 (dd, *J* = 5.7, 2.4 Hz, 1H, 2-H).



(±)-*cis*-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol ((±)-139)

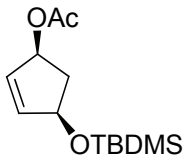
Under a nitrogen atmosphere $LiAlH_4$ (1.97 g, 51.9 mmol, 0.7 eq.) and LiI (4.97 g, 37.1 mmol, 0.5 eq.) were dissolved in abs. toluene (150 ml) and cooled to -30 °C. (±)-4-(*tert*-butyl-dimethylsilyloxy)cyclopent-2-enone (±)-**138** (15.76 g, 74.2 mmol, 1.0 eq.) dissolved in abs. TBME (80 ml) was added slowly over 30 min. After complete conversion of the starting material (TLC) sat. NH_4Cl (100 ml) was added slowly. The mixture was warmed to rt and filtered. The layers were separated and the aqueous layer was extracted with toluene (5x50 ml). The combined org. layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 5:1) afforded 13.48 g (62.9 mmol, 85%, *dr* = 92:8) product as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiMe_2$), 0.90 (s, 9H, Si^{t}Bu), 1.52 (dt, *J* = 13.8, 4.7 Hz, 1H, 5-H), 2.69 (dt, *J* = 13.8, 7.1 Hz, 1H, 5-H), 2.8 (bs, 1H, OH), 4.50 (m, 1H, 1-H), 4.6 (m, 1H, 4-H), 5.84 (dt, *J* = 5.5, 1.6 Hz, 1H, 3-H), 5.93 (dt, *J* = 5.5, 1.7 Hz, 1H, 2-H).

Representative procedure for enzymatic resolution:

Racemic (±)-*cis*-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol ((±)-**139**) (17.9 g, 83 mmol, 1.0 eq.) was dissolved in TBME (220 ml). NEt_3 (5.7 g, 7.97 ml, 57 mmol, 0.68 eq.), PPLE[251] (9.96 g, 120 mg/mmol) and vinylacetate (32 g, 35 ml, 4.50 eq.) were added and the mixture was stirred at rt for 48 h. The progress was monitored by chiral GC.[252] The reaction mixture was filtered over celite and concentrated in vacuo. The resulting yellow oil was purified by chromatography on silica gel (hexanes:ethylacetate 9:1-3:1) affording (+)-**140** (8.56 g, 33.4 mmol, 80%, >99%*ee*) and (-)-**139** (8.47 g, 39.5 mmol, 95%, 92%*ee*) as slightly yellowish oils.

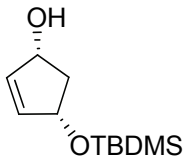
Upper spot:



(+)-(1*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enyl acetate ((+)-140)

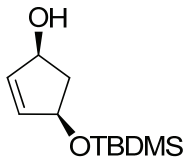
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6H, $SiMe_2$), 0.91 (s, 9H, Si^{t}Bu), 1.6 (m, 1H, 5-H), 2.05 (s, 3H, OAc), 2.80 (m, 1H, 5-H), 4.70 (m, 1H, 4-H), 5.50 (m, 1H, 1-H), 5.90 (m, 1H, 3-H), 6.00 (m, 1H, 2-H).

Lower spot:



(-)-(1*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol ((-)-139)

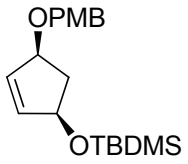
^{1}H NMR of (-)-**139:** identical to (±)-**139**.



(+)-(1*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol ((+)-139)

(+)-**140** (3.75 g, 14.64 mmol, 1.0 eq.) was dissolved in THF/MeOH/H_2O (3:1:1, 25 ml) and LiOH (0.42 g, 17.56 mmol, 1.20 eq.) was added in portions at rt. After stirring for 2 h the reaction mixture was diluted with Et_2O (40 ml) and H_2O (20 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (20 ml) and the combined org. layers were washed with 5% $NaHCO_3$ (10 ml) and brine (10 ml). After drying (Na_2SO_4), the solution was filtered and concentrated to afford 3.00 g (13.99 mmol, 96%) crude product as a colorless oil which was used without further purification.

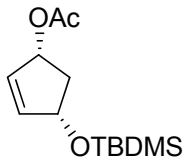
^{1}H NMR of (+)-**139:** identical to (±)-**139** and (-)-**139**.



(+)-((1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enyloxy)(*tert*-butyl)dimethylsilane ((+)-141)

Under an N_2-atmosphere NaH (60% in paraffin oil, 1.02 g, 25.5 mmol, 1.25 eq.) was dissolved in abs. THF (75 ml) and cooled to 0 °C. Alcohol (+)-**139** (4.372 mg, 20.39 mmol, 1.00 eq.) dissolved in abs. THF (25 ml) was added over 30 min and the solution was stirred for further 30 min and allowed to warm to rt. NaI (3.06 g, 20.39 mmol, 1.0 eq.) and *p*-methoxybenzylbromid (6.66 g, 4.78 ml, 26.5 mmol, 1.30 eq.) was added and the reaction mixture was stirred for 5 h at rt. H_2O (50 ml) and CH_2Cl_2 (100 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x100 ml). The combined org. layers were washed with brine (20 ml) and H_2O (20 ml), dried over Na_2SO_4, filtered and concentrated at rt in vacuo. Chromatography on silica gel (hexanes:ethylacetate 9:1) afforded 5.89 g (17.59 mmol, 86%) product as a colorless oil.

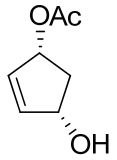
R_f (hexanes:ethylacetate 9:1) = 0.46.- $[\alpha]_D^{20}$ = +2.1 (c = 0.45, $CHCl_3$).- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6H, $SiMe_2$), 0.85 (s, 9H, ^{t}Bu), 1.62 (dt, *J* = 13.2, 5.6 Hz, 1H, 5-H), 2.65 (dt, *J* = 13.2, 7.1 Hz, 1H, 5-H), 3.76 (s, 3H, OMe), 4.32-4.41 (m, 1H, 4H), 4.41-4.48 (m, 2H, PMB), 5.58-5.66 (m, 1H, 1-H), 5.80-5.93 (m, 2H, CH=CH), 6.81-6.86 (m, 2H, PMB), 7.19-7.27 (m, 2H, PMB).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.55 (+, SiMe), -4.61 (+, SiMe), 18.18 (Cq, SiC), 25.91 (+, $SiCMe_3$), 41.53 (-, 5-C), 55.33 (+, OMe), 70.03 (-, PMB), 74.90 (+, 1-C), 81.10 (+, 4-C), 113.77 (+, 2xPMB), 129.35 (+, 2x PMB), 130.79 (Cq, PMB), 132.94 (+, 2-C), 137.38 (+, 3-C), 159.1 (Cq, PMB).- IR (neat): $\tilde{\nu}$ = 2954, 2930, 2884, 2856, 2361, 2341, 1612, 1512, 1462, 1367, 1300, 1249, 1172, 1078, 1038, 906, 836, 776, 669 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 335.2 (0.63) [M+H$^+$], 352.2 (45.3) [M+NH_4^+].- HRMS (PI-LSIMS): 335.2044 ($C_{19}H_{31}O_3Si$: calc. 335.2042 [M+H$^+$]).



(-)-(1*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enyl acetate ((-)-140)

(-)-(1*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enol (-)-**139** (4.07 g, 19.0 mmol, 1.0 eq.) was dissolved in dry pyridine (40 ml). Acetic anhydride (8.73 g, 8.07 ml, 86 mmol, 4.5 eq.) was added at rt. After stirring for 6 h the reaction mixture was diluted with Et_2O (100 ml) and extracted with 1N HCl (2x100 ml). The organic layer was washed with sat. $NaHCO_3$ (50 ml), brine (50 ml), dried (Na_2SO_4) and concentrated in vacuo to yield 4.70 g (18.4 mmol, 97%) product as a colorless oil.

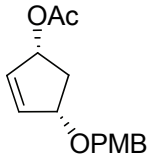
^{1}H NMR of (-)-**140:** identical to (+)-**140**.



(1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate ((+)-143)

(-)-**140** (3.67 g, 14.29 mmol, 1.0 eq.) and NEt_3 (0.15 g, 0.2 ml, 1.43 mmol, 0.10 eq.) were dissolved in THF (55 ml). TBAF (4.60 g, 14.58 mmol, 1.02 eq.) was added in portions at rt and the reaction mixture was stirred for 2 h. After complete conversion of the starting material (TLC) H_2O (2 ml) was added and stirring was continued for 20 min. After removal of the solvent, chromatography on silica gel (hexanes:ethylacetate 1:1) afforded 1.94 g (13.7 mmol, 95%) product, which solidified with time to a colorless solid and was recrystallized from diethylether.

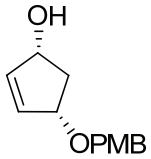
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.6 (dt, *J* = 14.5, 3.8 Hz, 1H, 5-H), 2.08 (s, 3H, OAc), 2.22 (d, *J* = 7.8 Hz, 1H, OH), 2.83 (dt, *J* = 14.5, 7.3 Hz, 1H, 5-H), 4.8 (m, 1H, 4-H), 5.5 (m, 1H, 1-H), 6.0 (m, 1H, 2-H) 6.1 (m, 1H, 3-H).



(+)-(1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enyl acetate ((+)-144)

Under a N_2-atmosphere *p*-methoxybenzyl-2,2,2-trichloroacetimidate (8.323 g, 29.46 mmol, 1.67 eq.) was dissolved in abs. CH_2Cl_2 (40 ml). (1*R*,4*S*)-4-hydroxycyclopent-2-enyl acetate (+)-**143** (3.100 g, 14.46 mmol, 1.0 eq.) and $Cu(OTf)_2$ (262 mg, 0.723 mmol, 5 mol%) was added at 0 °C. The solution was stirred for 24 h at rt. The solvent was removed in vacuo and the crude mixture was purified by column chromatography on silica gel (hexanes:ethylacetate 9:1) affording 4.000 g (11.96 mmol, 83%) product as a colorless oil.

R_f (hexanes:ethylacetate 5:1) = 0.36.- $[\alpha]_D^{20}$ = +0.8 (c = 1.05 $CHCl_3$).- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (ddd, *J* = 14.3, 4.4, 4.4 Hz, 1H, 5-H), 1.05 (s, 3H, OAc), 2.76 (ddd, *J* = 14.3, 7.1, 7.3 Hz, 1H, 5-H), 3.80 (s, 3H, OMe), 4.47-4.51 (m, 3H, OCH_2, 4-H), 5.46- 5.54 (m, 1H, 1-H), 5.95-6.02 (m, 1H, 2-H), 6.08-6.14 (m, 1H, 3-H), 6.82-6.94 (m, 2H, PMB), 7.21-7.32 (m, 2H, PMB).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.21 (+, Ac), 37.59 (-, 5-C), 55.31 (+, OMe), 70.74 (-, PMB), 76.87 (+, 1-C), 80.90 (+, 4-C), 113.84 (+, 2xPMB), 129.43 (+, 2xPMB), 130.39 (Cq, PMB), 132.75 (+, 2-C), 136.30 (+, 3-C), 159.26 (Cq, PMB), 170.93 (Cq, C=O).- IR (neat): $\tilde{\nu}$ = 3065, 2999, 2938, 2909, 2860, 2837, 1732, 1613, 1586, 1514, 1464, 1440, 1365, 1302, 1247, 1175, 1094, 1072, 1033, 954, 908, 821, 769, 680 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 121.0 (100) [$CH_2C_6H_4OMe^+$], 263.0 (1.82) [$M+H^+$], 280.1 (24.31) [$M+NH_4^+$].- HRMS (EI, 70eV): 262.1201 ($C_{15}H_{18}O_4$): calc. 262.1205 [M+]).



(-)-(1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enol ((-)-142)

Starting from TBDMS-protected precursor (+)-**141**:

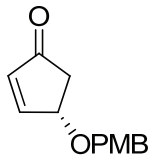
TBDMS-protected (+)-**141** (8.60 g, 25.7 mmol, 1.00 eq.) was dissolved in THF (100 ml) at rt and NEt_3 (260 mg, 361 µl, 0.10 eq.) and TBAF (8.13 g, 25.8 mmol, 1.01 eq.) was added in small portions. The mixture was stirred at rt for 24 h and then the solvent was removed in

vacuo. Chromatography on silica gel (hexanes:ethylacetate 1:1) afforded 4.83 g (21.93 mmol, 85%) product as a colorless oil.

Starting from Ac-protected precursor (+)-**144**:

Ac-protected (+)-**144** (1.178 g, 4.491 mmol, 1.0 eq.) was dissolved in THF/MeOH/H_2O (10 ml, 3:1:1). LiOH (0.129 g, 5.39 mmol, 1.2 eq.) was added at rt and the reaction mixture was stirred for 2 h. H_2O (20 ml) was added and the mixture was extracted with Et_2O (3x 20 ml). The combined org. layers were washed with 5% $NaHCO_3$ (10 ml) and brine (10 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated, affording 0.911 g product (4.146 mmol, 92%) as a colorless oil.

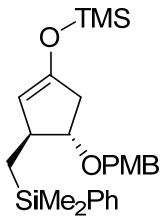
R_f (hexanes:ethylacetate 5:1) = 0.15.- $[\alpha]_D^{20}$ = -21.5 (c = 1.01, $CHCl_3$).- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59-1.69 (m, 1H, 5-H), 1.75 (bs, 1H, OH), 2.66 (m, 1H, 5-H), 3.79 (s, 3H, OMe), 4.37-4.45 (m, 1H, 1-H), 4.45-4.51 (m, 2H, 2-H, 3H), 4.56-4.68 (m, 1H, 4-H), 5.98-6.05 (s, 2H, PMB), 6.83-6.90 (m, 2H, PMB), 7.22-7.29 (m, 2H, PMB).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.1 (-, 5-C), 55.3 (+, OCH_3), 70.8 (-, OCH_2), 75.1 (+, 1-C), 81.2 (+, 4-C), 113.9 (+, 2xPMB), 129.4 (+, 2xPMB), 130.4 (Cq, PMB), 134.3 (+, 2-C), 137.1 (+, 3-C), 159.3 (Cq, PMB).- IR (neat): $\tilde{\nu}$ = 3394, 3059, 2998, 2935, 2905, 2860, 2837, 1612, 1585, 1513, 1462, 1441, 1392, 1359, 1319, 1302, 1248, 1174, 1072, 1033, 821, 766, 598, 520 cm^{-1}.- MS (EI, 70eV): *m/z* (%) = 121.1 (100) [$CH_2C_6H_4OCH_3^+$], 220.0 (19.89) [M+].- HRMS (EI, 70eV): 220.1097 ($C_{13}H_{16}O_3$: calc. 220.1099 [M^+]).



(-)-(*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enone ((-)-145))

Under a N_2-atmosphere alcohol (-)-**142** (4.00 g, 18.16 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (100 ml) and crushed molecular sieve (1.50 g, 4 Å) was added. PCC (4.70 g, 21.79 mmol, 1.2 eq.) was added over a period of 30 min at rt. The reaction mixture was stirred for 24 h, filtered over celite and the solvent removed in vacuo. Chromatography on silica gel (hexanes: ethylacetate 2:1) afforded 3.40 g product (15.59 mmol, 86%) as a yellowish oil.

R_f (hexanes:ethylacetate 2:1) = 0.49.- $[\alpha]_D^{20}$ = -36.0 (c = 0.98, $CHCl_3$).- ^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (dd, *J* = 18.3, 2.3 Hz, 1H, 5-H), 2.71 (dd, *J* = 18.1, 5.8 Hz, 1H, 5-H), 3.81 (s, 3H, OMe), 4.49-4.62 (m, 2H, OCH_2), 4.71-4.77 (m, 1H, 4-H), 6.22-6.27 (m, 1H, 2-H), 6.86-6.93 (m, 2H, PMB), 7.24-7.32 (m, 2H, PMB), 7.56-7.61 (m, 1H, 3-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.84 (-, 5-C), 55.33 (+, OCH_3), 71.67 (-, OCH_2), 76.54 (+, 4-C), 114.02 (+, 2xPMB), 129.51 (Cq, PMB), 129.61 (+, 2xPMB), 135.66 (+, 2-C), 159.55 (Cq, PMB), 161.34 (+, 3-C), 206.05 (Cq, C=O).- IR (neat): $\tilde{\nu}$ = 3066, 3001, 2954, 2935, 2908, 2863, 2837, 1717, 1612, 1585, 1514, 1463, 1402, 1350, 1322, 1302, 1248, 1177, 1107, 1070, 1033, 822, 793, 765, 589 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 121.0 (84.46) [$CH_2C_6H_4OMe^+$], 219.2 (1.6) [$M+H^+$], 236.1 (100) [$M+NH_4^+$].- HRMS (EI, 70eV): 218.0946 ($C_{13}H_{14}O_3$: calc. 218.0943, [M+]).



(+)-((3*S*,4*S*)-3-((dimethyl(phenyl)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopent-1-enyloxy)trimethylsilane (150)

Formation of Grignard:

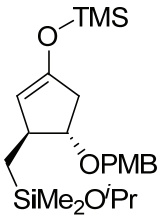
Under a N_2-atmosphere chloromethyl-(dimethylphenylsilane) (924 mg, 5.00 mmol, 1.0 eq.) was dissolved in abs. THF (5 ml). At rt 2 ml of this solution was added at once to Mg curls (365 mg, 15 mmol, 3.0 eq.). After initiation the rest of the solution was added dropwise. After complete addition the Grignard-reagent was stirred for 2 h at rt.
(Titration:[253] c($PhMe_2SiCH_2MgCl$) = 1.09 mmol/ml)

Formation of silylenolether:

Under a N_2-atmosphere LiCl (47 mg, 1.10 mmol, 0.3 eq.) and CuI (105 mg, 0.55 mmol, 0.15 eq.) were dissolved in abs. THF (14 ml) and stirred for 30 min until a clear solution was obtained. Cyclopentenon (-)-**145** (800 mg, 3.67 mmol, 1.0 eq.) dissolved in abs. THF (4 ml) was added and the mixture stirred for further 30 min. and then cooled to -78 °C before TMSCl (1.593 g, 1.874 ml, 14.66 mmol, 4.0 eq.) was added dropwise. The prepared Grignard solution (4.20 ml, 1.09 mmol/ml, 4.58 mmol, 1.25 eq.) was added slowly and the resulting mixture was stirred for 3 h at -78 °C until no more starting material was detected by TLC. The mixture

was quenched by adding NEt_3 (6.18 ml, 44.0 mmol, 12 eq.) and allowed to come to 0 °C before being poured into *n*-pentane (100 ml). After stirring for 5 min. at rt the liquid was filtered over celite and the residue was washed with *n*-pentane (2x20 ml). The combined layers were extracted with $NaHCO_3$ (4x10 ml) until a clear solution was obtained. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo at rt. The resulting crude enolether (1.59 mg, 3.61 mmol, 99%, *dr* >99:1) was obtained as a colorless liquid and used without further purification.

$[\alpha]_D^{20}$ = + 62.2 (c = 0.675, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.19 (s, 9H, $SiMe_3$), 0.35 (s, 3H, SiMe), 0.37 (s, 3H, SiMe), 0.86 (dd, *J* = 14.6, 9.9 Hz, 1H, $SiCH_2$), 1.14 (dd, *J* = 14.6, 5.2 Hz, 1H, $SiCH_2$), 2.35 (dd, *J* = 16.0, 4.8 Hz, 1H, 5-H), 2.58 (dd, *J* = 16.0, 7.1 Hz, 1H, 5-H), 2.77-2.88 (m, 1H, 3-H), 3.70-3.77 (m, 1H, 4-H), 2.85 (s, 3H, OMe), 4.32-4.49 (m, 2H, PMB), 4.44 (m, 1H, 2-H), 6.89-6.96 (m, 2H, PMB), 7.27-7.32 (m, 2H, PMB), 7.37-7.43 (m, 3H, Ph), 7.54-7.61 (m, 2H, Ph).- ^{13}C NMR (75 MHz): δ = -2.0 (+, SiMe), -1.9 (+, SiMe), 0.28 (+, $SiMe_3$), 22.9 (-, $SiCH_2$), 39.9 (-, 5-C), 45.2 (+, 3-C), 55.6 (+, OMe), 71.1 (-, PMB), 86.0 (+, 4-C), 106.6 (+, 2-C), 114.0 (+, 2x PMB), 128.1 (+, Ph), 129.1 (+, Ph), 129.6 (+, 2x PMB), 131.1 (Cq, PMB), 133.9 (+, SiPh), 139.9 (Cq, Ph), 150.9 (Cq, 1-C), 159.4 (Cq, PMB).- IR (neat): $\tilde{\nu}$ = 3068, 3048, 2999, 2955, 2899, 2864, 1880, 1746, 1644, 1613, 1586, 1512, 1464, 1426, 1348, 1300, 1249, 1212, 1172, 1112, 1087, 1037, 1011, 920, 843, 758, 727, 700 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 121.1 (100), 231.2 (44.9), 248.2 (87.6), 441.2 (83.6) [$M+H^+$].



(+)-*iso*-propoxy(((1*S*,5*S*)-5-(*p*-methoxybenzyloxy)-3-(trimethylsilyloxy)cyclopent-2-enyl) methyl)dimethylsilane (151)

Formation of Grignard:

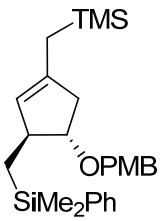
Under a N_2-atmosphere chloromethyldimethylisopropoxysilane (834 mg, 5.00 mmol, 1.0 eq.) was dissolved in abs. THF (5 ml). At rt 2 ml of this solution was added at once to Mg curls (365 mg, 15 mmol, 3.0 eq.). After initiation the rest of the solution was added dropwise. After complete addition the Grignard-reagent was stirred for 2 h at rt.

(Titration:[253] c($Me_2{}^iPrOSiCH_2MgCl$) = 0.97 mmol/ml)

Formation of silylenolether:

Under a N_2-atmosphere LiCl (23 mg, 0.550 mmol, 0.3 eq.) and CuI (52 mg, 0.28 mmol, 0.15 eq.) were dissolved in abs. THF (7 ml) and stirred for 30 min until a clear solution was obtained. Cyclopentenon (-)-**145** (400 mg, 1.83 mmol, 1.0 eq.) dissolved in abs. THF (2 ml) was added and the mixture stirred for further 30 min. and then cooled to -78 °C before TMSCl (796 mg, 0.937 ml, 7.33 mmol, 4.0 eq.) was added dropwise. The prepared Grignard solution (4.68 ml, 0.97 mmol/ml, 4.58 mmol, 1.15 eq.) was added slowly and the resulting mixture was stirred for 3 h at -78 °C until no more starting material was detected by TLC. The mixture was quenched by adding NEt_3 (3.09 ml, 21.99 mmol, 12 eq.) and was allowed to come to 0 °C before being poured into *n*-pentane (50 ml). After stirring for 5 min. at rt the liquid was filtered over celite and the residue was washed with *n*-pentane (2x10 ml). The combined layers were extracted with $NaHCO_3$ (4x 10 ml) until a clear solution was obtained. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo at rt. The resulting crude enolether (699 mg, 1.65 mmol, 90%, *dr* >99:1) was obtained as a colorless liquid and used without further purification.

$[\alpha]_D^{20}$ = +50.3 (c = 0.465, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.09 (s, 6H, $SiMe_2$), 0.18 (s, 9H, $SiMe_3$), 0.59 (dd, *J* = 14.4, 10.0 Hz, 1H, $SiCH_2$), 0.87 (dd, *J* = 14.4, 5.2 Hz, 1H, $SiCH_2$), 1.12 (d, *J* = 6.0 Hz, 6H, ^{i}Pr), 2.29 (dd, *J* = 15.9, 4.7 Hz, 1H, 4-H), 2.54 (dd, 15.9, 7.3 Hz, 1H, 4-H), 2.69-2.80 (m, 1H, 1-H), 3.65-3.73 (m, 1H, 5-H), 2.77 (s, 3H, OMe), 3.96 (sept, *J* = 6.0 Hz, 1H, ^{i}Pr), 4.34-4.48 (m, 2H, PMB), 4.59 (d, *J* = 1.9 Hz, 1H, 2-H), 6.81-6.88 (m, 2H, PMB), 7.20-7.28 (m, 2H, PMB).- ^{13}C NMR (75 MHz): δ = -0.3 (+, SiMe), -0.27 (+, SiMe), 0.4 (+, $SiMe_3$), 23.8 (-, $SiCH_2$), 26.2 (+, 2xMe), 39.9 (-, 4-C), 44.6 (+, 1-C), 55.6 (+, OMe), 65.1 (+, ^{i}Pr), 71.1 (-, PMB), 86.0 (+, 5-C), 106.9 (+, 2-C), 114.1 (+, 2x PMB), 129.6 (+, 2x PMB), 131.2 (Cq, PMB), 150.9 (Cq, 3-C), 159.4 (Cq, PMB).- IR (neat): $\tilde{\nu}$ = 3066, 2959, 2901, 2870, 2636, 1747, 1725, 1645, 1612, 1586, 1513, 1464, 1402, 1380, 1349, 1330, 1251, 1212, 1172, 1123, 1086, 1025, 920, 863, 842, 756 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 230.1 (100), 285.1 (66), 423.1 (30) [$M+H^+$].



(+)-1-((((1*S*,5*S*)-5-(*p*-methoxybenzyloxy)-3-((trimethylsilyl)methyl)cyclopent-2-enyl)methyl) dimethylsilyl)benzene (152)

Formation of the Grignard reagent:

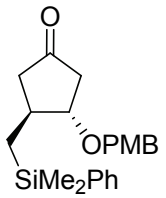
Mg curls (524 mg, 21.56 mmol) were stirred in abs. Et_2O (10 ml) under a nitrogen atmosphere. At rt chloromethyltrimethylsilane (1.587 g, 1.797 ml, 12.93 mmol) was added slowly via a syringe to form the Grignard reagent.
(Titration: [253] c($TMSCH_2MgCl$) = 1.0 mmol/ml)

$Ni(acac)_2$ - coupling:

Silylenolether **150** (1.900 g, 4.31 mmol, 1.0 eq.) was dissolved in abs. Et_2O (10 ml) under a nitrogen atmosphere and cooled to 0 °C. $Ni(acac)_2$ (431 mg, 0.431 mmol, 0.1 eq.) was added and after stirring for 10 min the fresh prepared Grignard solution (8.62 ml, 1.0 mmol/ml, 8.62 mmol, 2.0 eq.) was added slowly. The resulting black mixture was stirred for 5 days at rt. After cooling to 0 °C the reaction was quenched with sat. $NaHCO_3$ (5 ml) and the mixture was extracted with Et_2O (4x50 ml). The combined org. layers were washed with brine (20 ml) and water (20 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 98:2) afforded 750 mg (1.71 mmol, 40%) product as a yellowish oil.

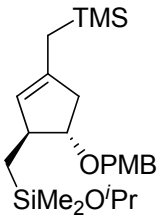
R_f (hexanes:ethylacetate 98:2, Vanilline) = 0.61.- $[\alpha]_D^{20}$ = + 68.2 (c = 0.55, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.00 (s, 9H, $SiMe_3$), 0.31 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.81 (dd, *J* = 14.6, 9.3 Hz, 1H, CH_2SiMe_2Ph), 1.02 (dd, *J* = 14.6, 5.8 Hz, 1H, CH_2SiMe_2Ph), 1.41-1.55 (m, 2H, CH_2SiMe_3), 2.21 (dd, *J* = 16.3, 3.99 Hz, 1H, 4-H), 2.49 (dd, *J* = 15.8, 6.5 Hz, 1H, 4-H), 2.47-2.87 (m, 1H, 1-H), 3.68-3.76 (m, 1H, 5-H), 3.81 (s, 3H, OMe), 4.27-4.44 (m, 2H, PMB), 4.97-5.03 (m, 1H, 2-H), 6.84-6.91 (m, 2H, PMB), 7.20-7.26 (m, 2H, PMB), 7.33-7.38 (m, 3H, SiPh), 7.50-7.56 (m, 2H, SiPh).- ^{13}C NMR (75 MHz): δ = -1.04 (+, SiMe), -0.74 (+, SiMe), 0.00 ($SiMe_3$), 22.92 (-, CH_2SiMe_3), 22.98 (-,CH_2SiMe_2Ph), 44.04 (-, 4-C), 49.05 (+, 1-C), 56.55 (+, OMe), 71.90 (-, PMB), 89.55 (+, 5-C), 114.95 (+, 2xPMB), 127.31 (+, 2-C), 128.99 (+, SiPh), 130.04 (+, SiPh), 130.47 (+, 2xPMB), 132.27 (Cq), 134.87 (+, SiPh), 139.06 (Cq),

141.07 (Cq), 160.27 (Cq).- IR (neat): $\tilde{\nu}$ = 3068, 3046, 2999, 2953, 2898, 2866, 1725, 1639, 1613, 1585, 1513, 1464, 1425, 1402, 1348, 1300, 1248, 1172, 1112, 1085, 1038, 838, 789, 727 cm^{-1}.- MS (CI, NH_3): *m/z* = 439.0 (48.3) [M+H^+], 456.1 (58.2) [M+NH_4^+].- HRMS (EI, 70eV): 438.2402 ($C_{26}H_{38}O_2Si_2$: calc. 438.2410 [M^+]).



(+)-(3*S*,4*S*)-4-(*p*-methoxybenzyloxy)-3-((dimethyl(phenyl)silyl)methyl)cyclopentenone (154)

R_f (hexanes:ethylacetate 3:1) = 0.43.- $[\alpha]_D^{20}$ = +42.4 (c = 0.50, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.30 (s, 3H, SiMe), 0.31 (s, 3H, SiMe), 0.68 (dd, *J* = 14.7, 10.0 Hz, 1H, CH_2Si), 1.21 (dd, *J* = 14.7, 4.3 Hz, 1H, CH_2Si), 1.74 (dd, *J* = 17.4, 6.4 Hz, 1H, 2-H), 2.17 (dd, *J* = 18.7, 5.5 Hz, 1H, 2-H), 2.30-2.56 (m, 3H, 3-H, 5-H), 3.71 (m, 1H, 4-H), 3.81 (s, 3H, OMe), 4.33-4.46 (m, 2H, PMB), 6.84-6.91 (m, 2H, PMB), 7.17-7.24 (m, 2H, PMB), 7.32-7.40 (m, 3H, Si-Ph), 7.45-7.52 (m, 2H, SiPh).- ^{13}C NMR (75.4 MHz): δ = -2.3 (+, SiMe), -2.2 (+, SiMe,), 20.5 (-, $SiCH_2$), 38.5 (+, 3-C), 43.7 (-, 2-C), 45.4 (-, 5-C), 55.5 (+, OMe), 71.4 (-, PMB), 83.3 (+, 4-C), 114.1 (+, 2xPMB), 128.2 (+, 2xSiPh), 129.4 (+, SiPh), 129.5 (+, 2xPMB), 130.3 (Cq), 133.7 (+, 2xSiPh), 138.8 (Cq), 159.5 (Cq), 216.3 (Cq, 1-C).- IR (neat): $\tilde{\nu}$ = 3068, 3046, 3000, 2954, 2901, 2836, 1744, 1712, 1612, 1586, 1512, 1464, 1425, 1402, 1349, 1302, 1248, 1173, 1153, 1112, 1033, 832, 732, 702 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 121.1 (100), 368.2 (1) [M^+].- HRMS (EI, 70 eV): 368.1802 ($C_{22}H_{28}O_3Si$: calc. 368.1808 [M^+]).



(+)-(((3*S*,4*S*)-3-((dimethyl(*iso*-propoxy)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopent-1-enyl)methyl)trimethylsilane (153)

Formation of the Grignard reagent:

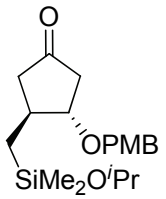
Mg curls (524 mg, 21.56 mmol) were stirred in abs. Et_2O (10 ml) under a nitrogen atmosphere. At rt chloromethyltrimethylsilane (1.587 g, 1.797 ml, 12.93 mmol) was added slowly via a syringe to form the Grignard reagent.
(Titration:[253] c($TMSCH_2MgCl$) = 0.77 mmol/ml)

$Ni(acac)_2$ - coupling:

Silylenolether **151** (354 mg, 0.837 mmol, 1.0 eq.) was dissolved in abs. Et_2O (7 ml) under a nitrogen atmosphere and cooled to 0 °C. $Ni(acac)_2$ (215 mg, 0.837 mmol, 1.0 eq.) was added and after stirring for 10 min the fresh prepared Grignard solution (1.63 ml, 0.77 mmol/ml, 1.256 mmol, 1.5 eq.) was added slowly. The resulting black mixture was stirred for 5 d at rt. After cooling to 0 °C the reaction was diluted with Et_2O (30 ml) and quenched with sat. $NaHCO_3$ (10 ml) and the mixture was extracted with Et_2O (3x30 ml). The combined org. layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 95:5) afforded 120 mg (0.285 mmol, 34%) product as a yellowish oil.

R_f (hexanes:ethylacetate 95:5, Vanillin) = 0.61.- $[\alpha]_D^{20}$ = + 61.4 (c = 0.560, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.00 (s, 9H, $SiMe_3$), 0.17 (s, 6H, $SiMe_2$), 0.57 (dd, *J* = 14.5, 9.6 Hz, 1H, 5-H), 0.83 (dd, *J* = 14.5, 5.9 Hz, 1H, 5-H), 1.13 (d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$), 1.47-1.52 (m, 2H, CH_2SiMe_3), 2.21 (dd, *J* = 16.2, 4.1 Hz, 1H, CH_2SiO^iPr), 2.49 (dd, *J* = 16.3, 6.7 Hz, 1H, CH_2SiO^iPr), 2.71-2.84 (m, 1H, 3-H), 3.69-3.77 (m, 1H, 4-H), 3.78 (s, 3H, OMe), 3.97 (sept, *J* = 6.0 Hz, 1H, $CH(CH_3)_2$), 4.35-4.50 (m, 2H, PMB), 5.07-5.14 (m, 1H, 2-H), 6.81-6.89 (m, 2H, PMB), 7.21-7.30 (m, 2H, PMB).- ^{13}C NMR (75 MHz): δ = -1.01 (+, $SiMe_3$), -0.29 (+, SiMe), -0.30 (+, SiMe), 21.94 (-, CH_2SiMe_3), 22.84 (-, $CH_2SiMe_2O^iPr$), 26.08 (+, 2xMe), 42.99 (-, 5-C), 47.40 (+, 3-C), 55.52 (+, OMe), 65.01 (+, ^{i}Pr), 70.97 (-, PMB), 88.57 (+, 4-C), 113.93 (+, 2x PMB), 126.30 (+, 2-C), 129.45 (+, 2x PMB), 131.28 (Cq, PMB), 137.95 (Cq, 1-C), 159.24 (Cq, PMB).- IR (neat): $\tilde{\nu}$ = 3035, 2955, 2898, 2870, 1729, 1641, 1612, 1586,

1512, 1464, 1402, 1380, 1365, 1348, 1300, 1248, 1172, 1124, 1086, 1027, 841, 758, 694 cm^{-1}.- MS (LSIMS, MeOH/Glycerin): *m/z* = 421.5 (35) [MH^+].- HRMS (LSIMS, MeOH/Glycerin): 421.2585 ($C_{23}H_{41}O_3Si_2$: calc. 421.2594 [MH^+]).

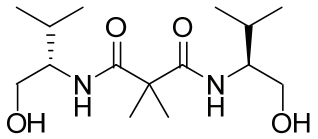


(3S,4S)-3-((dimethyl(*iso*-propoxy)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopentenone (155)

R_f (hexanes:ethylacetate 3:1) = 0.43.- ^{1}H NMR (300 MHz): δ = 0.1 (s, 6H, $SiMe_2$), 0.54 (dd, *J* = 14.7, 10.0 Hz, 1H, CH_2Si), 0.96 (dd, *J* = 14.8, 4.4 Hz, 1H, CH_2Si), 1.11 (d, *J* = 6.0 Hz, 6H, ^{i}Pr), 1.91 (dd, *J* = 18.4, 7.1 Hz, 1H, 2-H), 2.20 (dd, *J* = 18.4, 5.5 Hz, 1H, 2-H), 2.35-2.46 (m, 1H, 3-H), 2.46-2.65 (m, 2H, 5-H), 3.79 (s, 3H, OMe), 3.74-3.82 (m, 1H, 4-H), 3.95 (sept, *J* = 6.0 Hz, 1H, $CH(CH_3)_2$), 4.38-4.52 (m, 2H, PMB), 6.83-6.92 (m, 2H, PMB), 7.19-7.28 (m, 2H, PMB).- ^{13}C NMR (75 MHz): δ = -0.7 (+, SiMe), -0.6 (+, SiMe), 21.4 (-, CH_2Si), 25.9 (+, ^{i}Pr), 37.8 (+, 3-C), 43.6 (-, 2-C), 45.2 (-, 5-C), 55.4 (+, OMe), 65.1 (+, ^{i}Pr), 71.4 (-, PMB), 83.3 (+, 4-C), 124.0 (+, 2xPMB), 129.4 (+, 2xPMB), 130.3 (Cq, PMB), 159.4 (Cq, PMB), 216.6 (Cq, 1-C).

11.4 Synthesis of the cyclopropylcarbaldehyde

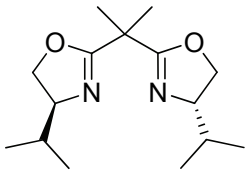
Representative procedure for the synthesis of bis(4-*iso*-propyloxazoline) (159)[181]



(-)-(*S*,*S*)-N,N'-Bis(1-hydroxymethyl-2-methylpropyl)-2,2-dimethyl-malonamide (165)[181]

An oven dried 250 ml, 3-necked round-bottom flask equipped with a stirring bar and two 50 ml pressure-equalizing addition funnels connected to a mineral oil bubbler is purged with nitrogen and charged with (*L*)-valinol (5.13 g, 0.050 mol, 2.0 eq.). The flask is immersed in an ice bath at 0 °C and NEt_3 (17.4 ml, 0.124 mol) is added dropwise via the first addition funnel. 2,2-Dimethylpropanedioyl dichloride (3.3 ml, 0.25 mol, 1.0 eq.) in dry CH_2Cl_2 (25 ml) is then added dropwise over 25 min. via the second addition funnel. The internal temperature increases from 0 °C to 10 °C during the addition. Subsequently, the ice bath is removed and the reaction mixture is allowed to warm to rt. Stirring is continued for 45 min, resulting in a colorless precipitate that is dissolved by addition of dry CH_2Cl_2 (120 ml). After addition of aqueous HCl (1N, 30 ml), the aqueous layer is separated and extracted with CH_2Cl_2 (3x15 ml). The combined organic layers are washed with sat. $NaHCO_3$ (30 ml) and brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude product as a pale yellow solid. Recrystallization of the crude product from ethyl acetate (40 ml) yields **165** (4.30 g, 14.2 mmol, 57%) as white crystals. The mother liquor is concentrated and the residue recrystallized from ethyl acetate (10 ml) to yield a second crop of **165** (1.60 g, 5.27 mmol, 21%); the process is repeated to yield a third crop of **165** (0.440 g, 1.45 mmol, 6%, total yield: 6.40 g, 21.1 mmol, 84%).

R_f (ethylacetate:methanol 95:5) = 0.25.-$[\alpha]_D^{20}$ = -6.0 (c = 0.50, CH_2Cl_2).- mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 0.96 (d, *J* = 6.8 Hz, 6 H), 1.50 (s, 6 H), 1.82 (oct, *J* = 6.8 Hz, 2 H), 2.66 (bs, 2 H), 3.52 (m, 2 H), 3.69–3.86 (m, 4 H), 6.41 (d, *J* = 8.6 Hz, 2 H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 19.6, 23.7, 29.1, 50.2, 57.1, 63.5, 174.5.

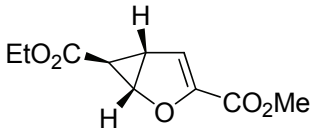


(-)-(*S,S*)-bis(4-*iso*-propyloxazoline) ((-)-159)[181]

An oven dried 500 ml, 2-necked round-bottom flask equipped with a stirring bar and a 50 ml, pressure-equalizing addition funnel connected to a mineral oil bubbler is purged with nitrogen and charged with (-)-(*S,S*)-*N,N'*-bis-(1-hydroxymethyl-2-methylpropyl)-2,2-dimethylmalon-amide (**165)** (5.5 g, 18.4 mmol), DMAP (0.204 g, 1.67 mmol) and dry CH_2Cl_2 (130 ml). The flask is immersed in a water bath at rt and NEt_3 (10.25 ml, 73.4 mmol) is added slowly via syringe. Subsequently, tosyl-chloride (7.10 g, 37 mmol, 2.0 eq.), dissolved in dry CH_2Cl_2 (15 ml), is added dropwise over 30 min. After completion of the addition the funnel is rinsed with dry CH_2Cl_2 (2.5 ml) and the reaction mixture is stirred for an additional 27 h at rt. The reaction mixture is treated with sat. NH_4Cl (70 ml) followed by water (40 ml). The aqueous layer is separated and extracted with CH_2Cl_2 (3x55 ml), and the combined organic layers are dried over $MgSO_4$. The organic solution is filtered and concentrated under vacuum. The oily residue is treated with hot pentane (40 ml), stirred for 5 min and the supernatant liquid is decanted. This procedure is repeated three times and the collected pentane layers are combined and concentrated under vacuum to yield (-)-**159** (4.05 g, 15.2 mmol, 83%) as a colorless oil, which rendered solid while stored at -35 °C under a N_2-atmosphere.
An analytically pure sample for characterization purposes was obtained by Kugelrohr-distillation (95-100 °C, 0.5 mm Hg) of the crude material.

R_f (dichloromethane/methanol 9:1) = 0.25.- $[\alpha]_D^{20}$ = -107.5 (c = 1.0, CH_2Cl_2).- ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (d, *J* = 6.8 Hz, 6 H), 0.91 (d, *J* = 6.8 Hz, 6 H), 1.51 (s, 6 H), 1.88-1.73 (m, 2 H), 4.06-3.93 (m, 4 H), 4.26-4.15 (m, 2 H).- ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.3, 18.5, 24.4, 32.2, 38.5, 69.9, 71.5, 168.7.

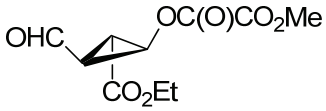
Representative procedure for the cyclopropanation of methyl-2-furoate (131):



(1*S*,2*S*,3*S*)-(-)-Oxalic acid 2-ethoxycarbonyl-3-formylcyclopropylester methyl ((-)-160)

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), (S,S)-*iso*-propyl-bis(oxazoline) (-)-**159** (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 **131** (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 ethyl diazoacetate (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 a 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 (-)-**160** (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 enantiomerical 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 (-)-**160** (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 (-)-**160** (0.609 g, 2.87 mmol, 3%, >99% *ee*, total yield: 7.51 g, 35.39 mol, 37% yield, 62% yield based on recovered starting material) as colorless crystals.

R_f(hexanes:ethyl acetate 5:1) = 0.29.- m.p. = 42 °C.- $[\alpha]_D^{20}$ = -272 (c = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (dd, *J* = 2.6, 1.1 Hz, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 2.87 (ddd, *J* = 5.3, 2.9, 2.7 Hz, 1 H), 3.81 (s, 3 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.98 (dd, *J* = 5.2, 1.1 Hz, 1 H), 6.40 (d, *J* = 3.0 Hz, 1 H,).- ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.20, 21.43, 31.97, 52.26, 61.08, 67.54, 116.19, 149.15, 159.54, 171.78.

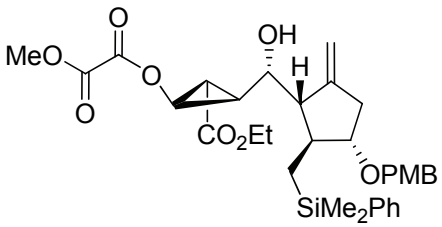


(1*S*,2*S*,3*S*)-(-)-oxalic acid 2-ethoxycarbonyl-3-formyl-cyclopropyl ester methyl ester ((-)-130)

A 100 ml flask was charged with a solution of (-)-**160** (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 (-)-**130** (3.124 g, 12.78 mmol) in 90% yield.

m.p. = 52 °C.- $[\alpha]_D^{20}$ = -37.6 (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 = 14.10, 26.36, 34.86, 54.00, 58.87, 62.03, 156.59, 156.86, 168.13, 192.13.

11.5 Formation of the anti-substituted lactone aldehyde

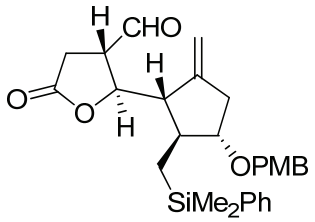


(1*R*,2*S*,3*R*)-2-((*R*)-((1´*S*,2´*S*,3´*S*)-2-((dimethyl(phenyl)silyl)methyl)-3-(*p*-methoxybenzyloxy)-5´-methylenecyclopentyl)(hydroxy)methyl)-3-(ethoxycarbonyl)cyclopropyl methyl oxalate (171)

Under a nitrogen atmosphere cyclopropylcarbaldehyde (+)-**130** (370 mg, 1.516 mmol, 0.95 eq.) was dissolved in abs. CH_2Cl_2 (10 ml) and cooled to -78 °C. $BF_3{\cdot}OEt_2$ (249 mg, 216 µl, 1.10 eq.) was added via a syringe and after stirring for 30 min. Allylsilane **152** (700 mg, 1.595 mmol, 1.0 eq.) dissolved in abs. CH_2Cl_2 (5 ml) was added slowly resulting in a color change to red brown. After stirring for 16 h at -78 °C, sat. $NaHCO_3$ (2 ml) was added and the mixture was allowed to warm to rt. The layers were separated and the aqueous layer was again extacted with CH_2Cl_2 (2x2 ml). The combined org. layers were washed with brine (2 ml), H_2O (2 ml), dried (Na_2SO_4) and concentrated in vacuo to yield 928 mg (1.519 mmol, 95%) product as a yellowish oil containing only a single stereoisomer which was used without further purification.

$[\alpha]_D^{20}$ = + 14.9 (c = 1.06, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 0.30 (s, 3H, $SiCH_3$), 0.32 (s, 3H, $SiCH_3$), 0.85 (d, *J* = 7.4 Hz, 2H, CH_2Si), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.75-1.86 (m, 1H, 2-H), 2.16 (dd, *J* = 5.9, 2.6 Hz, 1H, 3-H), 2.39-2.44 (m, 1H, 1´-H), 2.49-2.59 (m, 3H, 2´-H, 4´-H), 3.55-3.59 (m, 1H, 3´-H), 3.69 (dd, *J* = 8.8, 3.3 Hz, 1H, CHOH), 3.81 (s, 3H, PMB), 3.89 (s, 3H, CO_2Me), 4.09- 4.19 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.22-4.35 (m, 2H, PMB), 4.58 (dd, *J* = 7.3, 2.6 Hz, 1H, 1-H), 5.00-5.12 (m, 2H, C=CH_2), 6.83-6.91 (m, 2H, PMB), 7.13-7.19 (m, 2H, PMB), 7.33-7.39 (m, 3H, Ph), 7.46-7.52 (m, 2H, Ph).- ^{13}C NMR (150 MHz) δ = -2.4 (+, $SiCH_3$), -2.3 (+, $SiCH_3$), 14.1 (+, CH_2CH_3), 22. 5 (-, $SiCH_2$), 28.1 (+, 3-C), 31.1 (+, 2-C), 37.4 (-, 4´-C), 41.1 (+, 2´-C), 53.6 (+, PMB), 55.3 (+, OMe), 58.4 (+, 1-C), 58.9 (+, 1´-C), 61.12 (-, CH_2CH_3), 69.8 (-, PMB), 71.3 (+, C-OH), 84.5 (+, 3´-C), 109.1 (-, C=CH_2), 113.9 (+, 2xPMB), 127.9 (+, 2x Ph), 129.1 (+, Ph), 129.4 (Cq, PMB), 129.4 (+, 2xPMB), 133.5 (+, 2x Ph), 138.8 (Cq, SiPh), 150.1 (Cq, C=CH_2), 157.0 (Cq, CO), 157.3 (Cq, CO), 159.3 (Cq, PMB), 170.7 (Cq, CO_2Et).- IR (neat): $\tilde{\nu}$ = 3392, 3069, 2978, 2955, 2905, 1779, 1753, 1728,

1612, 1586, 1514, 1443, 1427, 1370, 1305, 1249, 1199, 1159, 1112, 1035, 835, 734, 702 cm^{-1}.- MS (FAB): *m/z* = 611.2 [M+H^+], 703.3 8 [MH^++Glyc].- HRMS (FAB): 611.2662 ($C_{33}H_{43}O_9Si$: calc. 611.2676 [MH^+]).

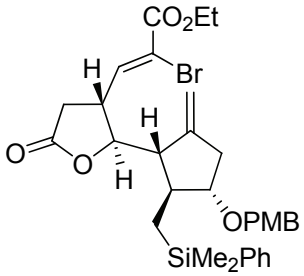


(2*R*,3*S*)-2-((1′*S*,2′*S*,3′*S*)-3′-(*p*-methoxybenzyloxy)-2′-((dimethyl(phenyl)silyl)methyl)-5′-methylenecyclopentyl)-tetrahydro-5-oxofuran-3-carbaldehyde (175)

The crude cyclopropylalcohol **171** (503 mg, 0.824 mmol, 1.0 eq.) was dissolved in MeOH (20 ml) and cooled to 0 °C. $Ba(OH)_2 \cdot 8H_2O$ (143 mg, 0.453 mmol, 0.55 eq.) was added over a period of 1 h and the mixture was stirred for additional 1 h. CH_2Cl_2 (20 ml) and H_2O (20 ml) were added and the layers separated. The aqueous layer was again extracted with CH_2Cl_2 (4x20 ml). The combined org. layers were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on flash silica gel (hexanes:ethylacetate 2:1) afforded 283 mg product (0.591 mmol, 72%) as a single diastereomer as a colorless oil.

R_f (hexanes:ethylacetate 2:1, Mostain) = 0.26.- $[\alpha]_D^{20}$ = - 1.9 (c = 0.54, $CHCl_3$).- ^{1}H NMR (400 MHz): δ = 0.31 (s, 3H, SiMe), 0.35 (s, 3H, SiMe), 0.74-0.78 (m, 2H, CH_2Si), 2.25-2.30 (m, 1H, 1′-H), 2.34-2.41 (m, 1H, 4′-H), 2.49 (dd, *J* = 18, 10 Hz, 1H, 4-H), 2.45-2.50 (m, 1H, 2′-H), 2.67-2.75 (m, 1H, 4′-H), 2.81 (dd, *J* = 18, 7 Hz, 1H, 4-H), 3.15-3.22 (m, 1H, 3-H), 3.58-3.63 (m, 1H, 3′-H), 3.80 (s, 3H, OMe), 4.27 (dd, *J* = 24, 11 Hz, 2 H, PMB), 4.86 (dd, *J* = 8, 6 Hz, 1H, 2-H), 4.92 (m, 1H, C=CH_2), 5.50 (m, 1H, C=CH_2), 6.83-6.88 (m, 2H, PMB), 7.13-7.18 (m, 2H, PMB), 7.34-7.38 (m, 3H, Ph), 7.47-7.53 (m, 2H, Ph), 9.42 (d, *J* = 1 Hz, 1H, CHO).- ^{13}C NMR (75.5 MHz): δ = -2.8 (+, SiMe), -2.2 (+, SiMe), 20.9 (-, CH_2Si), 28.8 (-, 4-C), 38.5 (-, 4′-C) , 42.4 (+, 2′-C), 49.9 (+, 3-C), 55.3 (+, OMe), 56.5 (+, 1′-C), 70.4 (-, PMB), 80.3 (+, 2-C), 86.4 (+, 3′-C) , 112.7 (-, C=CH_2), 113.8 (+, 2xPMB), 127.9 (+, 2xPh), 129.1 (+, Ph), 129.3 (+, 2xPMB), 130.2 (Cq, PMB), 133.7 (+, 2xPh), 139.1 (Cq, Ph), 147.8 (Cq, PMB), 159.2 (Cq, 5′-C), 174.3 (Cq, 5-C), 197.8 (+, CHO).- IR (neat): $\tilde{\nu}$ = 2953, 2901, 1779, 1729, 1653, 1613, 1514, 1462, 1421, 1353, 1302, 1249, 1174, 1109, 1067, 1034, 906, 831, 731 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 135.0 (43.36) [$SiMe_2Ph^+$], 343.1 (1.12) [M-$SiMe_2Ph$], 478.1 (0.58) [M^+].- HRMS (EI): 478.2163 ($C_{28}H_{34}O_5Si$: calc. 478.2176 [M^+]).

11.6 Radical cyclization

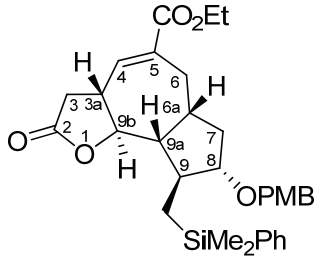


(*Z*)-ethyl 2-bromo-3-((2′*S*,3′*R*)-2′-((1′′*S*,2′′*S*,3′′*S*)-2′′-((dimethyl(phenyl)silyl)methyl)-3′′-(*p*-methoxybenzyloxy)-5′′-methylenecyclopentyl)-5′-oxo-tetrahydrofuran-3′-yl) acrylate (183)

Under a nitrogen atmosphere NaH (60% suspension, 18 mg, 0.439 mmol, 1.05 eq.) was dissolved in dry THF (2 ml) and cooled to 0 °C. Triethylposphonoacetate (98 mg, 88 µl, 0.439 mmol, 1.05 eq.) was added dropwise and the clear solution was stirred for 20 min at 0 °C. Bromine (74 mg, 24 µl, 0.466 mmol, 1.11 eq.) was added dropwise and the reaction mixture was stirred for 1 h at 0 °C. NaH (60% suspension, 18 mg, 0.439 mmol, 1.05 eq.) was added slowly to the reaction mixture and stirring was continued for 20 min. Aldehyde **175** (200 mg, 0.418 mmol, 1.00 eq.) was dissolved in dry THF (2 ml) and added slowly to the bromophosphonate. The mixture was allowed to warm to rt and stirred for further 60 min and the reaction was quenched with H_2O (3 mL). The mixture was extracted with CH_2Cl_2 (3x10 ml), the combined organic layers were washed with water (2 ml), dried over Na_2SO_4, filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 190 mg (0.303 mg, 72%, *E/Z* = 17:83) product as a colorless oil.

R_f (hexanes:ethylacetate 2:1) = 0.44.- ^{1}H NMR (600 MHz): δ = 0.31 (s, 3H, SiMe), 0.35 (s, 3H, SiMe), 0.74-0.75 (m, 2H, $SiCH_2$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.26 (dd, *J* = 17.8, 7.7 Hz, 1H, 4′-H), 2.20-2.26 (m, 1H, 1′′-H), 2.34-2.41 (m, 1H, 4′′-H), 2.49-2.55 (m, 1H, 2′′-H), 2.65-2.69 (m, 1H, 4′′-H),2.72 (dd, *J* = 17.8, 9.2 Hz, 1H, 4′-H), 3.33-3.39 (m, 1H, 3′-H), 3.56-3.61 (m, 1H, 3′′-H), 3.81 (s, 3H, OMe), 4.23-4.33 (m, 4H, CH_2CH_3, PMB), 4.60 (dd, *J* = 8.7, 6.3 Hz, 1H, 2′-H), 4.91-4.95 (m, 1H, C=CH_2), 5.00-5.04 (m, 1H, C=CH_2), 6.84-6.89 (m, 2H, PMB), 7.15 (d, *J* = 8.9 Hz, 1H, 3-H), 7.17-7.20 (m, 2H, PMB), 7.35-7.40 (m, 3H, Ph), 7.49-7.53 (m, 2H, Ph); *E*-isomer: 1.33 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 2.28 (dd, *J* = 17.5, 8.3 Hz, 1H, 4′-H), 2.75 (dd, *J* = 17.9, 9.2 Hz, 1H, 4′-H), 3.82 (s, 3H, OMe), 4.47 (dd, *J* = 8.6, 6.6 Hz, 1H, 2′-H), 6.44 (d, *J* = 9.7 Hz, 1H, 3-H).- ^{13}C NMR (150 MHz): δ = -2.76 (+, SiMe), -2.24 (+, SiMe), 14.12 (+, CH_2CH_3), 20.57 (-, SiCH2), 33.65 (-, 4′-C), 38.46 (-, 4′′-C), 42.02 (+, 2′′-C), 42.06 (+, 3′-C), 55.27 (+, OMe), 56.16 (+, 1′′-H), 62.81 (-, CH_2CH_3), 70.39 (-,

PMB), 84.71 (+, 2´-C), 86.25 (+, 3´´-C), 112.80 (-, C=CH2), 113.77 (+, 2xPMB), 117.78 (Cq, 5´´-C), 127.88 (+, 2x Ph), 129.03 (+, Ph), 129.23 (+, 2x PMB), 130.44 (Cq, CO_2Et), 133.64 (+, 2x Ph), 139.33 (Cq, SiC), 143.40 (+, 3-C), 146.68 (Cq, 2-C), 159.12 (Cq, PMB), 161.75 (Cq, PMB), 174.44 (Cq, CO); *E*-isomer: 34.66, 40.99, 42.14, 56.27, 62.51, 85.23, 112.67.- IR (neat): $\tilde{\nu}$ = 3069, 2982, 2954, 2904, 2872, 1783, 1729, 1652, 1612, 1586, 1514, 1464, 1425, 1369, 1300, 1250, 1198, 1172, 1112, 1038, 997, 898, 833, 728, 702 cm^{-1}.- MS (LSI): *m/z* = 627 [$M+H^+$], 629 [$M+H^+$], 719 [MH^++Glyc.], 721 [MH^++Glyc.].- HRMS (FAB): 627.17487 ($C_{32}H_{40}BrO_6Si$: calc. 627.1749 [$M+H^+$]).

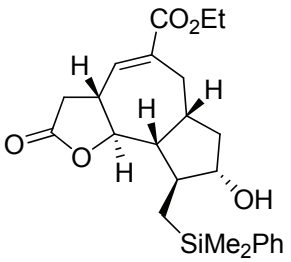


(3a*R*, 6a*R*,8*S*,9*S*,9a*R*,9b*S*,*E*)-ethyl 9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyl-oxy)-2-oxo-2,3,3a,6,6a,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-5-carboxylate (184)

Under a nitrogen atmosphere bromocompound **183** (158 mg, 0.252 mmol, 1.0 eq.) and AIBN (4 mg, 0.025 mmol, 0.1 eq.) were dissolved in abs. benzene (5 ml) and heated to reflux. Via a syringe pump Bu_3SnH (110 mg, 101 µl, 0.378 mmol, 1.5 eq.) and AIBN (4 mg, 0.025 mmol, 0.1 eq.) in abs. benzene (4 ml) were added slowly over a period of 1 h. After refluxing the reaction mixture for 1 h the reaction mixture was allowed to cool to rt and the solvent was removed in vacuo. Chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 123 mg (0.224 mmol, 89%) product as a colorless oil (*dr* = 87:13).

R_f (hexanes:ethylacetate 2:1) = 0.46.- ^{1}H NMR (400 MHz): δ = 0.33 (s, 3H, SiMe), 0.34 (s, 3H, SiMe), 0.85 (dd, *J* = 14.6, 8.6 Hz, 1H, CH_2Si), 1.06 (dd, *J* = 14.9, 6.3 Hz, 1H, CH_2Si), 1.28 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.46-1.55 (m, 1H, 7-H), 1.83-1.91 (m, 1H, 9a-H), 2.01-2.10 (m, 1H, 7-H), 2.33-2.39 (m, 1H, 9-H), 2.41-2.47 (m, 1H, 6a-H), 2.48 (dd, *J* = 16.9, 12.8 Hz, 1H, 3-H), 2.49-2.57 (m, 1H, 6-H), 2.76 (dd, *J* = 16.9, 8.1 Hz, 3-H), 2.78-2.88 (m, 1H, 6-H), 3.01-3.13 (m, 1H, 3a-H), 3.52-3.59 (m, 1H, 8-H), 3.80 (s, 3H, OMe), 4.03-4.22 (m, 4H, CH_2CH_3, PMB), 4.22-4.29 (m, 1H, 9b-H), 6.81-6.90 (m, 3H, PMB, 4-H), 7.12-7.19 (m, 1H, PMB), 7.29-7.37 (m, 3H, Ph), 7.49-7.59 (m, 2H, Ph).- ^{13}C NMR (100 MHz): δ = -2.59 (+, SiMe), -2.28 (+, SiMe), 14.23 (+, CH_2CH_3), 21.74 (-, CH_2Si), 29.39 (-, 6-C), 35.43 (-, 3-C), 36.36 (-, 7-C), 37.41 (+, 6a-C), 41.48 (+, 3a-C), 46.08 (+, 9-C), 55.29 (+, OMe), 56.03 (+, 9a-

C), 61.05 (-, CH_2CH_3), 70.57 (-, PMB), 83.73 (+, 9b-C), 87.90 (+, 8-C), 113.73 (+, 2xPMB), 127.74 (+, 2xPh), 128.86 (+, 1xPh), 129.16 (+, 2xPMB), 130.66 (Cq, CO_2Et), 133.77 (+, 2xPh), 135.28 (Cq, PMB), 138.04 (+, 4-C), 139.51 (Cq, SiC), 159.06 (Cq, PMB), 166.94 (Cq, 5-C), 174.98 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3066, 3045, 2953, 2906, 1784, 1708, 1644, 1612, 1586, 1513, 1443, 1425, 1392, 1361, 1353, 1300, 1248, 1205, 1173, 1113, 1034, 993, 925, 897, 829, 790, 730, 701 cm^{-1}.- MS (EI, 70eV): *m/z* = 533.2 (1.35) [M-CH_3^+], 547.2 (0.94) [M-H^+], 548.2 [M+].- HRMS (PI-LSIMS, MeOH/Glycerin): 549.26710 ($C_{32}H_{41}O_6Si$: calc. 549.2672 [M+H^+]).



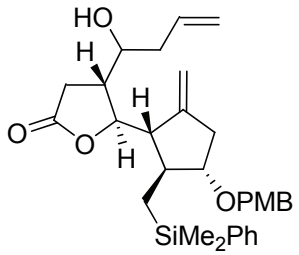
(3a*R*,6a*R*,8*S*,9*S*,9a*R*,9b*S*,*E*)-ethyl-9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-2-oxo-2,3,3a, 6,6a,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-5-carboxylate (185)

Compound **184** (104 mg, 0.19 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (8 ml) and pH 7 phosphate buffer (3 ml). At rt DDQ (56 mg, 0.25 mmol, 1.3 eq.) was added in small portions and the solution was stirred for 4 h. H_2O (5 ml) and CH_2Cl_2 (10 ml) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 10 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 72 mg (0.17 mmol, 89%) product as a colorless oil (*dr* = 87:13).

R_f (hexanes:ethylacetate 3:1) = 0.13.- ^{1}H NMR (600 MHz): δ = 0.35 (s, 3H, SiMe), 0.39 (s, 3H, SiMe), 0.86 (dd, *J* = 15.1, 10.0 Hz, 1H, CH_2Si), 1.21 (dd, *J* = 14.9, 4.4 Hz, 1H, CH_2Si), 1.29 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.32-1.37 (m, 1H, 7-H), 1.87-1.94 (m, 1H, 9a-H), 2.02-2.09 (m, 1H, 9-H), 2.15-2.23 (m, 1H, 7-H), 2.38-2.44 (m, 1H, 6a-H), 2.48 (dd, *J* = 17.0, 13.1 Hz, 1H, 3-H), 2.55-2.62 (m, 1H, 6-H), 2.67-2.75 (m, 1H, 6-H), 2.79 (dd, *J* = 16.9, 8.3 Hz, 1H, 3-H), 3.10-3.18 (m, 1H, 3a-H), 3.68-3.74 (m, 1H, 8-H), 4.19 (q, *J* = 7.1 Hz, CH_2CH_3), 4.28-4.33 (m, 1H, 9a-H), 6.84-6.87 (m, 1H, 4-H), 7.36-7.40 (m, 3H, Ph), 7.57-7.61 (m, 2H, Ph).- ^{13}C NMR (150 MHz): δ =-2.88 (+, $SiCH_3$), -1.91 (+, $SiCH_3$), 14.22 (+, CH_2CH_3), 20.55 (-, CH_2Si), 30.65 (-, 6-C), 35.18 (-, 3-C), 37.29 (+, 6a-C), 40.16 (-, 7-C), 41.39 (+, 3a-C), 49.17 (+, 9-C), 55.91 (+, 9a-C), 61.09 (-, CH_2CH_3), 80.35 (+, 8-C), 84.71 (+, 9b-C), 128.04 (+, 2xPh), 129.20 (+, Ph), 133.68 (+, 2x Ph), 135.11 (Cq, CO_2Et), 137.39 (+, 4-C), 139.31 (Cq,

Si-C), 166.96 (Cq, 5-C), 174.96 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3519, 3068, 3048, 2979, 2953, 2907, 2361, 2252, 1789, 1760, 1713, 1644, 1444, 1426, 1366, 1253, 1208, 1112, 1053, 1014, 911, 837, 729, 701 cm^{-1}.- MS (FAB): *m/z* = 429.2 [MH^+], 521.2 [MH^++Glyc], 857.3 [2M+H^+].- HRMS (FAB): 429.20869 ($C_{24}H_{33}O_5Si$: calc. 429.2097 [MH^+]).

11.7 Precursors for ring closing metathesis

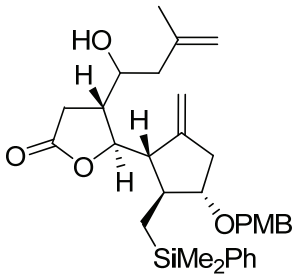


(4*R*,5*R*)-5-((1′*S*,2′*S*,3′*S*)-2′-((dimethyl(phenyl)silyl)methyl)-3′-(*p*-methoxybenzyloxy)-5′-methylenecyclopentyl)-4-(1′′*R*/*S*-hydroxybut-3′′-enyl)dihydrofuran-2(3H)-one (195)

Aldehyde **175** (200 mg, 0.418 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (5 ml) under a N_2-atmosphere and cooled to -78 °C. Allyltrimethylsilane (80 µl, 62 mg, 1.3 eq.) was added and the mixture stirred for 30 min. $BF_3 \cdot Et_2O$ (60 µl, 68 mg, 1.15 eq.) was added and the mixture was stirred at -78 °C for 24 h. The reaction was quenched by adding $NaHCO_3$ (1 ml), the mixture was diluted with CH_2Cl_2 (10 ml) and allowed to warm to rt. The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (2x6 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 159 mg (0.305 mmol, 73%) product as a colorless oil (*dr* = 50:50).

R_f (hexanes:ethylacetate 2:1, Mostain) = 0.32.- ^{1}H NMR (300 MHz): δ = 0.29 (s, 3H, SiMe, diast: 0.31), 0.34 (s, 3H, SiMe, diast: 0.35), 0.71-0.85 (m, 2H, $SiCH_2$), 1.70-2.60 (m, 8H, 3-H, 4-H, 1′-H, 2′-H, 4′-H, 2′′-H), 2.71 (dd, *J* = 17.3, 6.3 Hz, 1H, 3-H), 3.37-3.48 (m, 1H, 1′′-H), 3.53-3.63 (m, 1H, 3′-H), 3.79 (s, 3H, OMe), 4.21-4.38 (m, 2H, PMB), 4.71 (dd, *J* = 7.8, 2.3 Hz, 1H, 5-H, diast: 4.59, dd, *J* = 8.2, 3.6 Hz), 4.82-4.89 (m, 1H, =CH_2), 4.99-5.04 (m, 1H, =CH_2), 5.04-5.16 (m, 2H, =CH_2), 5.55-5.75 (m, 1H, 3′′-H), 6.81-6.88 (m, 2H, PMB), 7.15-7.23 (m, 2H, PMB), 7.30-7.39 (m, 3H, Ph), 7.45-7.55 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.8 (+, SiMe, diast: -2.6), -2.2 (+, SiMe, diast: -2.1), 20.7 (-, CH_2Si, diast: 21.1), 28.7 (-, 4′-C, diast: 31.5), 38.8 (-, 3-C), 38.9 (-, 2′′-C, diast: 39.7), 41.7 (+, 4-C, diast: 41.4), 42.1 (+, 2′-C, diast: 41.9), 55.2 (+, OMe), 56.1 (+, 1′-C, diast: 56.0), 70.2 (+, 1′′-C, diast: 72.0), 70.4

(-, PMB, diast: 70.3), 83.3 (+, 5-C, diast: 82.9), 86.5 (+, 3´-C, diast: 86.4), 112.0 (-, $=CH_2$, diast: 111.8), 113.7 (+, 2xPMB), 119.0 (-, $=CH_2$, diast: 118.9), 127.8 (+, 2xPh), 128.8 (+, Ph, diast: 128.9), 129.4 (+, 2xPMB, diast: 129.3), 130.4 (Cq, PMB, diast: 130.2), 133.6 (+, 2xPh, diast: 133.5), 133.8 (+, 3´´-C, diast: 133.7), 139.4 (Cq, Ph, diast: 139.3), 148.5 (Cq, PMB, diast: 147.8), 159.0 (Cq, 5´-C), 176.8 (Cq, 2-C, diast: 176.7).- IR (neat): $\tilde{\nu}$ = 3460, 3009, 2954, 2903, 1770, 1642, 1612, 1512, 1423, 1353, 1300, 1249, 1179, 917, 831, 755, 702 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 137.1 (22.8), 154.1 (82.3), 538.2 (100) $[M+NH_4^+]$.- HRMS (EI, 70 eV): 520.2635 ($C_{31}H_{40}O_5Si$: calc. 520.2645 $[M^+]$).

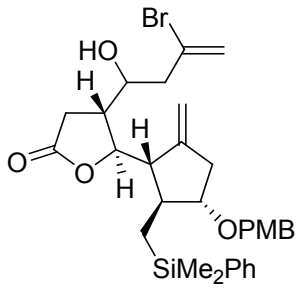


(4*R*,5*R*)-5-((1´*S*,2´*S*,3´*S*)-3´-(*p*-methoxybenzyloxy)-2´-((dimethyl(phenyl)silyl)methyl)-5´-methylenecyclopentyl)-dihydro-4-(1´´*R*/*S*-hydroxy-3´´-methylbut-3´´-enyl)furan-2(3H)-one (196)

Aldehyde **175** (395 mg, 0.825 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (8 ml) under a N_2-atmosphere and cooled to -78 °C. Trimethyl(2-methylallyl)silane (300 µl, 220 mg, 2.0 eq.) was added and the mixture stirred for 30 min. $BF_3{\cdot}Et_2O$ (133 µl, 150 mg, 1.06 eq.) was added and the mixture was stirred at -78 °C for 24 h. The reaction was quenched by adding $NaHCO_3$ (1 ml), the layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 316 mg (591 mmol, 72%) product as an inseparable 80:20 mixture of both diastereomers as a colorless oil.

R_f (hexanes:ethylacetate 3:1, Mostain) = 0.14.- ^{1}H NMR (400 MHz): δ = 0.31 (s, 3H, SiMe, diast: 0.29), 0.34 (s, 3H, SiMe, diast: 0.35), 0.72-0.84 (m, 2H, $SiCH_2$), 1.63 (s, 3H, CH_3, diast: 1.66), 1.69-1.79 (bs, 1H, OH), 1.89-2.02 (m, 2H, 2´´-H), 2.17-2.23 (m, 1H, 1´-H), 2.26-2.42 (m, 3H, 3-H, 4´-H, 4-H), 2.47-2.54 (m, 1H, 2´-H), 2.54-2.63 (m, 1H, 4´-H), 2.71 (dd, *J* = 17.0, 6.3 Hz, 1H, 3-H), 3.51-3.63 (m, 2H, 1´´-H, 3´-H), 3.79 (s, 3H, OMe, diast: 3.80), 4.21-4.38 (m, 2H, PMB), 4.63 (dd, *J* = 8.4, 3.7 Hz, 1H, 5-H), 4.70-4.75 (m, 1H, $=CH_2$), 4.84-4.89 (m, 2H, $=CH_2$), 5.00-5.05 (m, 1H, $=CH_2$), 6.81-6.88 (m, 2H, PMB), 7.15-7.20 (m, 2H, PMB), 7.33-7.38 (m, 3H, Ph), 7.48-7.53 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.5 (+, SiMe), -2.0

(+, SiMe), 20.9 (-, CH_2Si), 22.3 (+, CH_3), 28.9 (-, 4′-C), 39.1 (-, 3-C), 41.9 (+, 4-C), 42.5 (+, 2′-C), 43.9 (-, 2′′-C), 55.4 (+, OMe), 56.4 (+, 1′-C), 68.4 (+, 1′′-C), 70.5 (-, PMB), 83.4 (+, 5-C), 86.6 (+, 3′-C), 112.1 (-, $=CH_2$), 113.9 (+, 2xPMB), 114.4 (-, $=CH_2$), 128.0 (+, 2xPh), 129.1 (+, Ph), 129.4 (+, 2xPMB), 130.6 (Cq, PMB), 133.8 (+, 2xPh), 139.5 (Cq, Ph), 141.7 (Cq, 3′′-C), 148.1 (Cq, PMB), 159.2 (Cq, 5′-C), 177.0 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3468, 3070, 2951, 2903, 1774, 1648, 1613, 1586, 1514, 1462, 1425, 1373, 1354, 1302, 1248, 1192, 1174, 1112, 1090, 1069, 1036, 894, 833, 727, 702 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 121.1 (13.3), 137.2 (17.6), 154.1 (64.9), 552.3 (100) [$M+NH_4^+$].- HRMS (EI, 70 eV): 534.2786 ($C_{32}H_{42}O_5Si$: calc. 534.2802 [M^+]).

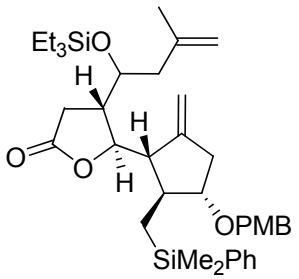


(4*R*,5*R*)-4-(3′-bromo-1′-hydroxybut-3-enyl)-5-((1′′S,2′′S,3′′S)-2′′-((dimethyl(phenyl) silyl)methyl)-3′′-(*p*-methoxybenzyloxy)-5′′-methylenecyclopentyl)-dihydrofuran-2(3H)-one (197)

Under an Ar-atmosphere aldehyde **175** (294 mg, 0.614 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) and cooled to -78 °C. 2-Bromo-trimethylallylsilane[254] (158 mg, 141 µl, 0.737 mmol, 1.2 eq.) was added and the mixture was stirred for 15 min. $BF_3{\cdot}OEt_2$ (100 mg, 87 µl, 0.706 mmol, 1.15 eq.) was added dropwise and the mixture was stirred for 10 h at -78 °C. The reaction mixture was quenched with sat. $NaHCO_3$ (0.5 ml) and allowed to warm to rt. CH_2Cl_2 (10 ml) was added and the layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (3 ml) and the combined organic layers were washed with brine (3 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 130 mg (0.217 mmol, 35%, *dr* = 78:22) product as a colorless oil, along with 120 mg (0.250 mmol, 41%) recovered starting material **175**.

R_f (hexanes:ethylacetate 2:1, Mostain) = 0.34.- ^{1}H NMR (500 MHz): δ = 0.31 (s, 3H, SiMe, diast: 0.29), 0.34 (s, 3H, SiMe, diast: 0.35), 0.74-0.79 (m, 2H, $SiCH_2$), 2.19-2.25 (m, 1H, 1′′-H), 2.30-2.36 (m, 4H, 4-H, 2′-H, 4′′-H), 2.36-2.39 (m, 1H, 3-H), 2.47-2.53 (m, 1H, 2′′-H), 2.55-2.60 (m, 1H, 4′′-H), 2.71 (dd, *J* = 17.3, 6.3 Hz, 1H, 3-H), 3.57-3.62 (m, 1H, 3′′-H), 3.79 (s, 3H, OMe), 3.77-3.82 (m, 1H, 1′-H),4.21-4.37 (m, 2H, PMB), 4.60 (dd, *J* = 8.4, 4.3 Hz,

1H, 5-H diast: 4.73), 4.87-4.91 (m, 1H, C=CH2), 5.02-5.06 (m, 1H, C=CH_2), 5.45-5.64 (m, 2H, CBr=CH2), 6.82-6.87 (m, 2H, PMB), 7.16-7.21 (m, 2H, PMB), 7.33-7.38 (m, 3H, Ph), 7.48-7.53 (m, 2H, Ph).- ^{13}C NMR (125.8 MHz): δ= -2.41 (+, SiMe), -1.98 (+, SiMe), 20.93 (-, $SiCH_2$), 28.85 (-, 4´´-C), 39.01 (-, 3-C), 42.23 (+, 4-C, 2´´-C), 47.38 (-, 2´-C), 55.49 (+, OMe), 56.54 (+, 1´´-C), 68.85 (+, 1´-C), 70.60 (-, PMB), 83.34 (+, 5-C), 86.73 (+, 3´´-C), 112.52 (-, C=CH_2), 113.99 (+, 2x PMB), 120.53 (-, CBr=CH_2), 128.12 (+, 2x Ph), 129.24 (+, Ph), 129.57 (+, 2xPMB), 129.69 (+, Ph), 130.55 (Cq, Ph), 133.92 (+, 2xPh), 133.85 (Cq, 3´-C), 139.54 (Cq, PMB), 147.96 (Cq, 5´´-C), 159.33 (Cq, PMB), 176.70 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3458, 3068, 2999, 2952, 2902, 2871, 2837, 2358, 1770, 1731, 1629, 1612, 1514, 1463, 1427, 1415, 1396, 1353, 1301, 1247, 1193, 1174, 1112, 1089, 1066, 1035, 987, 896, 833, 730, 702 cm^{-1}.- MS (ES+): *m/z* = 599.2 ($M+H^+$), 616.2 ($M+NH_4^+$), 617.2 ($M+NH_4^+$), 618.2 ($M+NH_4^+$).- HRMS (EI): 616.2099 ($C_{31}H_{43}O_5SiBrN$: calc. 616.2094 [$M+NH_4^+$]).

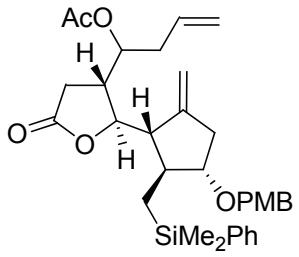


(4*S*,5*R*)-5-((1´*S*,2´*S*,3´*S*)-3´-(*p*-methoxybenzyloxy)-2´-((dimethyl(phenyl)silyl)methyl)-5´-methylenecyclopentyl)-dihydro-4-(1´´*R/S*-triethylsilanyloxy-3´´-methylbut-3´´-enyl) furan-2(3H)-one (198a)

Under a N_2-atmosphere alcohol **196** (353 mg, 0.66 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (3 ml) and abs. NEt_3 (134 mg, 183 µl, 1.32 mmol, 2.0 eq.) was added. Via a syringe TESCl (149 mg, 0.99 mmol, 1.5 eq.) was added dropwise and the solution was stirred for 48 h at rt. The solution was diluted with 50 ml CH_2Cl_2 and the reaction mixture was extracted with sat. $NaHCO_3$ (8 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 9:1) afforded 293 mg (0.452 mmol, 68%) product as a colorless oil in an inseparable mixture of 80:20.

R_f (hexanes:ethylacetate 6:1, Mostain) = 0.47.- ^{1}H NMR (300 MHz): δ = 0.28 (s, 3H, SiMe, diast: 0.27), 0.31 (s, 3H, SiMe, diast: 0.34), 0.52 (q, *J* = 8.1 Hz, 6H, 3x $SiCH_2CH_3$, diast: 0.54),0.68-0.79 (m, 2H, CH_2SiMe_2Ph), 0.87 (t, *J* = 7.8 Hz, 9H, $SiCH_2CH_3$, diast: 0.89), 1.63 (s, 3H, CH_3, diast: 1.58), 1.94-2.41 (m, 6H, 2x 2´´-H, 1´-H, 4´-H, 3´-H, 3-H), 2.45-2.76 (m, 2H, 2´-H, 4´-H), 2.62 (dd, *J* = 16.7, 4.1 Hz, 1H, 3-H), 3.50-3.58 (m, 1H, 4-H, diast: 3.58-

3.63), 3.81-3.87 (m, 1H, 1´´-H, diast: 3.68-3.76), 3.79 (s, 3H, OMe, diast: 3.79),4.23-4.28 (m, 2H, PMB), 4.51 (dd, *J* = 8.8, 4.1 Hz, 1H, 5-H), 4.62-4.66 (m, 1H, $=CH_2$, diast: 4.95-4.61), 4.74-4.77 (m, 1H, $C=CH_2$, diast: 4.71-4.73), 4.77-4.81 (m, 1H, $=CH_2$), 4.95-5.00 (m, 1H, $=CH_2$), 6.79-6.88 (m, 2H, PMB), 7.13-7.21 (m, 2H, PMB), 7.29-7.37 (m, 3H, Ph), 7.43-7.51 (m, 2H, Ph).- ^{13}C NMR (75 MHz): δ = -2.4 (+, SiMe), -2.2 (+, SiMe), 5.2 (-, $SiCH_2CH_3$), 6.9 (+, $SiCH_2CH_3$), 21.0 (-, CH_2Si, diast: 20.7), 22.8 (+, CH_3, diast: 23.1), 27.6 (-, 4´-C, diast: 31.2), 39.1 (-, 3-C), 41.4 (+ , 4-C, diast: 41.2), 41.8 (+, 2´-C), 44.9 (-, 2´´-C), 55.2 (+, OMe), 57.3 (+, 1´-C), 70.3 (-, PMB), 71.1 (+, 1´´-C), 83.8 (+, 5-C), 86.6 (+, 3´-C), 111.7 (-, $=CH_2$), 113.6 (+, 2xPMB), 113.7 (-,$=CH_2$), 127.8 (+, 2x Ph), 128.8 (+, Ph), 129.2 (+, 2x PMB), 130.7 (Cq, PMB), 133.6 (+, 2x Ph), 139.6 (Cq, Ph), 141. 5 (Cq, 3´´-C), 148.0 (Cq, PMB), (158.9 (Cq, 5´-C), 177.2 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3070, 2998, 2954, 2910, 2876, 1776, 1648, 1613, 1587, 1514, 1458, 1423, 1414, 1375, 1352, 1302, 1248, 1186, 1173, 1110, 1066, 1036, 1008, 962, 893, 833, 746, 728, 701 cm^{-1}.- MS (ES-MS): *m/z* (%)= 666.6 (100) $[M+NH_4^+]$, 707.7 (10) $[M+NH_4^+ + CH_3CN]$.- HRMS (EI, 70 eV): 648.3667 ($C_{38}H_{56}O_5Si_2$: calc. 648.3666 $[M^+]$).

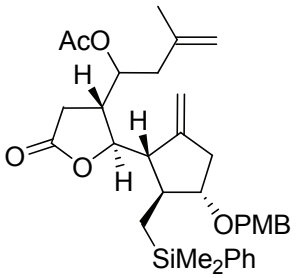


1-((2*R*,3*R*)-2-((1*S*,2*S*,3*S*)-2-((dimethyl(phenyl)silyl)methyl)-3-(*p*-methoxybenzyloxy)-5-methylenecyclopentyl)-5-oxotetrahydrofuran-3-yl)but-3-enyl acetate (198b)

Alcohol **195** (154 mg, 0.296 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (5 ml). NEt_3 (62 µl, 0.444 mmol, 1.5 eq.), DMAP (4 mg, 0.1 eq.) and Ac_2O (42 µl, 0.444 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 24 h under an N_2-atmosphere. Subsequently the solvent was removed and chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 133 mg (0.236 mmol, 80%) product as a colorless oil (*dr* = 50:50).

R_f (hexanes:ethylacetate 2:1) = 0.31.- ^1H NMR (300 MHz): δ = 0.28 (s, 3H, SiMe, diast: 0.29), 0.34 (s, 3H, SiMe, diast: 0.36), 0.63-0.81 (m, 2H, $SiCH_2$), 1.86 (s, 3H, OAc, diast: 1.96), 2.00-2.80 (m, 9H, 3-H, 4-H, 1´-H, 2´-H, 4´-H, 2´´-H), 3.50-3.61 (m, 1H, 3´-H, diast: 3.61-3.67), 3.79 (s, 3H, OMe), 4.18-4.44 (m, 2H, PMB), 4.75 (dd, *J* = 9.6, 1.7 Hz, 1H, 5-H, diast: 4.51, dd, *J* = 9.2, 4.3 Hz), 4.80-5.08 (m, 5H, 2x $=CH_2$, 1´´-H), 5.55-5.67 (m, 1H, 3´´-H),

6.81-6.88 (m, 2H, PMB), 7.15-7.23 (m, 2H, PMB), 7.30-7.39 (m, 3H, Ph), 7.45-7.55 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -3.2 (+, SiMe, diast: -2.9), -2.2 (+, SiMe, diast: -2.0), 20.5 (-, CH_2Si, diast: 20.6), 20.7 (+, OAc, diast: 20.8), 28.9 (-, 4´-C, diast: 31.0), 35.9 (-, 3-C, diast. 36.6), 38.2 (-, 2´´-C, diast: 38.4), 39.3 (+, 4-C, diast: 40.3), 41.0 (+, 2´-C, diast: 42.4), 55.2 (+, OMe), 56.2 (+, 1´-C, diast: 57.2), 70.2 (-, PMB), 72.6 (+, 1´´-C, diast: 74.2), 81.6 (+, 5-C, diast: 82.7), 86.5 (+, 3´-C, diast: 86.8), 112.1(-, $=CH_2$, diast: 112.6), 113.7 (+, 2xPMB), 118.4 (-, $=CH_2$), 127.8 (+, 2xPh), 128.9 +, Ph, diast: 128.9), 129.1 (+, 2xPMB, diast: 129.2), 130.4 (Cq, PMB, diast: 130.5), 132.6 (+, 2xPh), 133.6 (+, 3´´-C), 139.3 (Cq, Ph), 147.9 (Cq, PMB, diast: 148.1), 158.9 (Cq, 5´-C, diast: 159.0), 170.2 (Cq, OAc, diast: 170.5), 175.9 (Cq, 2-C, diast: 176.2).- IR (neat): $\tilde{\nu}$ = 3070, 2953, 2905, 1778, 1738, 1644, 1612, 1512, 1425, 1371, 1300, 1244, 1178, 1109, 1035, 920, 833, 726, 702 cm^{-1}.- MS (LSIMS, MeOH, CH_2Cl_2, Glycerin): *m/z* (%) = 425.4 (30), 485.4 (25), 545.4 (20), 563.4 (35) [MH^+], 655.0 (24) [MH^++Gly.].- HRMS (LSIMS): 563.2819 ($C_{33}H_{43}O_6Si$: calc. 563.2829).

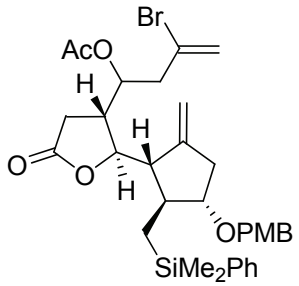


1-((2´*R*,3´*R*)-2´-((1´´*S*,2´´*S*,3´´*S*)-2´´-((dimethyl(phenyl)silyl)methyl)-3´´-(*p*-methoxy-benzyloxy)-5´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3´-yl)-3-methylbut-3-enyl acetate (198c)

Alcohol **196** (300 mg, 0.561 mol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (12 ml). NEt_3 (118 µl, 0.842 mol, 1.5 eq.), DMAP (7 mg, 0.1 eq.) and Ac_2O (79 µl, 0.842 mol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 24 h under an argon atmosphere. Subsequently the solvent was removed and chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 323 mg (0.560 mmol, 99%) product as a colorless oil (*dr* = 80:20).

R_f (hexanes:ethylacetate 2:1) = 0.47.- ^{1}H NMR (500 MHz): δ = 0.29 (s, 3H, SiMe, diast: 0.28), 0.34 (s, 3H, SiMe, diast: 0.36), 0.64-0.78 (m, 2H, CH_2Si), 1.66 (s, 3H, CH_3, diast: 1.64), 1.85 (s, 3H, OAc, diast: 1.94), 1.99 (dd, *J* = 13.4, 6.2 Hz, 1H, 4´´-H), 2.05-2.11 (m, 1H, 1´´-H), 2.20 (dd, *J* = 8.0, 13.4 Hz, 1H, 4´-H), 2.33-2.51 (m, 4H, 2-H, 3´-H, 4´´-H), 2.52-2.59 (m, 1H, 2´´-H), 2.64-2.74 (m, 1H, 4´´-H), 3.56-3.60 (m, 1H, 3´´-H, diast: 3.62-3.65), 3.79 (s, 3H, OMe), 4.18-4.30 (m, 2H, PMB), 4.53 (dd, *J* = 9.4, 4.1 Hz, 1H, 2´-H), 4.64-4.67 (m, 1H,

=CH_2, diast: 4.56-4.58), 4.75-4.79 (m, 1H, =CH_2, diast: 4.70-4.72), 4.81-4.85 (m, 1H, =CH_2), 5.00-5.03 (m, 1H, =CH_2), 5.03-5.09 (m, 1H, 1-H), 6.81-6.88 (m, 2H, PMB), 7.14-7.22 (m, 2H, PMB), 7.31-7.38 (m, 3H, Ph), 7.45-7.53 (m, 2H, Ph).- ^{13}C NMR (MHz): δ = -3.79 (+, SiMe, diast: -4.10), -3.19 (+, SiMe, diast: -2.99), 19.60 (-, $SiCH_2$, diast: 21.73), 19.73 (+, OAc, diast: 19.79), 21.16 (+, CH_3, diast: 21.29), 27.95 (-, 2-C, diast: 28.06), 37.22 (-, 4´´-C, diast: 37.43), 39.49 (+, 3´-C, diast: 38.93), 39.70 (-, 4´-C, diast: 39.11), 41.03 (+, 2´´-C, diast: 40.11), 54.30 (+, OMe), 56.34 (+, 1´´-C, diast: 55.43), 69.21 (-, PMB), 70.39 (+, 1-C, diast: 71.63), 80.76 (+, 2´-C, diast: 81.77), 85.51 (+, 3´´-C, diast: 85.83), 111.07 (-, =CH_2, diast: 111.74), 112.68 (+, 2x PMB), 113.08 (-, =CH_2, diast: 112.92), 126.88 (+, 2x Ph, diast: 126.94), 127.99 (+, 1x Ph, diast: 128.04), 128.13 (+, 2x PMB, diast: 128.23), 129.58 (Cq, Ph), 132.66 (+, 2x Ph), 138.42 (Cq, PMB), 139.64 (Cq, C=CH_2, diast: 139.55), 147.19 (Cq, C=CH_2, diast: 146.95), 158.02 (Cq, PMB), 169.19 (Cq, Ac, diast: 169.53), 175.12 (Cq, 5´-C, diast: 175.29).- IR (neat): $\tilde{\nu}$ = 3070, 3047, 2997, 2952, 2906, 2869, 2837, 2358, 2341, 1778, 1739, 1652, 1612, 1514, 1456, 1442, 1427, 1373, 1355, 1301, 1245, 1174, 1112, 1083, 1068, 1033, 989, 896, 835, 732, 702 cm^{-1}.- MS (EI): *m/z* = 594 ($M+NH_4^+$), 600 [$M+Na^+$].- HRMS (EI): 594.3239 ($C_{34}H_{48}O_6Si$: calc. 594.3251 [$M+NH_4^+$]).



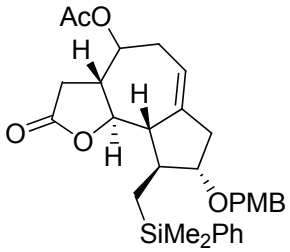
3-bromo-1-((2´*R*,3´*R*)-2´-((1´´*S*,2´´*S*,3´´*S*)-2´´-((dimethyl(phenyl)silyl)methyl)-3´´-(*p*-methoxybenzyloxy)-5´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (198d)

Alcohol **197** (130 mg, 0.217 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml). NEt_3 (44 mg, 61 µl, 0.434 mmol, 2.0 eq.), DMAP (3 mg, 0.022 mmol, 0.1 eq.) and Ac_2O (44 mg, 41 µl, 0.434 mmol, 2.0 eq.) was added, and the mixture was stirred for 16 h at rt. Subsequently the solvent was removed in vacuo and chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 120 mg product (0.187 mmol, 86%) as a colorless oil (*dr* = 75:25).

R_f (hexanes:ethylacetate 2:1, Mostain) = 0.47.- ^{1}H NMR (500 MHz): δ = 0.28 (s, 3H, SiMe, diast: 0.27), 0.34 (s, 3H, SiMe, diast: 0.36), 0.65-0.78 (m, 2H, $SiCH_2$), 1.87 (s, 3H, OAc), 2.09-2.14 (m, 1H, 1´´-H), 2.30-2.50 (m, 4H, 2-H, 4´´-H, 4´-H), 2.52-2.59 (m, 2H, 3´-H, 2´´-

H), 2.65 (dd, *J* = 14.5, 7.9 Hz, 1H, 4′-H), 2.68-2.76 (m, 1H, 4′′-H), 3.56-3.61 (m, 1H, 3′′-H, diast: 3.63-3.68), 3.79 (s, 3H, OMe), 4.19-4.31 (m, 2H, PMB), 4.55 (dd, *J* = 9.4, 4.1 Hz, 1H, 2′-H), 4.84-4.87 (m, 1H, C=CH_2, diast: 4.81-4.84), 5.02-5.05 (m, 1H, C=CH_2, diast: 5.05-5.07), 5.16-5.22 (m, 1H, 1-H), 5.44-5.47 (m, 1H, CBr=CH_2, diast: 5.36-5.39), 5.55-5.57 (m, 1H, CBr=CH_2, diast: 5.41-5.43), 6.81-6.88 (m, 2H, PMB), 7.17-7.25 (m, 2H, PMB), 7.31-7.38 (m, 3H, Ph), 7.46-4.53 (m, 2H, Ph).- ^{13}C NMR (75 MHz): δ = -2.9 (+, SiMe, diast: -3.3), -2.2 (+, SiMe, diast: -2.0), 20.5 (-, CH_2Si, diast: 20.4), 20.5 (+, OAc, diast: 20.6), 28.9 (-, 4′′-C, diast: 30.9), 38.1 (-, 4′-C, diast: 38.2), 40.1 (+, 2′′-C, diast: 39.4), 41.9 (+, 3′-C, diast: 41.0), 43.6 (-, 2-C, diast: 43.5), 55.3 (+, 1′′-C, diast: 56.3), 57.0 (+, OMe), 70.2 (-, PMB), 71.2 (+, 1-C, diast: 72.2), 82.5 (+, 2′-C, diast: 81.5), 86.5 (+, 3′′-C, diast: 86.9), 112.4 (-, C=CH_2, diast: 113.0), 113.7 (+, 2x PMB), 120.2 (-, CBr=CH_2, diast: 120.1), 127.8 (Cq, 3-C, diast: 127.9), 127.8 (+, 2xPh), 129.1 (+, 2xPMB), 129.2 (+, Ph), 130.5 (Cq, Ph, diast: 130.4), 133.6 (+, 2xPh), 139.4 (Cq, PMB, diast: 139.3), 147.7 (Cq, 5′′-C, diast: 147.9), 158.9 (Cq, PMB, diast: 159.0), 169.8 (Cq, OAc, diast: 170.2), 175.7 (Cq, 5′-C, diast: 175.9).- IR (neat): $\tilde{\nu}$ = 3068, 2999, 2952, 2916, 2871, 2837, 1778, 1745, 1612, 1514, 1427, 1373, 1355, 1301, 1247, 1228, 1174, 1112, 1106, 1033, 989, 896, 835, 756, 727, 702 cm^{-1}.- MS (EI): *m/z* = 371, 658 [M+NH_4^+], 663 [M+Na^+], 665 [M+Na^+], 666 [M+Na^+].- HRMS (EI): 658.2185 ($C_{33}H_{45}O_6SiBrN$: calc. 658.2199 [M+NH_4^+]).

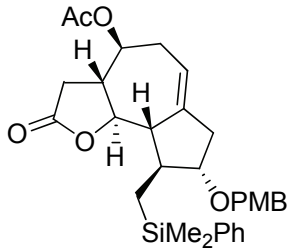
11.8 Ring closing metathesis



(3a*R*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (199a)

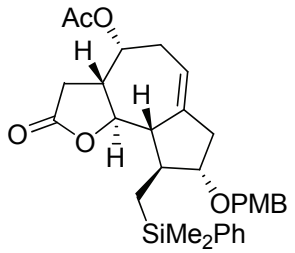
Ac-protected diene **198b** (127 mg, 0.226 mmol, 1.0 eq, *dr* = 50:50) was dissolved in abs. toluene (5 ml). A gentle stream of N_2 was introduced into the solution throughout the reaction and the reaction setup was put down into a preheated 90 °C hot oil bath. Grubbs 2nd catalyst (9 mg, 11.3 µmol 5 mol%) dissolved in abs. toluene (1 ml) was added followed by two additional 5 mol% batches every 2 h (total catalyst loading 15 mol%). After cooling to rt the

solvent was removed and chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 45 mg (0.084 mmol, 75%) pure 4*S*-diastereomer and 54 mg (0.101 mmol, 90%) pure 4*R*-diastereomer.



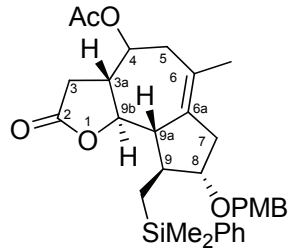
(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*S*-199a)

R_f (hexanes:ethylacetate 3:1, Mostain) = 0.27.- $[\alpha]_D^{20}$ = -32.7 (c = 1.00, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.33 (s, 3H, SiMe), 0.39 (s, 3H, SiMe), 0.71-0.78 (m, 2H, CH_2Si), 2.02 (s, 3H, OAc), 1.90-2.09 (m, 2H, 5-H, 3a-H), 2.20-2.29 (m, 1H, 9a-H), 2.30-2.40 (m, 2H, 5-H, 7-H), 2.33 (dd, *J* = 16.6, 12.8 Hz, 1H, 3-H), 2.53 (dd, *J* = 16.6, 7.0 Hz, 1H, 3-H), 2.57-2.69 (m, 1H, 7-H), 2.70-2.80 (m, 1H, 9-H), 3.45 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 3.92 (dd, *J* = 10.3, 10.3 Hz, 1H, 9b-H), 4.21-4.36 (m, 2H, PMB), 4.61 (dt, *J* = 10.7, 3.0 Hz, 1H, 4-H), 5.52-5.67 (m, 1H, 6-H), 6.77-6.89 (m, 2H, PMB), 7.09-7.22 (m, 2H, PMB), 7.29-7.41 (m, 3H, Ph), 7.46-7.59 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.9 (+, SiMe), -2.4 (+, SiMe), 20.9 (+, OAc), 21.6 (-, CH_2Si), 33.6 (-, 5-C), 35.2 (-, 3-C), 39.1 (-, 7-C), 42.1 (+, 9-C), 52.9 (+, 3a-C), 53.4 (+, 9a-C), 55.2 (+, OMe), 69.5 (-, PMB), 71.5 (+, 4-C), 82.8 (+, 9b-C), 85.3 (+, 8-C), 113.7 (+, 2xPMB), 117.6 (+, 6-C), 127.7 (+, 2xPh), 128.9 (+, Ph), 129.2 (+, 2xPMB), 130.4 (Cq, PMB), 133.8 (+, 2xPh), 139.2 (Cq, 6a-C), 146.1 (Cq, Ph), 159.0 (Cq, PMB), 169.9 (Cq, OAc), 174.3 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3068, 3044, 2998, 2952, 2900, 1781, 1738, 1732, 1613, 1586, 1513, 1443, 1426, 1371, 1301, 1244, 1181, 1112, 1062, 1029, 959, 905, 881, 821, 727, 701 cm^{-1}.- MS (LSIMS, MeOH, CH_2Cl_2,Glycerin): *m/z* = 399.3 (10), 415 (15), 457.3 (20), 507.3 (15), 535.3 (40) [MH^+], 627.3 (50) [MH^++Glyc.], 719.3 (10) [MH^++2Glyc.].- HRMS (LSIMS): 535.2527 ($C_{31}H_{39}O_6Si$: calc.535.216 [MH^+]).



(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*R*-**199a)**

R_f (hexanes:ethylacetate 3:1, Mostain) = 0.14.- $[\alpha]_D^{20}$ = -87.8 (c = 1.00, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.32 (s, 3H, SiMe), 0.39 (s, 3H, SiMe), 0.72-0.89 (m, 2H, CH_2Si), 1.87-2.10 (m, 2H, 5-H, 3a-H), 2.01 (s, 3H, OAc), 2.21-2.30 (m, 1H, 9a-H), 2.31-2.44 (m, 3H, 3-H, 5-H, 7-H), 2.54 (dd, *J* = 8.9, 5.3 Hz, 1H, 3H), , 2.60-2.70 (m, 1H, 7-H), 2.70-2.79 (m, 1H, 9-H), 3.48-3.56 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 4.22 (dd, *J* = 10.4, 10.4 Hz, 1H, 9b-H), 4.26-4.39 (m, 2H, PMB), 4.90-5.05 (m, 1H, 4-H), 5.40-5.50 (m, 1H, 6-H), 6.80-6.87 (m, 2H, PMB), 7.14-7.19 (m, 2H, PMB), 7.30-7.38 (m, 3H, Ph), 7.49-7.57 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.9 (+, SiMe), -2.2 (+, SiMe), 20.9 (+, OAc), 21.6 (-, CH_2Si), 31.1 (-, 5-C), 33.4 (-, 3-C), 39.0 (-, 7-C), 42.6 (+, 9-C), 50.7 (+, 9a-C), 54.3 (+, 3a-C), 55.4 (+, OMe), 68.1 (+, 4-C), 69.4 (-, PMB), 80.1 (+, 9b-C), 85.6 (+, 8-C), 113.6 (+, 2xPMB), 117.9 (+, 6-C), 127.6 (+, 2xPh), 128.8 (+, Ph), 128.9 (+, 2xPMB), 130.7 (Cq, PMB), 133.9 (+, 2xPh), 139.4 (Cq, 6a-C), 144.9 (Cq, Ph), 158.9 (Cq, PMB), 170.5 (Cq, OAc), 174.4 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2951, 2899, 1783, 1739, 1612, 1512, 1426, 1369, 1300, 1246, 1112, 1076, 999, 910, 833, 731, 644 cm^{-1}.- MS (LSIMS, MeOH, CH_2Cl_2, Glycerin): *m/z* = 415.3 [M-PMB], 535.4 [M+H^+], 627.4 [MH^++Gly].- HRMS (LSIMS): 535.2520 ($C_{31}H_{39}O_6Si$: calc.535.2516 [M+H^+]).

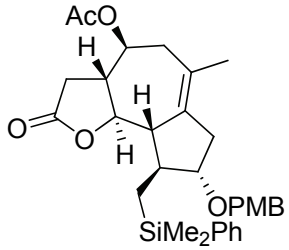


(3a*R*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (199b)

Ac-protected diene **198c** (100 mg, 0.173 mmol, 1.0 eq, *dr* = 80:20) was dissolved in abs. toluene (5 ml). A gentle stream of argon was introduced into the solution throughout the reaction and the reaction setup was put down into a preheated 90 °C hot oil bath. Grubbs 2nd catalyst (7 mg, 7.7 µmol 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%). After cooling to rt the solvent was removed and chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 70 mg (0.128 mmol, 93%) pure 4*S*-Diastereomer) and 19 mg mixture of both diastereomers.

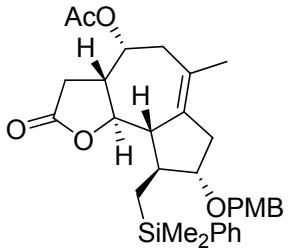
Major isomer:



(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (*4S*-199b)

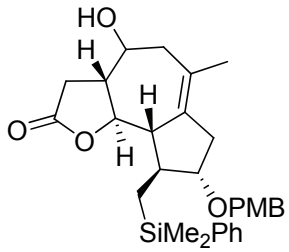
R_f (hexanes:ethylacetate 2:1, Mostain) = 0.39.- $[\alpha]_D^{20}$ = -32.5 (c = 0.65, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 0.32 (s, 3H, SiMe), 0.38 (s, 3H, SiMe), 0.57-0.73 (m, 2H, CH_2Si), 1.71 (s, 3H, CH_3), 1.87-1.98 (m, 1H, 9a-H), 2.02 (s, 3H, OAc), 2.04-2.12 (m, 1H, 5-H), 2.14-2.26 (m, 2H, 5-H, 3a-H), 2.29 (dd, *J* = 16.6, 13.2 Hz, 1H, 3-H), 2.35-2.57 (m, 1H, 7-H), 2.49 (dd, *J* = 16.6, 6.6 Hz, 1H, 3-H), 2.45-2.55 (m, 1H, 7-H), 2.75-2.85 (m, 1H, 9-H), 3.52-3.58 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 3.87-3.94 (m, 1H, 9b-H), 4.32 (dd, *J* = 68.2, 10.8 Hz, 2H, PMB), 4.56 (dt, *J* = 10.7, 2.2 Hz, 1 H, 4-H), 6.77-6.89 (m, 2H, PMB), 7.09-7.19 (m, 2H, PMB), 7.30-7.40 (m, 3H, Ph), 7.46-7.57 (m, 2H, Ph).- ^{13}C NMR (125.8 MHz): δ = -2.7 (+, SiMe), -2.2 (+, SiMe), 21.2 (-, CH_2Si), 21.3 (+, OAc), 23.6 (+, CH_3), 35.6 (-, 3-C), 36.8 (-, 7-C), 40.7 (+, 9-C), 41.4 (-, 5-C), 53.8 (+, 3a-C), 53.8 (+, 9a-C), 55.5 (+, OMe), 69.8 (-, PMB), 71.04 (+, 4-C), 82.95 (+, 9b-C), 86.05 (+, 8-C), 113.96 (+, 2xPMB), 126.44 (Cq, Ph), 127.96 (+, 2xPh), 129.18 (+, Ph), 129.55 (+, 2xPMB), 130.65 (Cq, PMB), 134.07 (+, 2xPh), 138.13 (Cq, 6-C), 139.39 (Cq, 6a-C), 159.27 (Cq, PMB), 170.14 (Cq, OAc), 174.76 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3068, 3045, 2997, 2950, 2904, 2858, 2837, 1784, 1737, 1612, 1514, 1463, 1427, 1371, 1301, 1245, 1172, 1112, 1081, 1064, 1031, 997, 958, 835, 729, 702, 605 cm^{-1}.- MS (EI): *m/z* = 121.1, 351.2, 383.2, 549.3 [M+H$^+$], 566.3 [M+NH_4^+].- HRMS (EI): 549.2676 ($C_{32}H_{41}O_6Si$: calc. 549.2673 [M+H$^+$]).

Minor isomer:



(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (*4R*-**199b**)

R_f (hexanes:ethylacetate 2:1, Mostain) = 0.30.- $[\alpha]_D^{20}$ = -79.3 (c = 0.67, $CHCl_3$).- ^{1}H NMR (500 MHz): δ = 0.34 (s, 3H, SiMe), 0.41 (s, 3H, SiMe), 0.71-0.79 (m, 2H, $SiCH_2$), 1.64 (s, 3H, CH_3), 1.77-1.86 (m, 1H, 9a-H), 2.05 (s, 3H, OAc), 2.13-2.19 (m, 1H, 5-H), 2.23-2.29 (m, 1H, 5-H), 2.31-2.38 (m, 2H, 3-H, 7-H), 2.41-2.50 (m, 2H, 3-H), 2.54-2.63 (m, 1H, 7-H), 2.78-2.87 (m, 1H, 9-H), 3.57-3.65 (m, 1H, 8-H), 3.83 (s, 3H, OMe), 4.10-4.19 (m, 1H, 9b-H), 4.27-4.15 (m, 2H, PMB), 4.96-5.07 (m, 1H, 4-H), 6.84-6.93 (m, 2H, PMB), 7.17-7.25 (m, 2H, PMB), 7.34-7.42 (m, 3H, Ph), 7.52-7.61 (m, 2H, Ph).- ^{13}C NMR (125.8 MHz): δ =-2.01 (+, SiMe), -1.93 (+, SiMe), 21.15 (-, CH_2Si), 21.24 (+, OAc), 24.63 (+, CH_3), 33.59 (-, 3-C), 36.62 (-, 7-C), 37.99 (+, 9-C), 41.00 (-, 5-C), 51.79 (+, 3a-C), 54.56 (+, 9a-C), 55.48 (+, OMe), 68.39 (-, PMB), 69.87 (+, 4-C), 80.43 (+, 9b-C), 86.35 (+, 8-C), 113.92 (+, 2xPMB), 126.49 (Cq, Ph), 127.93 (+, 2xPh), 129.12 (+, Ph), 129.44 (+, 2xPMB), 130.89 (Cq, PMB), 134.19 (+, 2xPh), 137.18 (Cq, 6-C), 139.68 (Cq, 6a-C), 159.22 (Cq, PMB), 170.81 (Cq, OAc), 174.85 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3068, 3045, 2950, 2902, 2858, 2837, 2358, 2331, 1784, 1731, 1612, 1585, 1514, 1463, 1440, 1427, 1373, 1301, 1247, 1201, 1182, 1112, 1062, 1035, 989, 948, 925, 835, 756, 730, 702 cm^{-1}.- MS (EI+): *m/z* = 371.16, 387.16, 529.26, 566.29 [$M+NH_4^+$], 571.2 [$M+Na^+$].- HRMS (EI): 549.2688 ($C_{32}H_{41}O_6Si$: calc. 549.2673 [$M+H^+$]).



(3a*R*, 4*R*/*S*, 8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-4-hydroxy-8-(*p*-methoxy benzyloxy)-6-methyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one (199c)

In a 50-ml Schlenk flask equipped with a condenser, TES-protected diene **198a** (100 mg, 154 mmol, 1.0 eq, *dr* = 80:20) was dissolved in abs. toluene (5 ml). A gentle stream of argon was introduced into the solution throughout the reaction and the reaction setup was put down into a preheated 90 °C hot oil bath. Grubbs 2nd catalyst (7 mg, 7.7 µmol 5 mol%) dissolved in 1 ml abs. toluene was added followed by two additional 5 mol% batches every 2 h (total catalyst loading 15 mol%). After cooling to rt TBAF (385 µl, 385 mmol, 2.5 eq, 1N in THF) was added and the mixture was allowed to stir over night. The solvent was removed and chromatography on silica gel (hexanes:ethylacetate 1:1) afforded 60 mg (118 mmol, 77%) product as a inseparable mixture of diastereomers (*dr* = 80:20).

R_f (hexanes:ethylacetate 1:1, Mostain) = 0.37.- H NMR (600 MHz): δ = 0.32 (s, 3H, SiMe), 0.38 (s, 3H, SiMe), 0.65-0.72 (m, 2H, CH_2Si), 1.68 (s, 3H, CH_3), 1.72-1.84 (m, 1H, 9a-H), 2.01-2.08 (m, H, 5-H), 2.19-2.26 (m, 2H, 3a-H, 7-H), 2.36 (dd, *J* = 16.7, 13.1 Hz, 3-H), 2.28-2.41 (m, 1H, 7-H), 2.48-2.58 (m, 1H, 7-H), 2.67 (dd, *J* = 16.7, 6.6 Hz, 1H, 3-H), 2.78-2.86 (m, 1H, 9-H), 3.33-3.53 (m, 1H, 4-H), 3.53-3.62 (m, 1H, 8-H), 3.79 (s, 3H, PMB), 3.81-3.88 (m, 1H, 9b-H), 4.31 (dd, *J* = 97.4, 11.4 Hz, 2H, PMB), 5.77-6.88 (m, 2H, PMB), 7.12-7.21 (m, 2H, PMB), 7.31-7.50 (m, 3H, Ph), 7.49-7.58 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ =-2.65 (+, SiMe), -2.13 (+, SiMe), 21.26 (-, CH_2Si), 23.86 (+, CH_3), 35.91 (-, 3-C), 36.90 (-, 7-C), 40.54 (+, 9-C), 45.46 (-, 5-C), 53.76 (+, 3a-C), 55.47 (+, 9b-C), 56.47 (+, 9a-C), 69.81 (-, PMB), 69.85 (+, 4-C), 83.07 (+, OMe), 86.16 (+, 8-C), 113.97 (+, 2x PMB) , 126.62 (Cq, 6-C) , 127.97 (+, 2xPh), 129.20 (+, 2xPh), 129.66 (+, 2xPMB), 130.68 (Cq, PMB), 134.08 (+, Ph), 137.71 (Cq, Ph), 139.42 (Cq, 6a-C), 159.28 (Cq, PMB), 175.58 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3434, 2950, 2933, 2358, 2329, 1749, 1733, 1614, 1515, 1301, 1247, 1217, 1172, 1112, 1091, 1064, 1039, 962, 838, 729, 702 cm^{-1}.- MS (EI): *m/z* = 507 [M+H+], 524 [M+NH4+].- HRMS (EI): 507.2570 ($C_{30}H_{39}O_5Si$: calc. 507.2567 [M+H$^+$]).

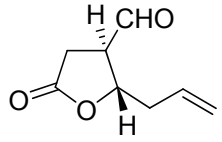
11.9 Synthesis of a 3x3 scaffold library

11.9.1 Preparation of lactone aldehydes

General procedure for preparation of lactone aldehydes **210**:

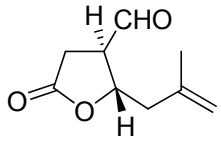
Under a N_2-atmosphere cyclopropylcarbaldehyde (-)-**130** (1.00 eq.) was dissolved in abs. CH_2Cl_2 (5 ml/mmol) and cooled to -78 °C. $BF_3{\cdot}OEt_2$ (1.10 eq.) was added and the mixture stirred for 30 min. Allylsilane (1.10 eq.) was added via a syringe and the reaction mixture was stirred for 18 h at -78 °C. The reaction was quenched with $NaHCO_3$ sat. (0.2 ml/mmol $BF_3{\cdot}OEt_2$) and allowed to warm to rt. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated in vacuo.

The crude alcohol (1.0 eq.) was dissolved in MeOH (10 ml/mmol) and cooled to 0 °C. $Ba(OH)_2{\cdot}8H_2O$ (0.55 eq.) was added in small portions over 4 h. After 5 h stirring at 0 °C CH_2Cl_2 (10 ml/mmol) and H_2O (10 ml/mmol) were added and the layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (3x10 ml/mmol). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 1:1) afforded the corresponding lactone aldehyde as a colorless oil.



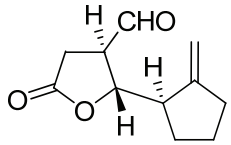
(2*S*,3*R*)-2-allyl-5-oxo-tetrahydrofuran-3-carbaldehyde (210a)

Yield: 51%, *dr* = 95:5.- R_f (hexanes:ethylacetate 1:1, Mostain) = 0.20.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67-2.44 (m, 2H, 1´-H), 2.75 (dd, *J* = 17.9, 10.1 Hz, 1H, 4-H), 2.93 (dd, *J* = 17.9, 7.5 Hz, 1H, 4-H), 3.26-3.16 (m, 1H, 3-H), 4.77 (dd, *J* = 12.1, 6.1 Hz, 1H, 2-H), 5.30-5.17 (m, 2H, 3´-H), 5.87-5.70 (m, 1H, 2´-H), 9.73 (d, *J* = 1.6 Hz, 1H, CHO); diast: δ = 3.00 (dd, *J* = 17.7, 5.8 Hz, 1H, 4-H), 9.86 (d, *J* = 1.6 Hz, 1H, CHO).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.9 (-, 4-C, diast: 30.2), 39.2 (-,1´-C, diast: 39.4), 51.3 (+, 3-C, diast: 49.6), 78.0 (+, 2-C, diast: 79.6), 120.5 (-, 3´-C, diast: 120.0), 130.9 (+, 2´-C, diast: 131.3), 174.0 (Cq, CO), 197.3 (+, CHO, diast: 198.0).- IR (neat): $\tilde{\nu}$ = 3080, 2980, 2939, 2841, 1774, 1727, 1642, 1419, 1359, 1193, 1111, 1000, 924 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 154.2 (5) [M^+], 113.1 (100) [M-C_3H_5], 85.1 (95), 57.1 (95).- CH: $C_8H_{10}O_3$ calc. C 62.33, H 6.54; found: C 62.36, H 6.83.



(2*S*,3R)-2-(2-methylallyl)-5-oxo-tetrahydrofuran-3-carbaldehyde (210b)

Yield: 50%, *dr* = 96:4.- R_f (hexanes:ethylacetate 1:1, Mostain) = 0.21. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3H, CH_3), 2.39 (dd, *J* = 14.1, 8.1 Hz, 1H, 1´-H), 2.60 (dd, *J* = 14.1, 6.5 Hz, 1H, 1´-H), 2.76 (dd, *J* = 17.8, 9.9 Hz, 1H, 4-H), 2.96 (dd, *J* = 17.9, 7.6 Hz, 1H, 4-H), 3.15-3.25 (m, 1H, 3-H), 4.79-4.88 (m, 2H, 3´-H), 4.92-4.97 (m, 1H, 2-H), 9.72 (d, *J* = 1.4 Hz, 1H, CHO, diast: d, 9.83, *J* = 1.9 Hz).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7 (+, CH_3), 28.9 (-, 4-C), 43.3 (-, 1´-C), 51.9 (+, 2-C), 77.5 (+, 3-C), 115.2 (-, 3´-C), 139.6 (Cq, 2´-C), 173.8 (Cq, CO), 197.2 (+, CHO).- IR (neat): $\tilde{\nu}$ = 3078, 2934, 2854, 2735, 1778, 1726, 1651, 1420, 1360, 1193, 1018, 986, 898, 827 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 169.1 (100) [$M+H^+$].



(2*S*,3*R*)-2-((*R*)-2-methylenecyclopentyl)-5-oxo-tetrahydrofuran-3-carbaldehyde (210c)

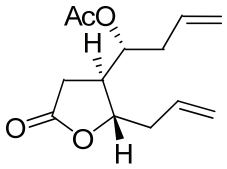
Yield: 45%, *dr* = 95:5:0:0.- R_f (hexanes:ethylacetate 1:1, Mostain) = 0.36. - ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.57-1.69 (m, 2 H, CH_2), 1.73-1.84 (m, 1 H, CH_2), 1.86-1.96 (m, 1 H, CH_2), 2.25-2.40 (m, 2 H, CH_2), 2.73 (dd, *J* = 18.1, 10.2 Hz, 1 H, 4-H), 2.75-2.80 (m, 1 H, 1'-H), 2.88 (dd, *J* = 18.1, 7.5 Hz, 1 H, 4-H), 3.29 (dddd, *J* = 10.2, 7.4, 6.5, 1.1 Hz, 1 H, 3-H), 4.72 (t, *J* = 6.2 Hz, 1 H, 2-H), 4.97 (d, *J* = 2.0 Hz, 1 H, =CH_2), 5.06 (d, *J* = 2.0 Hz, 1 H, =CH_2), 9.71 (d, *J* = 1.3 Hz, 1 H, CHO, diast.: 9.67).- ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 23.94 (-, CH_2), 27.88 (-, CH_2), 29.34 (-, 4-C), 33.61 (-, CH_2), 47.74 (+, 1'-C), 50.08 (+, 3-C), 80.48 (+,2-C), 108.91 (-, =CH_2), 150.83 (Cq, 2'-C), 174.13 (Cq, 5-C), 197.61 (+, CHO).- IR (neat): $\tilde{\nu}$ = 3426, 2955, 2873, 1771, 1653, 1435, 1198, 882 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 212.2 (100) [$M+NH_4^+$].- HRMS (EI, 70 eV): 194.0943 ($C_{11}H_{14}O_3$: calc. 194.0943 [M^+]).

11.9.2 Hosomi-Sakurai allylation and acetyl-protection

General procedure for Hosomi-Sakurai allylation and acetyl-protection:

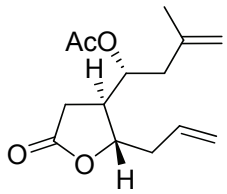
Aldehyde **210** (1.00 eq.) was dissolved in abs. CH_2Cl_2 (4 ml/mmol) under a N_2-atmosphere and cooled to -78 °C. Allylsilane **211** (1.50 eq.) was added via a syringe and the solution was stirred for 15 min. $BF_3{\cdot}OEt_2$ (1.15 eq.) was added dropwise via a syringe and the reaction mixture was stirred for 18 h at -78 °C. $NaHCO_3$ sat. (1 ml/mmol $BF_3{\cdot}OEt_2$) was added and the solution was warmed to rt. The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (1x4 ml/mmol). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo.

The crude alcohol (1.00 eq.) was dissolved in abs. CH_2Cl_2 (1x5 ml/mmol), DMAP (0.10 eq.), abs. NEt_3 (1.75 eq.) and Ac_2O (1.50 eq.) were added and the reaction mixture was stirred for 18 h at rt. The solvent was removed in vacuo and chromatography on silica gel (hexanes:ethylacetate 3:1) afforded the product as a slightly yellowish oil.



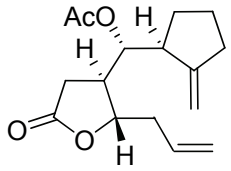
(*R/S*)-1-((2′*S*,3′*S*)-2′-allyl-5′-oxo-tetrahydrofuran-3′-yl)but-3-enyl acetate (213a)

Yield: 67%, *dr* = 73:27.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.30.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H, Ac, diast: 2.04), 2.15-2.72 (m, 7H, 2-H, 3′-H, 4′-H, 1′′-H), 4.23-4.31 (m, 1H, 1-H, diast: 4.44-4.51), 4.95-5.17 (m, 4H, 4-H, 3′′-H), 5.17-5.20 (m, 1H, 2′-H), 5.58-5.86 (m, 2 H, 3-H, 2′′-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (+, CH_3), 29.1 (-, 4′-C, diast: 31.8), 37.3 (-, 1′′-C, diast: 36.8), 38.6 (-, 2-C, diast: 39.55), 42.4 (+, 3′-C, diast: 41.5), 71.2 (+, 1-C, diast: 73.9), 80.9 (+, 2′-C), 118.9 (+, $=CH_2$), 119.5 (-, $=CH_2$), 131.7 (+, CH=C, diast: 131.9), 132.3 (+,CH=C diast: 132.2), 170.4 (Cq, OAc, diast: 170.3), 175.5 (Cq, 5′-C, diast: 175.2).- IR (neat): $\tilde{\nu}$ = 3628, 3535, 3079, 2939, 1779, 1738, 1644, 1422, 1371, 1234, 1180, 1030, 997, 921, 833 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 43.1 (100.00) [H_3C-C=O^+], 239.0 (0.90) [MH^+].- HRMS (EI, 70 eV): 238.1201 ($C_{13}H_{18}O_4$: calc. 238.1205 [M^+]).



(*R/S*)-1-((2′*S*,3′*R*)-2′-allyl-5′-oxo-tetrahydrofuran-3′-yl)-3-methylbut-3-enyl-acetate (213b)

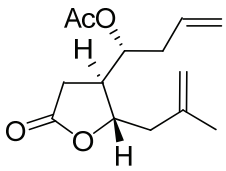
Yield: 49%, *dr* = 67:33.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.35. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 3H, CH_3, diast: 1.75), 2.05 (s, 3H, Ac, diast: 2.04), 2.06-2.56 (m, 6H, 2-H, 3′-H, 4′-H, 1′′-H), 2.60 (dd, *J* = 8.5, 2.5 Hz, 1H, 4′-H, diast: 2.69 dd, *J* = 17.6, 9.61 Hz), 4.29 (dd, *J* = 12.1, 6.0 Hz, 1H, 1-H, diast: 4.52, dd, *J* = 11.3, 4.9 Hz), 4.72-4.75 (m, 1H, 4-H), 4.81-4.85 (m, 1H, 4-H), 5.07-5.23 (m, 3H, 3′′-H, 2′-H), 5.69-5.87 (m, 1H, 2′′-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (+, CH_3), 22.1 (+, OAc, diast: 22.3), 28.9 (-, 4′-C, diast: 31.9), 38.65 (-, 1′′-C, diast: 39.65), 41.3 (-, 2-C, diast: 41.0), 42.5 (+, 3′-C, diast: 41.8), 69.9 (+, 1-C, diast: 72.65), 80.9 (+, 2′-C, diast: 80.7), 114.4 (-, $=CH_2$, diast: 114.5), 119.5 (-, $=CH_2$), 131.75 (+, 2′′-C, diast: 131.85), 140.4 (Cq, 3-C, diast: 140.3), 170.4 (Cq, Ac), 175.5 (Cq, 5′-C, diast: 175.4).- IR (neat): $\tilde{\nu}$ = 3078, 2939, 1780, 1738, 1645, 1429, 1374, 1236, 1186, 1032, 985, 911 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 43.0 (100.00) [H_3C-C=O^+], 252.8 (3) [MH^+].- HRMS (EI, 70 eV): 252.1361 ($C_{14}H_{20}O_4$: calc. 252.1362 [M^+]).



(*R/S*)-((2′*S*,3′*R*)-2′-allyl-5′-oxo-tetrahydrofuran-3′-yl)((*S*)-2-methylenecyclopentyl) methyl acetate (213c)

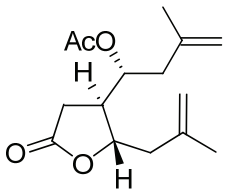
Yield: 53%, *dr* = 82:18:0:0.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.43.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57-1.67 (m, 2H, CH_2), 1.71-1.88 (m, 2H, CH_2), 2.09 (s, 3H, OAc, diast: 2.08), 2.19-2.77 (m, 8H, CH_2, 2-H, 3′-H, 4′-H, 1′′-H), 4.26 (dd, *J* = 11.7, 5.9 Hz, 1H, 1-H), 4.85-4.89 (m, 1H, $=CH_2$), 4.98-5.04 (m, 1H, $=CH_2$), 5.10-5.25 (m, 3H, 3′′-H, 2′-H), 5.71-5.89 (m, 1H, 2′′-H).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.8 (+, OAc), 23.8 (-, CH_2), 28.5 (-, 4-C), 29.6 (-, CH_2), 32.8 (-, CH_2), 38.5 (-, 1′′-C), 42.2 (+, 3′-C), 47.3 (+, 2-C), 72.1 (+, 1-C), 81.4 (+, 2′-C), 108.4 (-, $=CH_2$), 119.4 (-, $=CH_2$), 131.9 (+, 2′′-C), 151.45 (Cq, C=), 170.8 (Cq, OAc), 175.7 (Cq, 5′-C).- IR (neat): $\tilde{\nu}$ = 3076, 2954, 2873, 1779, 1738, 1644, 1431, 1371, 1234, 1177, 1116, 1028, 986, 947, 914, 892, 857 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 43.0

(100.00) [H_3C-CO^+], 278.9 (0.80) [$M+H^+$].- HRMS (EI, 70 eV): 278.1512 ($C_{16}H_{22}O_4$: calc. 278.1518 [M^+]).



(*R/S*) – 1 - ((2′*S*,3′*S*) -2′- (2′′- methylallyl)-5′-oxo-tetrahydrofuran-3′-yl) but-3-enyl acetate (213d)

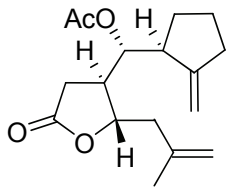
Yield: 73%, *dr* = 77:23.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.23.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3H, CH_3, diast: 1.77), 2.05 (s, 3H, OAc, diast: 2.04), 2.14-2.73 (m, 7H, 2-H, 3′-H, 4′-H, 1′′-H), 4.31-4.39 (m, 1H, 1-H, diast: 4.50-4.58), 4.76-4.82 (m, 1H, 3′′-H), 4.84-4.89 (m, 1H, 3′′-H), 4.56-5.09 (m, 2H, 4-H), 5.10-5.15 (m, 1H, 2′-H), 5.58-5.76 (m, 1H, 3-H).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (+, CH_3), 22.7 (+, OAc, diast: 22.8), 28.9 (-, 4′-C, diast: 31.6), 37.3 (-, 1′′-C, diast: 36.8), 42.8 (+, 3′-C, diast: 42.2), 43.0 (-, 2-C, diast: 43.8), 71.2 (+, 1-C, diast: 73.9), 80.4 (+, 2′-C, diast: 80.3), 114.4 (-, $=CH_2$), 118.9 (-, $=CH_2$), 132.4 (+, 3-C, diast: 132.2), 140.3 (Cq, 2′′-C), 170.3 (Cq, OAc), 175.5 (Cq, 5′-C, diast: 175.2).- IR (neat): $\tilde{\nu}$ = 3078, 2976, 2939, 1775, 1736, 1644, 1425, 1374, 1234, 1199, 1030, 986, 947, 921, 830 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 253.2 (100.00) [$M+H^+$].- HRMS (EI, 70 eV): 253.1438 ($C_{14}H_{21}O_4$: calc. 253.1440 [$M+H^+$]).



(*R/S*)-3-methyl-1-((2′*S*,3′*S*)-2′-(2′′-methylallyl)-5′-oxo-tetrahydrofuran-3′-yl)but-3-enyl-acetate (213e)

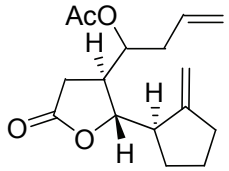
Yield: 57%, *dr* = 70:30.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.25.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 3H, Me, diast: 1.75), 1.77 (s, 3H, Me, diast: 1.79), 2.05 (s, 3H, OAc, diast: 2.04), 2.08-2.77 (m, 7H, 2-H, 3′-H, 4′-H, 1′′-H), 4.33-4.42 (m, 1H, 1-H, diast: 4.54-4.61), 4.07-4.75 (m, 1H, $=CH_2$), 4.78-4.85 (m, 2H, $=CH_2$), 4.87-4.92 (m, 1H, $=CH_2$), 5.09-5.23 (m, 1H, 2′-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (+, CH_3), 22.1 (+, CH_3, diast: 22.4), 22.7 (+, OAc, diast: 22.8), 28.7 (-, 4′-C, diast: 31.8), 41.3 (-, 1′′-C, diast: 41.0), 42.9 (+, 3′-C, diast: 42.7), 43.1 (-, 2-C, diast: 43.9), 69.9 (+, 1-C, diast: 72.7), 80.2 (+, 2′-C), 114.4

(-, 2x =CH_2), 140.3 (2x Cq, 3-C, 2´´-C), 170.4 (Cq, OAc), 175.6 (Cq, 5´-C, diast: 175.3).- IR (neat): $\tilde{\nu}$ = 3077, 2971, 2939, 1779, 1738, 1649, 1445, 1429, 1374, 1235, 1189, 1029, 985, 937, 896, 830 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 267.2 (100.00) [$M+H^+$].- HRMS (EI, 70 eV): 267.1592 ($C_{15}H_{23}O_4$: calc. 267.1596 [$M+H^+$]).



(*R/S*)-((2´*S*,3´*R*)-2´-(2´´-methylallyl)-5´-oxo-tetrahydrofuran-3´-yl)(2-methylenecyclopentyl) methyl acetate (213f)

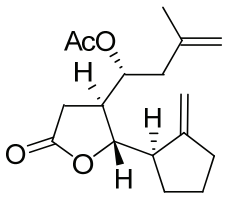
Yield = 59%, *dr* = 79:21:0:0.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.33.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53-1.67 (m, 2H, CH_2), 1.71-1.91 (m, 2H, CH_2), 1.79 (s, 3H, CH_3), 2.09 (s, 3H, OAc), 2.23-2.45 (m, 5H, CH_2, 2-H, 4´-H), 2.55-2.77 (m, 3H, 3´-H, 1´´-H), 4.34 (dd, *J* = 12.6, 6.3 Hz, 1H, 1-H), 4.77-5.04 (m, 4H, 2x =CH_2), 5.13 (dd, *J* = 7.6, 2.1 Hz, 1H, 2´-H).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.8 (+, CH_3), 22.7 (+, OAc), 23.7 (-, CH_2), 28.5 (-, 4´-C), 29.4 (-, CH_2), 32.8 (-, CH_2), 42.7 (-, 2´-C), 42.8 (+, 3´-C), 47.4 (+, 2-C), 72.0 (+, 1-C), 80.8 (+, 2´-C), 108.8 (-, =CH_2), 114.4 (-, =CH_2), 140.5 (Cq, C=CH_2), 151.5 (Cq, C=CH_2), 170.8 (Cq, OAc), 175.7 (Cq, 5´-C).- IR (neat): $\tilde{\nu}$ = 3075, 2952, 1780, 1738, 1652, 1431, 1373, 1233, 1090, 1024, 986, 946, 893, 719 cm^{-1}.-MS (CI, NH_3): *m/z* (%) = 293.2 (100.00) [$M+H^+$].- HRMS (EI, 70 eV): 293.1747 ($C_{17}H_{25}O_4$: calc. 293.1753 [$M+H^+$]).



(*R/S*)-1-((2´*S*,3´*S*)-2´-((*R*)-2´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3-yl)but-3-enyl-acetate (213g)

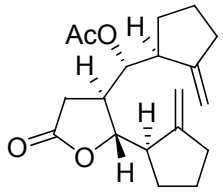
Yield = 57%, *dr* = 80:20.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.33.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51-1.67 (m, 2H, CH_2), 1.68-1.89 (m, 2H, CH_2), 2.05 (s, 3H, OAc, diast: 2.03), 2.12-2.39 (m, 5H, CH_2, 3´-H, 4´-H), 2.54-2.59 (m, 2H, CH_2), 2.62-2.71 (m, 1H, 1´´-H), 4.27-4.32 (m, 1H, 1-H, diast: 4.54-4.59), 4.87 (dd, *J* = 3.9, 2.0 Hz, 1H, 2´-H), 4.94-5.17 (m, 4H, =CH_2), 5.58-5.78 (m, 1H, 3-H).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.9 (+, OAc), 24.2 (-, CH_2, diast: 24.4), 27.3 (-, CH_2, diast: 26.7), 29.3 (-, 4´-C), 33.7 (-, CH_2, diast: 33.9), 37.2 (-

, CH_2, diast: 36.6), 41.2 (+, 3´-C, diast: 40.6), 47.1 (+, 1´´-C, diast: 47.6), 71.9 (+, 1-C, diast: 74.2), 83.6 (+ 2´-C, diast: 83.3), 107.9 (-, $=CH_2$, diast: 107.5), 118.9 (-, $=CH_2$), 132.4 (+, 3-C), 151.6 (Cq, 2´´-C, diast: 151.8), 170.4 (Cq, OAc), 175.8 (Cq, 5´-C, diast: 175.6).- IR (neat): $\tilde{\nu}$ = 3077, 2955, 2872, 1774, 1742, 1644, 1431, 1373, 1235, 1199, 1176, 1030, 993, 967, 920, 887 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 279.2 (100.00) [MH^+].- HRMS (EI, 70 eV): 279.1599 ($C_{16}H_{23}O_4$: calc. 279.1596 [M^+]).



(*R/S*)-3-methyl-1-((2´*S*,3´*S*)-2´-((*R*)-2´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (213h)

Yield: 47%, *dr* = 70:30.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.28. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52-1.69 (m, 2H, CH_2), 1.74 (s, 3H, CH_3), 1.77-1.90 (m, 2H, CH_2), 2.05 (s, 3H, OAc, diast: 2.03), 2.06-2.40 (m, 5H, CH_2, 3´-H, 4´-H), 2.55-2.70 (m, 3H, CH_2, 1´´-H), 4.27-4.34 (m, 1H, 1-H, diast: 4.55-4.61), 4.67-4.77 (m, 1H, $=CH_2$), 4.79-4.85 (m, 1H, $=CH_2$), 4.86-4.90 (m, 1H, $=CH_2$, diast: 4.90-4.94), 5.00-5.04 (m, 1H, $=CH_2$, diast: 5.04-5.07), 5.16-5.24 (m, 1H, 2´-H, diast: 5.10-5.16).- ^{13}C NMR (MHz, $CDCl_3$): δ = 20.9 (+, OAc, diast: 20.8), 22.2 (+, CH_3, diast: 22.4), 24.2 (-, CH_2, diast: 24.4), 27.4 (-, CH_2, diast: 26.7), 29.1 (-, CH_2), 33.7 (-, CH_2), 41.2 (-,CH_2, diast: 40.7), 41.3 (+, 3´-C, diast: 41.1), 47.2 (+, 1´´-C, diast: 47.7), 70.6 (+, 1-C, diast: 72.8), 83.6 (+, 2´-C, diast: 83.1), 107.9 (-, $=CH_2$, diast: 107.5), 114.3 (-, $=CH_2$), 140.4 (Cq, 4-C), 151.6 (Cq, 2´´-C, diast: 151.8), 170.4 (Cq, OAc), 175.5 (Cq, 5´-C, diast: 175.7).- IR (neat): $\tilde{\nu}$ = 3075, 2955, 2873, 1774, 1742, 1651, 1431, 1373, 1235, 1190, 1134, 1088, 1030, 967, 941, 893, 732 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 233.2 (38.58) [M-CH_3COOH], 293.3 (100.00) [MH^+].- HRMS (EI, 70 eV): 292.16849 ($C_{17}H_{24}O_4$ calc. 292.1685 [M^+]).



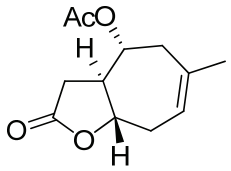
(*R/S*)-(2-methylenecyclopentyl)((2′*S*,3′*S*)-2′-((*R*)-2′′-methylenecyclopentyl)-5′-oxo-tetrahydro-furan-3′-yl)methyl acetate (213i)

Yield = 52%, *dr* = >99:1:0:0.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.46.- m.p. = 77 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50-1.69 (m, 4H, 2x CH_2), 1.72-1.91 (m, 4H, 2x CH_2), 2.09 (s, 3H, OAc), 2.27-2.40 (m, 4H, 2x CH_2), 2.51-2.87 (m, 5H, 2-H, 3′-H, 4′-H, 1′′-H), 4.26-4.32 (m, 1H, 1-H), 4.85-4.92 (m, 2H, =CH_2), 5.03-3.07 (m, 2H, =CH_2), 5.15 (dd, *J* = 7.7, 2.5 Hz, 1H, 2′-H).- ^{13}C NMR (MHz, $CDCl_3$): δ = 20.8 (+, OAc), 23.7 (-, CH_2), 24.3 (-, CH_2), 27.3 (-, CH_2), 28.6 (-, CH_2), 29.7 (-, CH_2), 32.7 (-, CH_2), 33.7 (-, CH_2), 41.0 (+, 3′-C), 47.0 (+, 1′′-C), 47.5 (+, 2-C), 72.6 (+, 1-C), 84.0 (+, 2′-C), 107.8 (-, =CH_2), 108.4 (-, =CH_2), 151.6 (Cq, C=), 151.8 (Cq, C=), 170.8 (Cq, OAc), 176.0 (Cq, 5′-C).- IR (KBr): $\tilde{\nu}$ = 3077, 2948, 2869, 1755, 1737, 1654, 1447, 1373, 1311, 1283, 1234, 1204, 1165, 1124, 1099, 1055, 1019, 988, 963, 947, 908, 886, 738, 702, 648, 628, 592 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 318.3 (4) [M^+].- HRMS (EI, 70 eV): 318.1835 ($C_{19}H_{26}O_4$: calc. 318.1831 [M^+]).

11.9.3 Ring Closing Metathesis

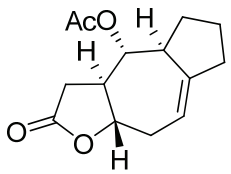
General procedure for RCM:

Diene **213** was dissolved in abs. toluene (10 ml/mmol dien) and a gentle stream of nitrogen was passed through the solution via a Teflon tube. The reaction vessel was heated to 95 °C in an oil bath and Grubbs 2nd gen (5 mol% in abs. toluene (1 ml)) was added every 2 h to a total of 15 mol%). The reaction mixture was cooled to rt and the solvent was evaporated in vacuo and flash chromatography (hexanes:ethylacetate 3:1) afforded the corresponding products.



(3a*R*,4*R/S*,8a*S*,*Z*)-6-methyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209b)

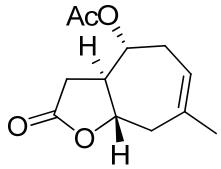
Yield: 96%, *dr* = 68:32.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.17.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3H, Me, diast: 1.73), 2.06 (s, 3H, OAc, diast: 2.09), 2.23-2.82 (m, 7H, 3-H, 3a-H, 5-H, 8-H), 3.94-4.06 (m, 1H, 4-H, diast: 4.29-4.41), 4.73-4.85 (m, 1H, 8a-H, diast: 5.15-5.23), 5.51-5.66 (m, 1H 7-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (+, OAc, diast: 21.0), 27.6 (+, Me, diast: 28.2), 32.0 (-, CH_2, diast: 32.7), 35.3 (-, 3-C, dist: 33.0), 39.4 (-, CH_2, diast: 37.0), 52.3 (+, 3a-C, diast: 50.3), 71.3 (+, 4-C, diast: 67.5), 77.4 (+, 8a-C, diast: 79.75), 119.9 (+, 7-C, diast: 120.7), 135.3 (Cq, 6-C, diast: 135.7) , 170.1 (Cq, OAc, diast: 170.35), 174.5 (Cq, 2-C, diast: 174.7).- IR (neat): $\tilde{\nu}$ = 3630, 3548, 3032, 2935, 2855, 1938, 1788, 1738, 1435, 1373, 1238, 1200, 1131, 1095, 1032, 1005, 964, 923, 904, 872, 817, 712 cm^{-1}.- MS (EI, 70V): *m/z* (%) = 43.1 (100) [CH_3CO^+], 164.0 (70) [M^+-CH_3COOH).- HRMS (EI, 70 eV): 225.1132 ($C_{12}H_{17}O_4$: calc. 225.1127 [$M+H^+$]).



(3a*R*,4*R/S*,4a*S*,9a*S*,*Z*)-2-oxo-2,3,3a,4,4a,5,6,7,9,9a-decahydroazuleno[6,5-b]furan-4-yl-acetate (209c)

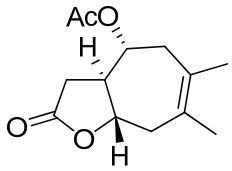
Yield: 76%, *dr* = 84:16.- R_f (hexanes:ethylacetate: 3:1, Mostain) = 0.25.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30-1.53 (m, 2H, CH_2), 1.59-1.77 (m, 2H, CH_2), 1.89-2.01 (m, 1H, 4a-H), 2.07

(s, 3H, OAc), 2.19-2.75 (m, 7H, 3-H, 3a-H, 2xCH_2), 3.92-4.06 (m, 1H, 4-H), 4.69-4.87 (m, 1H, 9a-H), 5.56-5.75 (m, 1H, 8-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (+, OAc), 24.4 (-, CH_2), 31.95 (-, CH_2), 32.2 (-, CH_2), 34.9 (-, 3-C), 36.45 (-, CH_2), 48.65 (+, 4a-C), 52.4 (+, 3a-C), 74.7 (+, 4-C), 80.2 (+, 9a-C), 116.3 (+, 8-C), 145.8 (Cq, 7a-C) 170.4 (Cq, OAc), 174.4 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2944, 2868, 1790, 1771, 1738, 1429, 1372, 1237, 1173, 1155, 1133, 1078, 1025, 1006, 954, 915, 869, 849, 822, 611 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 191.1 (100) [M-CH_3COO^-], 251.1 (12) [M+H^+], 267.1 (20) [M+NH_4^+].



(3a*S*,4*R/S*,8a*S*,*Z*)-7-methyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209d)

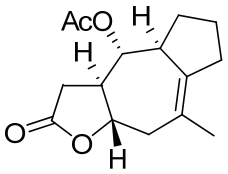
Yield: 93%, *dr* = 80:20.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.19, diast: 0.16.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79 (s, 3H, Me, diast: 1.66), 2.04 (s, 3H, OAc, diast: 2.08), 2.13-2.32 (m, 1H, 3a-H), 2.35-2,73 (m, 6H, 3-H, 5-H, 8-H), 3.98-4.11 (m, 8a-H, 1H diast: 4.34-4.51), 4.68-4.79 (m, 1H, 4-H, diast: 5.10-5.17), 5.42-5.52 (m, 1H, 6-H, diast: 5.29-5.39).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (+, OAc), 26.9 (+, CH_3), 33.4 (-, 5-C, diast: 31.2), 35.3 (-, 3-C, diast: 32.8), 37.8 (-, 8-C, diast: 39.0), 52.2 (+, 3a-C, diast: 49.4), 72.1 (+, 4-C, diast: 67.9), 79.1, (+, 8a-C, diast: 76.7), 120.2 (+, 6-C), 136.1 (Cq, 7-C, diast: 135.4), 170.1 (Cq, OAc, diast: 170.4), 174.7 (Cq, 2-C, diast: 174.9).- IR (neat): $\tilde{\nu}$ = 2937, 2855, 1788, 1743, 1664, 1445, 1373, 1242, 1203, 1149, 1133, 1069, 1030, 1001, 964, 908, 870, 831, 795, 699 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 43.1 (100) [CH_3CO+], 164.1 (32) [M^+-CH_3CO_2H), 225.2 (2) [MH^+].- HRMS (EI, 70 eV): 225.1121 ($C_{12}H_{17}O_4$: calc. 225.1127 [M+H^+]).



(3a*S*,4*R/S*,8a*S*,*Z*)-6,7-dimethyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209e)

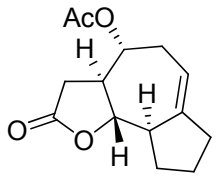
Yield: 91%, *dr* = 75:25.- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.26, diast: 0.20.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 6H, 2x Me, diast: 1.67, 1.77), 2.05 (s, 3H, OAc, diast: 2.08), 2.22 (dd, *J* = 14.0, 2.2 Hz, 1H, 3-H), 2.37-2.65 (m, 6H, 3-H, 3a-H, 5-H, 8-H), 3.87-3.97 (m,

1H, 8a-H, diast: 4.19-4.31), 4.61-4.74 (m, 1H, 4-H, diast: 4.09-5.19).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (+, OAc, diast: 20.9), 21.9 (+, CH_3, diast: 22.0), 22.3 (+, CH_3, diast: 23.2), 35.4 (-, 3-C, diast: 32.7), 38.9 (-, CH_2, diast: 38.0), 41.1 (-, CH_2, diast: 39.9), 52.7 (+, 3a-C, diast: 50.2), 71.4 (+, 4-C, diast: 67.7), 79.5 (+, 8a-C, diast: 77.4), 127.0 (Cq, C=C, diast: 126.7), 128.4 (Cq, C=C, diast: 127.7), 170.2 (Cq, OAc, diast: 170.4), 174.8 (Cq, 2-C, diast: 174.9).- IR (neat): $\tilde{\nu}$ = 2994, 2920, 2861, 1788, 1730, 1445, 1372, 1242, 1203, 1177, 1137, 1096, 1032, 984, 962, 912, 880, 857, 821, 701 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 43.1 (100) [CH_3CO+], 178.1 (34) [M^+-CH_3CO_2H), 238.2 (2) [MH^+].- HRMS (EI, 70 eV): 238.1203 ($C_{13}H_{18}O_4$: calc. 238.1205 [$M+H^+$]).



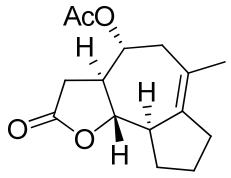
(3a*R*,4*R*,4a*S*,9a*S*,*Z*)-8-methyl-2-oxo-2,3,3a,4,4a,5,6,7,9,9a-decahydroazuleno[6,5-b] furan-4-yl acetate (209f)

Yield: 78%, *dr* >99:1.- $[\alpha]_D^{20}$ = +83.8 (c = 0.525, $CHCl_3$).- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.33.- m.p. = 106 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29-1.48 (m, 2H, CH_2), 1.52-1.69 (m, 2H, CH_2), 1.74 (s, 3H, CH_3), 1.81-1.96 (m, 1H, 4a-H), 2.0 (s, 3H, OAc), 2.08-2.29 (m, 2H, CH_2), 2.34-2.52 (m, 4H, 3-H, CH_2,), 2.53-2.68 (m, 1H, 3a-H), 3.93 (ddd, *J* = 8.9, 8.8, 4.3 Hz, 1H, 9a-H), 4.64-4.76 (m, 1H, 4a-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (+, OAc), 23.7 (+, CH_3), 24.3 (-, CH_2), 31.8 (-, CH_2), 33.6 (-, CH_2), 35.2 (-, 3-C), 38.9 (-, CH_2), 48.6 (+, 4a-C), 53.1 (+, 3a-C), 74.4 (+, 4-C), 79.7 (+, 9a-C), 124.8 (Cq, C=C), 138.1 (Cq, C=C), 170.5 (Cq, OAc), 174.6 (Cq, 2-C).- IR (KBr): $\tilde{\nu}$ = 2953, 2858, 1789, 1734, 1435, 1374, 1240, 1198, 1123, 1080, 1026, 989, 960, 916, 856, 670, 601, 563 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 205.2 (18.7) [$M+H^+$-CH_3CO_2H), 222.2 (1.9) [$M+NH_4^+$-CH_3CO_2H], 282.3 (100) [$M+NH_4^+$].- CH: $C_{15}H_{20}O_4$ calc. C 68.16, H 7.63; found: C 68.01, H 7.85.



(3a*S*,4*R/S*,9a*R*,9b*S*,*Z*)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (209g)

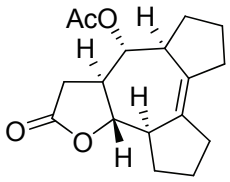
Yield: 87%, *dr* = 79:21.- R_f (hexanes:ehtylacetate 3:1, Mostain) = 0.21, diast: 0.15.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41-1.58 (m, 2H, CH_2, diast: 1.18-1.28), 1.60-1.83 (m, 3H, 9a-H, CH_2), 2.04 (s, 3H, OAc, diast: 2.08), 2.27-2.73 (m, 6H, 2xCH_2, 3-H, 3a-H), 2.63 (dd, *J* = 14.3, 5.21 Hz, 1H, 3-H), 3.74-3.83 (m, 1H, 9b-H), 4.72 (dt, *J* = 10.3, 3.3 Hz, 1H, 4-H, diast: 5.15), 5.56-5.66 (m, 1H, 6-H).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (+, OAc), 24.9 (-, 8-C, diast: 25.2), 32.1 (-, 9-C, diast: 32.2), 33.8 (-, 7-C), 35.0 (-, 5-C), 35.4 (-, 3-C), 46.9 (+, 9a-C), 49.6 (+, 3a-C, diast: 51.8), 71.7 (+, 4-C), 83.8 (+, 9b-C, diast: 81.1), 115.8 (+, 6-C, diast: 116.1), 146.9 (Cq, 6a-C), 170.1 (Cq, OAc), 174.7 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2969, 2948, 2864, 1769, 1734, 1433, 1376, 1239, 1190, 1159, 1121, 1084, 1028, 1002, 971, 953, 917, 895, 842, 768, 706, 659, 524 cm^{-1}.- MS (EI, 70V): *m/z* (%) = 43.1 (100) [CH_3CO^+], 190.1 (93) [M^+-CH_3COOH).- HRMS (EI, 70 eV): 251.1282 ($C_{14}H_{19}O_4$: calc. 251.1283 [M+H^+]).



(3a*S*,4*R/S*,9a*R*,9b*S*,*Z*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b] furan-4-yl acetate (209h)

Yield: 96%, *dr* = 72:28.- R_f (hexanes:ehtylacetate 3:1, Mostain) = 0.24, diast: 0.15.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39-1.56 (m, 2H, CH_2, diast: 1.11-1.33), 1.60-1.83 (m, 2H, CH_2), 1.74 (s, 3H, Me, diast: 1.66), 2.04 (s, 3H, OAc, diast: 2.07), 2.08-2.17 (m, 1H, 9a-H), 2.21 (dd, *J* = 14.1, 2.6 Hz, 1H, 3-H), 2.27-2.73 (m, 6H, 2xCH_2, 3-H, 3a-H), 3.66-3.77 (m, 1H, 9b-H), 4.70 (dt, *J* = 10.4, 2.3 Hz, 1H, 4-H, diast: 5.12).- ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (+, OAc, diast: 20.9), 23.9 (+, CH_3, diast: 24.7), 24.8 (-, 8-C, diast: 25.1), 31.9 (-, 9-C, diast: 32.0), 32.9 (-, 7-C, diast: 32.8), 35.2 (-, 3-C, diast: 33.3), 41.4 (-, 5-C, diast: 38.3), 46.8 (+, 9a-C, diast: 47.9), 52.3 (+, 3a-C, diast: 50.2), 71.0 (+, 4-C, diast: 67.7), 84.2 (+, 9b-C, diast: 81.7), 123.8 (Cq, C=C, diast: 123.9), 139.5 (Cq, C=C, diast: 138.6), 170.1 (Cq, OAc, diast: 170.5), 174.8 (Cq, 2-C, diast: 174.9).- IR (neat): $\tilde{\nu}$ = 2940, 2868, 1788, 1729, 1627, 1428,

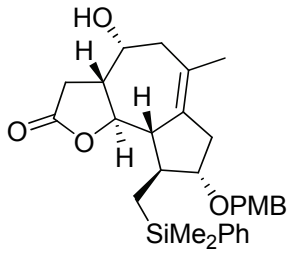
1372, 1254, 1186, 1113, 1091, 1030, 992, 955, 920, 850, 705, 675 cm^{-1}.- MS (EI, 70V): *m/z* (%) = 43.1 (100) [CH_3CO^+], 204.1 (71) [M^+-CH_3COOH).- HRMS (EI, 70 eV): 265.1442 ($C_{15}H_{21}O_4$: calc. 265.1440 [$M+H^+$]).



(3a*S*,4*R*,5*S*,9a*R*,9b*S*)-6,5-cyclopentanyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno [4,5-b]furan-4-yl acetate (209i)

Yield: 48%, *dr* = >99:1.- $[\alpha]_D^{20}$ = -34.2 (c = 0.500, $CHCl_3$).- R_f (hexanes:ethylacetate 3:1, Mostain) = 0.23.- mp = 125 °C.- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34-1.64 (m, 4H, 2x CH_2), 1.69-1.85 (m, 2H, CH_2), 1.91-2.01 (m, 1H, CH_2), 2.07 (s, 3H, OAc), 2.11-2.25 (m, 3H, CH_2), 2.27-2.40 (m, 2H, CH_2), 2.44-2.56 (m, 3H, 3a-H, CH_2), 2.56-2.67 (m, 2H, 4a-H, 10a-H), 3.74-3.86 (m, 1H, 10b-H), 4.74-4.87 (m, 1H, 4-H).- ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (+, OAc), 24.3 (-, CH_2), 24.8 (-, CH_2), 32.5 (-, CH_2), 32.8 (-, CH_2), 34.01 (-, CH_2), 34.6 (-, CH_2), 34.7 (-, CH_2), 47.6 (+, 4a-C), 49.0 (+, 10a-C), 50.9 (+, 3a-C), 75.3 (+, 4-C), 84.7 (+, 10b-C), 134.0 (Cq, 7a-C), 135.2 (Cq, 7b-C), 170.4 (Cq, OAc), 174.7 (Cq, 2-C).- IR (KBr): $\tilde{\nu}$ = 2962, 2887, 1785, 1733, 1448, 1425, 1371, 1340, 1235, 1190, 1114, 1084, 1057, 1022, 998, 957, 934, 916, 881, 667, 604, 588 cm^{-1}.- MS (EI, 70V): *m/z* (%) = 43.1 (100) [CH_3CO^+], 230.1 (85) [M^+-CH_3COOH).- HRMS (EI, 70 eV): 290.1525 ($C_{17}H_{22}O_4$: calc. 290.1518 [M^+]).

11.10 Towards Cynaropicrin and Ixerin Y



(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-4-hydroxy-8-(*p*-methoxy-benzyloxy)-6-methyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one (4*R*-216)

Deprotection of 4*R*-**199**:

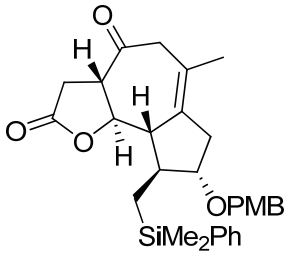
Minor diastereomer 4*R*-**199** (115 mg, 0.210 mmol, 1.0 eq.) was dissolved in MeOH (4 ml) and cooled to 0 °C. K_2CO_3 (16 mg, 0.115 mmol, 0.55 eq.) was added and the mixture was stirred for 1 h at 0 °C and over night at rt. Et_2O (20 ml) was added and the mixture was extracted with H_2O (5 ml) and brine (4 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes:ethylacetate 3:1 to 1:1) to give 80 mg (0.158 mmol, 75%) product as a colorless oil.

Reduction of ketone **217**:

Ketone **217** (29 mg, 0.058 mmol, 1.0 eq.) was dissolved in MeOH (2 ml) and $CeCl_3$ (28 mg, 0.075 mmol, 1.3 eq.) was added. The mixture was stirred until a clear solution was obtained and than cooled to -5 °C before $NaBH_4$ (3 mg, 0.075 mmol, 1.3 eq.) was added. The reaction mixture was stirred for 30 min and than quenched by addition of H_2O (1 ml). The reaction mixture was extracted with CH_2Cl_2 (5 ml). The aqueous layer was again extracted with CH_2Cl_2 (2x5 ml) and the combined org. layers were washed with brine (3 ml), dried (Na_2SO_4), filtered and concentrated to obtain 24 mg (0.048 mmol, 82%) pure product as a colorless oil.

R_f (hexanes:ethylacetate 1:1, Mostain) = 0.37.- $[\alpha]_D^{20}$ = -43.8 (c = 0.5, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 0.31 (s, 3H, SiMe), 0.38 (s, 3H, SiMe), 0.63-0.73 (m, 2H, CH_2Si), 1.56-1.77 (m, 1H, 3a-H), 1.69 (s, 3H, CH_3), 2.13-2.24 (m, 2H, 5-H, 9a-H), 2.25-2.34 (m, 1H, 5-H), 2.30 (dd, *J* = 16.5, 6.5 Hz, 1H, 3-H), 2.37-2.47 (m, 1H, 7-H), 2.50-2.59 (m, 1H, 7-H), 2.64 (dd, *J* = 16.4, 13.6 Hz, 1H, 3-H), 2.78-2.88 (m, 1H, 9-H), 3.55 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 3.81-3.86 (m, 1H, 4-H), 4.04 (dd, *J* = 10.6, 10.6 Hz, 1H, 9b-H), 4.18-4.48 (m, 2H, PMB), 6.77-

6.87 (m, 2H, PMB), 7.11-7.20 (m, 2H, PMB), 7.30-7.38 (m, 3H, Ph), 7.47-7.56 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.7 (+, SiMe), -2.0 (+, SiMe), 21.28 (-, CH_2Si), 25.4 (+, CH_3), 33.8 (-, 3-C), 37.0 (-, 7-C), 40.5 (+, 9-C), 41.7 (-, 5-C), 53.9 (+, 3a-C), 54.9 (+, 9a-C), 55.5 (+, OMe), 66.3 (+, 4-C), 69.8 (-, PMB), 79.6 (+, 9b-C), 86.3 (+, 8-C), 113.9 (+, 2xPMB), 126.2 (Cq, Ph), 127.9 (+, 2xPh), 129.1 (+, Ph), 129.7 (+, 2xPMB), 130.6 (Cq, PMB), 134.1 (+, 2xPh), 138.7 (Cq, 6-C), 139.5 (Cq, 6a-C), 159.3 (Cq, PMB), 175.6 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3442, 3068, 3045, 2950, 2916, 2900, 2398, 2341, 1772, 1743, 1716, 1612, 1514, 1425, 1247, 1197, 1110, 1076, 1037 cm^{-1}.- MS (ES): *m/z* (%) = 298 (72), 338 (73), 391 (59), 428 (40), 507 (100) [M+H$^+$], 524 (90) [M+NH_4^+], 529 (83) [M+Na$^+$].- HRMS (ES): 524.2828 ($C_{30}H_{42}O_5SiN$: calc. 524.2832 [M+NH_4^+]).

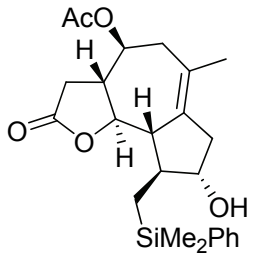


(3a*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-3,3a,7,8,9,9a-hexahydroazuleno[4,5-b]furan-2,4(5H,9bH)-dione (217)

Alcohol 4*R*-**216** (40 mg, 0.079 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (5 ml) under a N_2-atmosphere. Crushed activated molecular sieve (200 mg, 4 Å) was added and at rt PCC (25 mg, 0.116 mmol, 1.5 eq.) was added in portions over 5 min. The reaction mixture was stirred for 5 h. After filtration over celite, the solvent was removed under reduced pressure. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded the product (30 mg, 0.059 mmol, 75%) as a colorless oil.

R_f (hexanes:ethylacetate 2:1, Vanillin) = 0.39.- $[\alpha]_D^{20}$ = 227.8 (c = 0.500, $CHCl_3$).- ^{1}H NMR (400 MHz): δ = 0.32 (s, 3H, SiMe), 0.43 (s, 3H, SiMe), 0.71 (d, *J* = 7.4 Hz, 2H, $SiCH_2$), 1.73 (s, 3H, Me), 2.37 (dd, *J* = 16.2, 5.5 Hz, 1H, 3-H), 2.40-2.60 (m, 3H, 7-H, 3a-H), 2.61-2.72 (m, 2H, 9a-H, 5-H), 2.79 (dd, *J* = 16.2, 12.6 Hz, 1H, 3-H), 2.82-2.91 (m, 1H, 9-H), 3.10-3.20 (m, 1H, 5-H), 3.57-3.63 (m, 1H, 8-H), 3.79 (s, 3H, OMe), 3.95 (dd, *J* = 10.4, 10.4 Hz, 1H, 9b-H), 4.19-4.45 (m, 2H, PMB), 6.79-6.88 (m, 2H, PMB), 7.11-7.19 (m, 2H, PMB), 7.32-7.41 (m, 3H, Ph), 7.52-760 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -3.2 (+, SiMe), -2.1 (+, SiMe), 21.0 (-, $SiCH_2$), 23.6 (+, Me), 31.7 (-, 3-C), 37.7 (-, 7-C), 40.9 (+, 9-C), 50.1 (-, 5-C), 54.2 (+, 9a-C), 55.4 (+, OMe), 60.4 (+, 3a-C), 69.9 (-, PMB), 83.9 (+, 9b-C), 86.0 (+, 8-C), 113.9 (+,

2x PMB), 123.6 (Cq, Ph), 127.9 (+, 2xPh), 129.3 (+, Ph), 129.5 (+, 2x PMB), 130.4 (Cq, PMB), 134.2 (+, 2xPh), 138.9 (Cq, 6a-C), 139.4 (Cq, 6-C), 159.3 (Cq, PMB), 174.3 (Cq, 2-C), 198.9 (Cq, 4-C).- IR (neat): $\tilde{\nu}$ = 3014, 2953, 2904, 1784, 1715, 1610, 1512, 1426, 1300, 1249, 1193, 1112, 1064, 1035, 959, 925, 876, 835, 754, 701 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 44.0 (13.6), 121.0 (100), 135.0 (18.3), 305.1 (39.1), 398.1 (40.0), 426.1 (21.2), 489.2 (20.2) [M^+-CH_3], 504.4 (12.3) [M^+], 505.6 (3.0) [M+H^+].- HRMS (EI, 70eV): 504.2333 ($C_{30}H_{40}O_5Si$): calc. 504.2332 [M^+]).

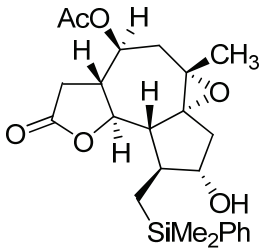


(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (218)

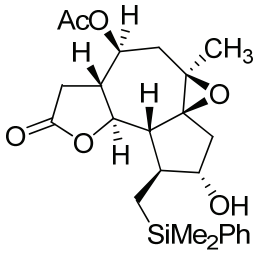
PMB protected 4*S*-**199** (85 mg, 155 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (4 ml) and water (0.2 ml). Subsequently DDQ (42 mg, 186 mmol, 1.2 eq.) was added at rt and the reaction mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (10 ml) and quenched with $NaHCO_3$ (4 ml). The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (2x5 ml). The combined org. layers were washed with water (3 ml), dried (Na_2SO_4) and concentrated in vacuo. Purification on flash silica gel (hexanes:ethylacetate 3:1) afforded 60 mg (140 mmol, 90%) product as a colorless oil.

R_f (hexanes:ethylacetate 3:1, Mostain) = 0.17.-$[\alpha]_D^{20}$ = -46.6 (c = 0.50, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 0.33 (s, 3H, SiMe), 0.36 (s, 3H, SiMe), 0.72-0.78 (m, 2H, $SiCH_2$), 1.72 (s, 3H, CH_3), 1.87-1.99 (m, 1H, 9a-H), 2.02 (s, 3H, OAc), 2.07-2.12 (m, 1H, 5-H), 2.16-2.21 (m, 1H, 5-H,), 2.21-2.25 (m, 1H, 3a-H), 2.31 (dd, *J* = 16.7, 13.3 Hz, 1H, 3-H), 2.26-2.34 (m, 1H, 7-H), 2.39-2.45 (m, 1H, 9-H), 2.49 (dd, *J* = 16.6, 6.8 Hz, 1H, 3-H), 2.52-2.58 (m, 1H, 7-H), 3.85-3.89 (m, 1H, 8-H), 3.93 (dd, *J* = 10.4, 10.4 Hz, 1H, 9b-H), 4.58 (dt, *J* = 10.6, 2.4 Hz, 1H, 4-H), 7.34-7.37 (m, 3H, Ph), 7.51-7.55 (m, 2H, Ph).- ^{13}C NMR (75.5 MHz): δ = -2.59 (+, SiMe), -2.23 (+, SiMe), 21.17 (-, CH_2Si), 21.26 (+, OAc), 23.39 (+, CH_3), 35.48 (-, 3-C), 38.67 (-, 7-C), 41.38 (-, 5-C), 46.14 (+, 9-C), 53.40 (+, 3a-C), 53.67 (+, 9a-C), 71.07 (+, 4-C), 79.76 (+, 8-C), 83.30 (+, 9b-C), 126.62 (Cq, Ph), 128.03 (+, 2xPh), 129.26 (+, Ph), 134.05 (+, 2xPh), 137.62 (Cq, 6-C), 139.36 (Cq, 6a-C), 170.19 (Cq, OAc), 174.70 (Cq, 2-C).- IR (neat):

$\tilde{\nu}$ = 3458, 3419, 3068, 3047, 2950, 2923, 2907, 2858, 2358, 2341, 1784, 1770, 1733, 1716, 1427, 1373, 1236, 1112, 1027, 835, 700 cm^{-1}.- MS (ES): *m/z* (%) = 220, 221, 295, 304, 429 ($M+H^+$), 446 ($M+NH_4^+$), 451 ($M+Na^+$).- HRMS (ES): 446.2355 ($C_{24}H_{36}O_5SiN$, calc. 446.2363 [$M+NH_4^+$]).



α-**219**



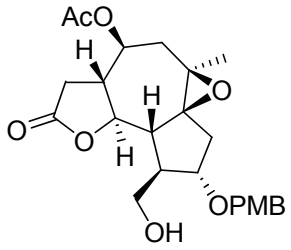
β-**219**

(3a*R*,4*S*,8*S*,9*S*,9*aS*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-6,6a-epoxy-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (219)

Alcohol **218** (60 mg, 0.14 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2 ml) and cooled to 0 °C. *m*CPBA (59 mg, 0.24 mmol, 1.7 eq.) was added and the reaction was allowed to warm slowly to rt over night. CH_2Cl_2 (10 ml) was added and the reaction mixture was extracted with sat. $NaHCO_3$ (2x5 ml) and washed with brine (5 ml). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (hexanes:ethylacetate 3:1) afforded 60 mg (0.135 mmol, 96%) product as a colorless oil (α:β = 20:80).

R_f (hexanes:ethylacetat 3:1, Mostain) = 0.10.- ^{1}H NMR (500 MHz): δ = 0.34 (s, 3H, SiMe, diast: 0.37), 0.36 (s, 3H, SiMe, 0.38), 0.83-0.98 (m, 2H, CH_2Si), 1.23-1.28 (m, 1H, 7-H), 1.37 (s, 3H, CH_3, diast: 1.31), 1.45-1.57, m, 1H, 5-H), 1.69-1.76 (m, 1H, 9a-H), 1.86-1.97 (m, 1H, 3a-H), 2.05 (s, 3H, OAc), 2.23 (dd, *J* = 13.6, 1.9 Hz, 1H, 5-H), 2.34 (dd, *J* = 16.7, 12.9 Hz, 1H, 3-H), 2.44-2.55 (m, 1H, 7-H), 2.55 (dd, *J* = 16.7, 6.9 Hz, 1H, 3-H), 4.05-4.09 (m, 1H, 8-H, diast: 3.70-3.78), 4.27 (dd, *J* = 11.0, 11.0 Hz, 1H, 9b-H, diast: 4.12), 4.71-4.78 (m, 1H, 4-H, diast: 4.84-4.90), 7.33-7.39 (m, 3H, Ph), 7.51-7.55 (m, 2H, Ph, diast: 7.55-7.59).- ^{13}C NMR (75.5 MHz): δ = -2.7 (+, SiMe, diast: -2.6), -2.6 (+, SiMe, diast: -2.3), 19.9 (-, CH_2Si, diast: 22.3), 20.9 (+, OAc, diast: 22.9), 21.4 (+, CH_3), 35.2 (-, 3-C, diast: 34.5), 38.6 (-, 7-C, diast: 39.6), 44.6 (-, 5-C, diast: 39.9), 46.5 (+, 9-C, diast: 48.7), 52.2 (+, 3a-C, diast: 50.8), 54.9 (+, 9a-C), 57.3 (Cq, 6-C, diast: 61.5), 72.4 (+, 4-C, diast: 72.1), 73.7 (Cq, 6a-C), 81.2 (+, 8-C, diast: 80.3), 83.1 (+, 9b-C, diast: 84.2), 130.2 (+, 2xPh, diast:130.27), 131.50 (+, Ph), 136.18 (+, 2xPh, diast: 136.12), 141.04 (Cq, Ph), 172.27 (Cq, OAc), 176.43 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3465, 3068, 3047, 2999, 2954, 2935, 1784, 1737, 1456, 1427, 1373, 1236, 1180,

1168, 1112, 1089, 1029, 999, 966, 891, 837, 792, 754, 734, 702, 667 cm^{-1}.- MS (ES): *m/z* (%) = 197 (50), 343 (22), 371 (30), 399 (25), 445 (10) [M+H^+], 462 (100) [M+NH_4^+], 468 (30) [M+Na^+].- HRMS (ES): 445.2030 ($C_{24}H_{33}O_6Si$: calc. 445.2046 [M+H^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(hydroxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (225)

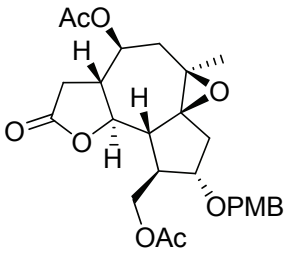
Method A:

Silane 4*S*-**199** (100 mg, 0.182 mmol, 1.0 eq.) was dissolved in glacial acetic acid (1 ml) and ethylacetate (0.5 ml). After cooling to 0 °C peracetic acid (30%, 1.22 ml) was added slowly and the reaction mixture was stirred for 3 h at 0 °C. Carefully $Hg(OAc)_2$ (73 mg, 0.228 mmol, 1.25 eq.) was added and the reaction mixture was stirred for 1 h at 0 °C. Ethylacetate (50 ml) and H_2O (2 ml) was added and the layers were separated. The organic layer was washed with H_2O (2 ml), $NaHCO_3$ sat. (2x2 ml) and brine (2x2 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 1:2) afforded 57 mg (0.128 mmol, 70%) product as a colorless oil.

Method B:

Acetic anhydride (5.4 ml, 57 mmol) was treated with 3 drops of conc. sulfuric acid and cooled to 0 °C. To this solution H_2O_2 (30%, 3.60 ml, 42 mmol) was added carefully and the resulting mixture was stirred for 30 min at rt. Silane 4*S*-**199** was dissolved in 0.1 ml THF and 6 ml of the above fresh prepared solution was added at 0 °C. $Hg(OAc)_2$ (93 mg, 0.202 mmol, 1.6 eq.) was added and the reaction mixture was stirred for 5 h at rt. After diluting the mixture with ethylacetate (30 ml) and H_2O (5 ml) the layers were separated and the aqueous layer was again extracted with ethylacetate (2x15 ml). The combined org. layers were washed (10% Na_2SO_3 (2x 7 ml), sat. $NaHCO_3$ (2x 15 ml) and brine (10 ml)), dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 1:2) afforded 36 mg (0.083 mmol, 46%) free alcohol **225** along with 9 mg (0.018 mmol, 10%) acetyl protected product **226**.

R_f (hexanes:ethylacetat 1:2, Mostain) = 0.30.- $[\alpha]_D^{20}$ = +31.8 (c = 0.425, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 1.39 (s, 3H, Me), 1.77 (dd, *J* = 13.1, 12.2 Hz, 1H, 5-H), 2.00-2.11 (m, 2H, 7-H, 9a-H), 2.06 (s, 3H, OAc), 2.17 (dd, *J* = 15.3, 5.1 Hz, 1H, 7-H), 2.30-2.46 (m, 3H, 3-H, 3a-H, 5-H), 2.63 (dd, *J* = 15.3, 5.4 Hz, 1H, 3-H), 2.70-2.77 (m, 1H, 9-H), 3.69 (d, *J* = 6.5 Hz, 2H, CH_2OH), 3.79 (s, 3H, OMe), 4.06-4.15 (m, 1H, 8-H), 4.21 (dd, *J* = 11.3, 9.9 Hz, 1H, 9b-H), 4.36-4.54 (m, 2H, PMB), 4.78-4.86 (m, 1H, 4-H), 6.84-6.89 (m, 2H, PMB), 7.22-7.28 (m, 2H, PMB).- ^{13}C NMR (75.5 MHz): δ = 21.0 (+, CH_3), 21.5 (+, OAc), 35.3 (-, 3-C), 38.2 (-, 7-C), 44.7 (-, 5-C), 49.1 (+, 9-C), 49.7 (+, 9a-C), 52.2 (+, 3a-C), 55.3 (+, PMB), 58.9 (Cq, 6-C), 63.6 (-, CH_2OH), 69.9 (+, 4-C), 70.7 (Cq, 6a-C), 71.1 (-, PMB), 79.5 (+, 8-C), 81.1 (+, 9b-C), 113.9 (+, 2xPMB), 129.7 (+, 2x PMB), 130.1 (Cq, PMB), 159.5 (Cq, PMB), 170.1 (Cq, OAc), 173.8 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3515, 2933, 2875, 1784, 1612, 1586, 1514, 1423, 1373, 1302, 1251, 1174, 1030, 997, 966, 914, 892, 825 cm^{-1}.- MS (EI, 70eV): *m/z* (%) = 121.0 (100) [$CH_2C_6H_4OMe^+$], 446.1 (3.8) [M^+].- HRMS (EI, 70eV): 446.1945 ($C_{24}H_{30}O_8$: calc. 446.1941 [M^+]).

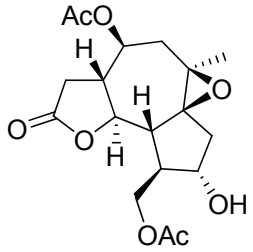


(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(acetoxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (226)

Alcohol **225** (35 mg, 78 µmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) under a N_2-atmosphere. NEt_3 (16 mg, 22 µl, 157 µmol, 2.0 eq.), DMAP (1 mg, 7.84 µmol, 10 mol%) and acetic anhydride (16 mg, 157 µmol, 2.0 eq.) were added at rt. The reaction mixture was stirred over night. The solvent was removed under reduced pressure and chromatography on silica gel (hexanes:ethylacetate 1:1) afforded 38 mg (78 µmol, 99%) product as a white foam.

R_f (hexanes:ethylacetat 1:1, Mostain) = 0.26.- $[\alpha]_D^{20}$ = +30.5 (c = 0.475, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 1.39 (s, 3H, CH_3), 1.69-1.82 (m, 1H, 5-H), 2.06 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.00-2.12 (m, 2H, 5-H, 9a-H), 2.19 (dd, *J* = 15.5, 4.5 Hz, 1H, 7-H), 2.29-2.48 (m, 3H, 3-H, 3a-H, 7-H), 2.64 (dd, *J* = 14.7, 5.0 Hz, 1H, 3-H), 2.87-2.96 (m, 1H, 9-H), 3.79 (s, 3H, OMe), 3.98-4.29 (m, 4H, CH_2OAc, 9b-H, 8-H), 4.33-4.54 (m, 2H, PMB), 4.76-4.88 (m, 1H, 4-H), 6.83-6.90 (m, 2H, PMB), 7.21-7.27 (m, 2H, PMB).- ^{13}C NMR (75.5 MHz): δ = 20.9 (+,

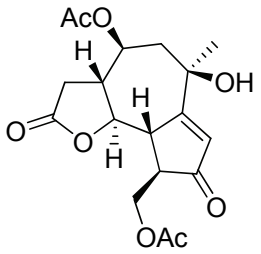
CH_3), 21.4 (+, 2xOAc), 35.3 (-, 3-C), 38.2 (-, 7-C), 44.8 (-, 5-C), 45.9 (+, 9-C), 50.2 (+, 9a-C), 52.2 (+, 3a-C), 55.3 (+, OMe), 58.5 (Cq, 6-C), 64.3 (-, CH_2OAc), 69.9 (+, 4-C), 70.6 (Cq, 6a-C), 70.9 (-, PMB), 79.2 (+, 8-C), 80.8 (+, 9b-C), 113.9 (+, 2xPMB), 129.7 (+, 2xPMB), 129.8 (Cq, PMB), 159.4 (Cq, PMB), 169.9 (Cq, OAc), 170.9 (OAc), 173.6 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2998, 2937, 2876, 1784, 1738, 1612, 1586, 1514, 1462, 1423, 1371, 1302, 1238, 1173, 1150, 1133, 1077, 1030, 998, 967, 871, 893, 848, 754 cm^{-1}.- MS (EI, 70eV): *m/z* (%) = 43.1 (35.4), 121.1 (100), 137.1 (29.3), 488.2 (1.66) [M+].- HRMS (EI, 70eV): 488.2044 ($C_{26}H_{32}O_9$: calc. 488.2046 [M^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(acetoxymethyl)-8-hydroxy-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (227)

Compound **226** (47 mg, 96 µmol, 1.00 eq.) was dissolved in CH_2Cl_2 (4 ml) and water (0.5 ml). DDQ (33 mg, 145 µmol, 1.51 eq.) was added in small portions at rt and the solution was stirred for 5 h. H_2O (2 ml) and CH_2Cl_2 (5 ml) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 3 ml), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 3:1) afforded 32 mg (87 µmol, 90%) product as a colorless solid.

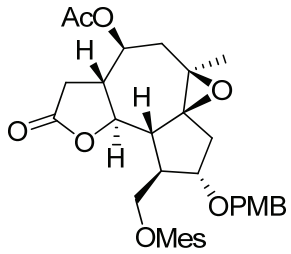
R_f (hexanes:ethylacetat 1:3, Mostain) = 0.21.- $[\alpha]_D^{20}$ = +12.7 (c = 0.245, $CHCl_3$).- m.p. = 63 °C.- ^{1}H NMR (600 MHz): δ = 1.41 (s, 3H, CH_3), 1.70-1.80 (m, 1H, 5-H), 1.95 (dd, *J* = 14.5, 6.3 Hz, 1H, 7-H), 2.07 (s, 3H, OAc), 2.08-2.10 (m, 1H, 9b-H), 2.09 (s, 3H, OAc), 2.16 (dd, *J* = 14.5, 6.9 Hz, 1H, 7-H), 2.31-2.40 (m, 2H, 3a-H, 5-H), 2.46 (dd, *J* = 16.7, 12.7 Hz, 1H, 3-H), 2.48-2.53 (m, 1H, 9-H), 2.64 (dd, *J* = 16.7, 6.7 Hz, 1H, 3-H), 4.17-4.26 (m, 3H, CH_2OAc, 9b-H), 4.27-4.32 (m, 1H, 8-H), 4.82-4.89 (m, 1H, 4-H).-^{13}C NMR (150 MHz): δ = 20.9 (+, 2x Ac), 21.2 (+, CH_3), 35.1 (-, 3-C), 39.8 (-, 7-C), 44.8 (-, 5-C), 49.6 (+, 9a-C), 50.2 (+, 9-C), 51.9 (+, 3a-C), 58.5 (Cq, 6-C), 64.4 (-, CH_2OAc), 69.8 (+, 4-C), 69.9 (Cq, 6a-C), 81.6 (+, 9b-C), 169.9 (Cq, OAc), 171.3 (Cq, OAc), 173.7 (Cq, 2-C).- IR (KBr): $\tilde{\nu}$ = 3448, 2937, 1783, 1735, 1458, 1375, 1238, 1168, 1133, 1093, 1066, 1029, 996, 967, 917, 873, 742, 669 cm^{-1}.- MS (EI, 70eV): *m/z* (%) = 350 (60) [M^+-H_2O], 368.2 (15) [M^+].- HRMS (EI, 70eV): 368.1472 ($C_{18}H_{24}O_8$: calc. 368.1471 [M^+]).



(3a*R*,4*S*,6*R*,9*R*,9a*S*,9b*R*)-6-hydroxy-9-(acetoxymethyl)-6-methyl-2,8-dioxo-2,3,3a,4,5,6, 8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (231)

Alcohol **227** (20 mg, 54 µmol, 1.0 eq.) was dissolved under a N_2-atmosphere in abs. CH_2Cl_2 (1 ml) and crushed MS (4 Å, 50 mg) was added. PCC (15 mg, 71 µmol, 1.30 eq.) was added in portions. The reaction mixture was stirred at rt for 5 h before being filtered over celite and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 1:2) afforded 16 mg (44 µmol, 80% product as a colorless solid, which can be recrystallized from acetonitrile.

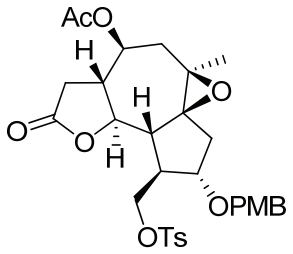
R_f (hexanes:ethylacetat 1:2, Mostain) = 0.10.- $[\alpha]_D^{20}$ = -0.8 (c = 0.40, CH_3CN).- m.p. = 191 °C (decomp).- ^{1}H NMR (600 MHz, CD_3CN): δ = 1.51 (s, 3H, CH_3), 1.96 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.07-2.10 (m, 2H, 5-H), 2.41 (dd, *J* = 17.2, 12.3 Hz, 1H, 3-H), 2.65 (dd, *J* = 17.2, 8.0 Hz, 1H, 3-H), 2.71-2.75 (m, 1H, 9-H), 3.37-3.41 (m, 1H, 9a-H), 3.46-3.52 (m, 1H, 3a-H), 3.53 (s, 1H, OH), 4.05 (dd, *J* = 10.6, 10.6 Hz, 1H, 9b-H), 4.21 (dd, *J* = 11.2, 5.3 Hz, 1H, CH_2OAc), 4.32 (dd, *J* = 11.2, 4.0 Hz, 1H, CH_2OAc), 4.95-4.99 (m, 1H, 4-H), 6.08 (d, *J* = 1.7 Hz, 1H, 7-H).- ^{13}C NMR (150 MHz, CD_3CN): δ = 20.9 (+, OAc), 21.4 (+, OAc), 30.8 (+, CH_3), 36.2 (-, 3-C), 45.2 (+, 3a-C), 45.5 (-, 5-C), 50.2 (+, 9a-C), 51.6 (+, 9-C), 63.6 (-, CH_2OAc), 72.4 (Cq, 6-C), 73.4 (+, 4-C), 83.2 (+, 9b-C), 130.3 (+, 7-C), 171.1 (Cq, OAc), 171.7 (Cq,OAc), 175.8 (Cq, 2-C), 182.3 (Cq, 6a-C), 206.8 (Cq, 8-C).- IR (KBr): $\tilde{\nu}$ = 3475, 2982, 2939, 1778, 1765, 1726, 1712, 1604, 1456, 1426, 1383, 1311, 1264, 1199, 1158, 1105, 1076, 1034, 1006, 971, 887 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 180.1 (73.8), 324.0 (32.1) [M-HOAc], 384.1 (100.0) [M+NH_4^+].- HRMS (PI-LSIMS, MeOH/Glycerin): 367.1383 ($C_{18}H_{22}O_8$: calc. 367.1393 [M+H^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(methylsulfinyloxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (233)

Under a N_2-atmosphere alcohole **225** (17.5 mg, 39 µmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) and cooled to 0 °C. NEt_3 (16 mg, 22 µl, 157 µmol, 4.0 eq.) and MesCl (13 mg, 9 µl, 118 µmol, 3.0 eq.) were added and the mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with 5% $NaHCO_3$ (2x 1 ml) and brine (1 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated at rt to afford the crude product (19 mg, 36 µmol, 92%) as a colorless oil, which was used without further purification.

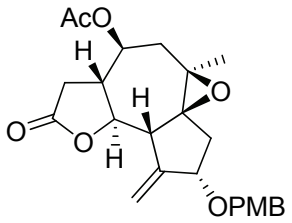
R_f (hexanes:ethylacetat 1:2, Mostain) = 0.41.- ^{1}H NMR (300 MHz): δ = 1.39 (s, 3H, CH_3), 1.68-1.82 (m, 1H, 5-H), 2.00-2.08 (m, 1H, 9a-H), 2.09-2.23 (m, 2H,7-H), 2.06 (s, 3H, OAc), 2.28-2.49 (m, 3H, 3-H, 3a-H, 5-H), 2.56-2.69 (m, 1H, 3-H), 2.82-2.91 (m, 1H, 9-H), 3.01 (s, 3H, Mes), 3.79 (s, 3H, OMe), 4.04-4.14 (m, 1H, 8-H), 4.14-4.24 (m, 1H, 9b-H), 4.28 (dd, *J* = 5.5, 2.5 Hz, 2H, CH_2OMes), 4.37-4.54 (m, 2H, PMB), 4.75-4.89 (m, 1H, 4-H), 6.80-6.94 (m, 2H, PMB), 7.19-7.29 (m, 2H, PMB).- IR (neat): $\tilde{\nu}$ = 3099, 3007, 2937, 2480, 2360, 2339, 1788, 1732, 1612, 1586, 1514, 1460, 1423, 1357, 1317, 1247, 1174, 1078, 1031, 968, 915, 895, 823, 801 cm^{-1}.- MS (CI, NH_4^+): *m/z* (%) = 542.1 (100) [M+NH_4^+].- HRMS (EI, 70eV): 524.1710 ($C_{25}H_{32}SO_{10}$: calc. 524.1716 [M+H^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(tosyloxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (234)

The primary alcohol **225** (34 mg, 76 µmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml). Dry pyridine (50 µl, 610 µmol, 8.0 eq.) and freshly recrystallized TosCl (58 mg, 304 µmol, 4.0 eq.) were added. The reaction mixture was stirred at rt over night and was diluted with CH_2Cl_2 (10 ml) and extracted with sat. $NaHCO_3$ (2x2 ml) and brine (2 ml), dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 1:1) afforded 30 mg (50 µmol, 66%) product as a white foam along with 6 mg (13 µmol, 18%) unreacted starting material **225**.

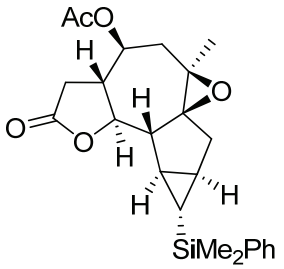
R_f (hexanes:ethylacetate 2:1, Mostain) = 0.12.- $[\alpha]_D^{20}$ = +21.3 (c = 0.60, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 1.36 (s, 3H, CH_3), 1.63-1.75 (m, 1H, 5-H), 1.90-2.00 (m, 2H, 5-H, 9a-H), 2.06 (m, 3H, OAc), 2.07-2.17 (m, 1H, 7-H), 2.17-2.27 (m, 1H, 3a-H), 2.27-2.39 (m, 2H, 3-H, 7-H), 2.43 (s, 3H, Tos), 2.59 (dd, *J* = 16.5, 6.6 Hz, 1H, 3-H), 2.68-2.78 (m, 1H, 9-H), 3.80 (s, 3H, OMe), 4.00-4.17 (m, 4H, 8-H, 9b-H, CH_2OTos), 4.26-4.42 (m, 2H, PMB), 4.72-4.84 (m, 1H, 4-H), 6.81-6.91 (m, 2H, PMB), 7.13-7.22 (m, 2H, PMB), 7.32-3.29 (m, 2H, Tos), 7.76-7.85 (m, 2H, Tos).-^{13}C NMR (75 MHz): δ = 20.9 (+, CH_3), 21.3 (+, OAc), 21.7 (+, Tos), 35.0 (-, 3-C), 37.8 (-, 7-C), 44.5 (-, 5-C), 46.7 (+, 9-C), 48.6 (+, 9a-C), 51.9 (+, 3a-C), 55.3 (+, OMe), 58.4 (Cq, 6-C), 69.1 (-, CH_2OTos), 69.7 (+, 4-C), 69.8 (Cq, 6a-C), 71.3 (-, PMB), 78.1 (+, 8-C), 80.9 (+, 9b-C), 113.9 (+, 2xPMB), 128.1 (+, 2xTos), 129.7 (+, 2x PMB), 129.9 (+, 2xTos), 132.8 (Cq, PMB), 145.0 (Cq, Tos), 159.4 (Cq, PMB), 169.9 (Cq, OAc), 173.4 (Cq, 2-C), 179.7 (Cq, Tos).- IR (neat): $\tilde{\nu}$ = 3003, 2933, 1784, 1734, 1613, 1514, 1456, 1423, 1359, 1301, 1240, 1174, 1095, 1078, 1030, 998, 968, 945, 914, 894, 816, 754, 665 cm^{-1}.- MS (EI, 70 eV): *m/z* (%) = 121.0, 136.1, 600.3 (100) [M^+].- HRMS (EI, 70eV): 600.2039 ($C_{31}H_{36}O_{10}S$: calc. 600.2029 [M^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9a*S*,9b*R*)-9-methylen-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (235)

Tosylate **234** (23 mg, 38 µmol, 1.0 eq.) was dissolved in abs. DMF (0.5 ml). NaI (11 mg, 77 µmol, 2.0 eq.) and DBU (23 µl, 153 µmol, 4.0 eq.) was added and the reaction mixture was slowly heated to 100 °C and stirred for 1 h. After cooling to rt the reaction mixture was diluted with ethylacetate (10 ml) and washed with H_2O (1 ml) and brine (1 ml). After drying over Na_2SO_4 the organic layer was filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 1:2) afforded 9 mg (21 µmol, 55%) product as a colorless oil.

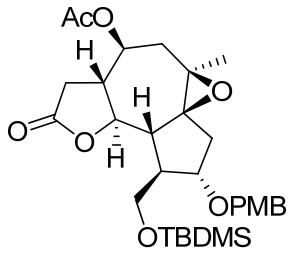
R_f (hexanes:ethylacetate 1:1, Mostain) = 0.46.- $[\alpha]_D^{20}$ = +33.5 (c = 0.20, $CHCl_3$).- ^{1}H NMR (400 MHz): δ = 1.39 (s, 3H, CH_3), 1.72-1.82 (m, 1H, 5-H), 2.06 (s, 3H, OAc), 2.15 (dd, *J* = 16.1, 6.9 Hz, 1H, 7-H), 2.29-2.44 (m, 4H, 3-H, 5-H, 7-H, 3a-H), 2.58-2.67 (m, 2H, 3-H, 9a-H), 3.79 (s, 3H, OMe), 4.25-4.29 (m, 1H, 8-H), 4.31-4.38 (m, 1H, 9b-H), 4.40 (dd, *J* = 130.1, 10.7 Hz, 2H, PMB), 4.78-4.87 (m, 1H, 4-H), 5.43-5.41 (m, 2H, $=CH_2$), 6.81-6.92 (m, 2H, PMB), 7.19-7.27 (m, 2H, PMB).- ^{13}C NMR (75 MHz): δ = 20.9 (+, OAc), 21.3 (+, CH_3) 35.3 (-, 3-C), 39.3 (-, 7-C), 44.8 (-, 5-C), 52.4 (+, 3a-C), 53.6 (+, 9a-C), 55.3 (+, OMe), 59.3 (Cq, 6-C), 69.5 (-, PMB) 69.9 (+, 4-C), 70.7 (Cq, 6a-C), 79.7 (+, 8-C), 80.2 (+, 9b-C), 113.9 (+, 2xPMB), 117.2 (-, $=CH_2$), 129.9 (+, 2xPMB), 130.1 (Cq, PMB), 145.4 (Cq, PMB) 159.3 (Cq, 9-C), 169.9 (Cq, OAc), 173.9 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2996, 2926, 1788, 1734, 1612, 1514, 1456, 1373, 1302, 1244, 1134, 1084, 1053, 1030, 1000, 968, 916, 825, 756 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 446.2 (100) [M+NH_4^+].- HRMS (EI, 70eV): 428.1839 ($C_{24}H_{28}O_7$: calc. 428.1835 [M^+]).



(3a*R*,4*S*,6*S*,6a*S*,9*R*,9a*S*,9b*R*)-6-methyl-2-oxo-1´(dimethyl(phenyl)silyl)-2,3,3a,4,5,7,8,9,9a, 9b-decahydro-1*H*-cyclopropa[*a*]azulen [4,5-b]furan-4-yl acetate (243)

Under an argon atmosphere the secondary alcohol **219** (50 mg, 0.112 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) and abs. pyridine (56 µl, 55 mg, 0.692 mmol, 6.0 eq.) was added. After cooling to 0 °C Tf_2O (30 µl, 45 mg, 0.216 mmol, 2.0 eq.) was added and the reaction mixture was allowed to warm to rt over night. The reaction was quenched by diluting with CH_2Cl_2 (5 ml) and addition of sat. $NaHCO_3$ (2 ml). The layers were separated and the organic layer was washed with brine (3 ml), dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 6 mg (13%, 0.014 mmol) product as a colorless solid, which was crystallized from CH_2Cl_2/hexane.

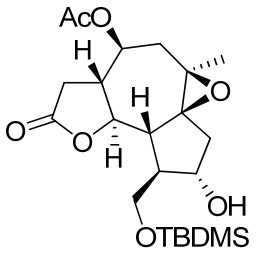
R_f (hexanes:ethylacetat 1:2, Mostain) = 0.69.- $[\alpha]_D^{20}$ = -30.89 (c = 0.60, CH_3Cl3).- m.p. = 159-160 °C.- ^{1}H NMR (600 MHz, $CDCl_3$): δ = -0.11 (dd, *J* = 5.2, 5.2 Hz, 1H, 1´-H), 0.21 (s, 3H, SiMe), 0.23 (s, 3H, SiMe), 1.35 (s, 3H, CH_3), 1.37 (m, 1H, 8-H), 1.63-1.72 (m, 2H, 5-H, 7-H), 1.76 (dd, *J* = 5.2, 5.2 Hz, 1H, 9-H), 2.07 (s, 3H, OAc), 2.20-2.33 (m, 2H, 9a-H, 7-H), 2.36-2.47 (m, 3H, 3-H, 5-H, 3a-H), 2.59-2.68 (m, 1H, 3-H), 3.77-3.87 (m, 1H, 9b-H), 4.78-4.86 (m, 1H, 4-H), 7.32.-7.39 (m, 3H, Ph), 7.50-7.57 (m, 2H, Ph).- ^{13}C NMR (150 MHz, $CDCl_3$): δ = -3.5 (+, SiMe), -3.3 (+, SiMe), 8.9 (+, 1´-C), 19.7 (+, 8-C), 21.1 (+, OAc), 21.2 (+, CH_3), 22.9 (+, 9-C), 35.2 (-, 3-C), 35.6 (-, 5-C), 44.9 (-, 7-C), 51.8 (+, 9a-C), 52.3 (+, 3a-C), 55.6 (Cq, 6-C), 70.2 (+, 4-C), 70.8 (Cq, 6a-C), 81.3 (+, 9b-C), 128.0 (+, 2xPh), 129.3 (+, Ph), 133.9 (+, 2xPh), 138.7 (Cq, Ph), 170.2 (Cq, OAc), 174.3 (Cq, 2-C).- IR (KBr): $\tilde{\nu}$ = 3000, 2953, 2925, 2851, 1778, 1734, 1646, 1462, 1426, 1369, 1248, 1236, 1165, 1147, 1116, 1092, 1027, 991, 940, 896, 871, 832, 806, 779, 733, 698, 679 cm^{-1}.- MS (ES, NH_3): *m/z* (%) = 311.2 (50), 444.21 (100) [M+NH_4^+].- HRMS (ES+): 444.2189 ($C_{24}H_{34}O_5SiN$: calc. 444.2206 [M+NH_4^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(*tert*-butyldimethylsiloxymethyl)-8-(-(*p*-methoxy-benzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (246)

Under a nitrogen atmosphere **225** (129 mg, 0.289 mmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) and NEt_3 (102 mg, 142 µl, 1.011 mmol, 3.5 eq.) was added at rt. TBDMSCl (131 mg, 0.867 mmol, 3.0 eq.) and DMAP (3.5 mg, 0.029 mmol, 10 mol%) dissolved in abs. CH_2Cl_2 (2 ml) was added and the reaction mixture was stirred over night. The reaction was diluted with CH_2Cl_2 (15 ml) and quenched with sat. $NaHCO_3$ (2 ml). The layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (3 ml). The combined org. layers were dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 131 mg (0.232 mmol, 80%) product as a colorless oil.

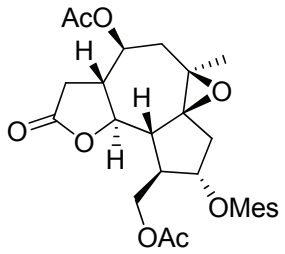
R_f (hexanes:ethylacetat 1:2, Mostain) = 0.68.- $[\alpha]_D^{20}$ = +22.5 (c = 0.40, $CHCl_3$).- ^{1}H NMR (300 MHz): δ = 0.05 (s, 3H, SiMe), 0.06 (s, 3H, SiMe), 0.89 (s, 9H, Si^{t}Bu), 1.38 (s, 3H, CH_3), 1.75 (dd, *J* = 12.5, 12.5 Hz, 1H, 5-H), 1.96-2.09 (m, 2H, 7-H, 9a-H), 2.06 (s, 3H, OAc), 2.17 (dd, *J* = 15.6, 4.1 Hz, 1H, 7-H), 2.25-2.48 (m, 3H, 3-H, 3a-H, 5-H), 2.62 (dd, *J* = 15.6, 5.8 Hz, 1H, 3-H), 2.73-2.85 (m, 1H, 9-H), 3.54 (dd, *J* = 10.2, 7.7 Hz, 1H, CH_2OSi), 3.66 (dd, *J* = 10.2, 5.5 Hz, 1H, CH_2OSi), 3.79 (s, 3H, OMe), 4.11-4.18 (m, 1H, 8-H), 4.26 (dd, *J* = 11.4, 10.0 Hz, 1H, 9b-H), 4.30-4.57 (m, 2H, PMB), 4.76-4.88 (m, 1H, 4-H), 6.82-6.90 (m, 2H, PMB), 7.22-7.29 (m, 2H, PMB).- ^{13}C NMR (75.5 MHz): δ = -5.4 (+, $SiMe_2$), 18.3 (Cq, Si^{t}Bu), 21.0 (+, CH_3), 21.4 (+, OAc), 25.9 (+, ^{t}Bu), 35.3 (-, 3-C), 38.0 (-, 7-C), 44.8 (-, 5-C), 49.0 (+, 9a-C), 49.4 (+, 9-C), 52.4 (+, 3a-C), 55.3 (+, PMB), 58.4 (Cq, 6-C), 62.4 (-, CH_2OSi), 69.9 (Cq, 6a-C), 70.0 (+, 4-C), 70.8 (-, PMB), 78.8 (+, 8-C), 81.0 (+, 9b-C), 113.9 (+, 2xPMB), 129.7 (+, 2xPMB), 130.3 (Cq, PMB), 159.3 (Cq, PMB), 169.9 (Cq, OAc), 173.9 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 2954, 2931, 2857, 1788, 1738, 1612, 1586, 1514, 1467, 1423, 1373, 1302, 1256, 1173, 1112, 1087, 1033, 997, 967, 916, 895, 837, 777, 743, 666 cm^{-1}.- MS (LSIMS, MeOH/Glycerin): *m/z* (%) = 561.4 (22) [MH^+], 653.4 (10) [MH^++Gly], 1121.5 (15) [2M+H^+].- HRMS (LSIMS, MeOH/Glycerin): 561.28760 ($C_{30}H_{45}O_8Si$: calc. 561.2884 [MH^+]).



(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(*tert*-butyldimethylsiloxymethyl)-8-hydroxy-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (247)

Compound **246** (131 mg, 0.234 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (5 ml) and pH 7 phosphate-buffer (1 ml) was added. At rt DDQ (66 mg, 0.292 mmol, 1.25 eq.) was added in portions and the mixture was stirred for 3 h. After diluting with CH_2Cl_2 (5 ml) and H_2O (2 ml) the layers were separated and the aqueous layer was again extracted with CH_2Cl_2 (3 ml). The combined org. layers were dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (hexanes:ethylacetate 2:1) afforded 91 mg (0.207 mmol, 88%) product as a colorless foam.

R_f (hexanes:ethylacetat 1:2, Mostain) = 0.44.- $[\alpha]_D^{20}$ = +12.5 (c = 0.40, $CHCl_3$).- ^{1}H NMR (600 MHz): δ = 0.09 (s, 6H, $SiMe_2$), 0.91 (s, 9H, Si^{t}Bu), 1.42 (s, 3H, Me), 1.55-1.64 (bs, 1H, OH), 1.75 (dd, *J* = 12.7, 12.7 Hz, 1H, 5-H), 1.81-1.90 (m, 2H, 7-H, 9a-H), 2.06 (s, 3H, OAc), 2.11 (dd, *J* = 13.8, 8.9 Hz, 1H, 7-H), 2.26-2.33 (m, 2H, 9-H, 3a-H), 2.32-2.38 (m, 1H, 5-H), 2.46 (dd, *J* = 16.9, 12.9 Hz, 1H, 3-H), 2.63 (dd, *J* = 16.8, 6.7 Hz, 1H, 3-H), 3.59 (dd, *J* = 9.5, 9.5 Hz, 1H, CH_2OSi), 3.91 (dd, *J* = 9.7, 4.8 Hz, 1H, CH_2OSi), 4.12 (dd, *J* = 10.9, 10.9 Hz, 1H, 9b-H), 4.32-4.38 (m, 1H, 8-H), 4.82-4.88 (m, 1H, 4-H).- ^{13}C NMR (75.5 MHz): δ = -5.5 (+, SiMe), -5.4 (+, SiMe), 18.2 (Cq, ^{t}Bu), 20.9 (+, CH_3), 21.2 (+, OAc), 25.9 (+, ^{t}Bu), 35.1 (-, 3-C), 39.6 (-, 7-C), 45.1 (-, 5-C), 48.6 (+, 9a-C), 51.9 (+, 3a-C), 52.6 (+, 9-C), 58.5 (Cq, 6-C), 65.4 (-, CH_2OSi), 69.7 (Cq, 6a-C), 69.8 (+, 4-C), 74.4 (+, 8-C), 82.3 (+, 9b-C), 169.9 (Cq, OAc), 173.6 (Cq, 2-C).- IR (neat): $\tilde{\nu}$ = 3445, 2955, 2929, 2857, 1789, 1731, 1588, 1456, 1373, 1257, 1116, 1003, 967, 917, 894, 838, 778, 742, 667 cm^{-1}.- MS (LSIMS, MeOH/Glycerin): *m/z* (%) = 441.4 (30) [MH^+], 533.3 (10) [MH^++Gly], 881.5 (5) [2M+H^+].- HRMS (LSIMS, MeOH/Glycerin): 441.2316 ($C_{22}H_{37}O_7Si$: calc. 441.2309 [MH^+]).



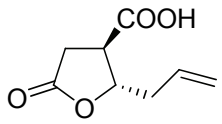
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(acetoxymethyl)- 8-(methylsulfinyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (248)

Under a N_2-atomsphere alcohol **227** (15 mg, 41 µmol, 1.0 eq.) was dissolved in abs. CH_2Cl_2 (2 ml) and cooled to 0 °C. NEt_3 (16 mg, 23 µl, 163 µmol, 4.0 eq.) and MesCl (14 mg, 9 µl, 122 µmol, 3.0 eq.) was added via a syringe. The mixture was stirred for 1 h, diluted with CH_2Cl_2 (4 ml). The reaction mixture was washed with $NaHCO_3$ (5%, 2x1 ml), brine (1 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated at rt affording the crude product (17 mg, 38 µmol, 94%) as a colorless foam, which was used without further purification.

R_f (hexanes:ethylacetat 1:2, Vanillin) = 0.32.- ^{1}H NMR (300 MHz): δ = 1.41 (s, 3H, CH_3), 1.69-1.83 (m, 1H, 5-H), 2.06 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.08-2.16 (m, 1H, 9b-H), 2.26 (dd, *J* = 15.5, 7.0 Hz, 1H, 7-H), 2.33-2.54 (m, 4H, 3-H, 3a-H, 5-H, 7-H), 2.67 (dd, *J* = 15.9, 6.3 Hz, 1H, 3-H), 2.81-2.91 (m, 1H, 9-H), 3.06 (s, 3H, Mes), 4.09 (dd, *J* = 11.5, 9.9 Hz, 1H, 9b-H), 4.22 (d, *J* = 5.5 Hz, 2H, CH_2OAc), 4.80-4.90 (m, 1H, 4-C), 5.08-5.19 (m, 8-H).- IR (neat): $\tilde{\nu}$ = 3019, 2956, 2937, 2856, 2256, 1784, 1770, 1743, 1731, 1455, 1354, 1241, 1173, 1091, 1031, 998, 964, 915, 878, 863, 847, 730 cm^{-1}.- MS (CI, NH_3): *m/z* (%) = 464.0 (100) [M+NH_4^+].- HRMS (EI, 70eV):447.1322 ($C_{19}H_{27}O_{10}S$: calc. 447.1325 [M+H^+].

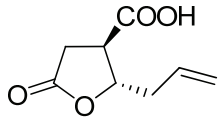
11.11 Stereoselective synthesis of Gcn5 inhibitors

Representative procedure for oxidation of lactone aldehyde 210a to carboxylic acid 261:



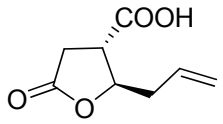
(-)-(2*S*,3*R*)-2-allyl-tetrahydro-5-oxofuran-3-carboxylic acid ((-)-261):

Aldehyde (-)-**210a (**809 mg, 5.25 mmol, 1.0 eq.) was dissolved in CH_3CN (60 ml) and cooled to 0 °C. KH_2PO_4 (430 mg, 3.10 mmol, 0.6 eq., dissolved in 8 ml H_2O), $NaClO_2$ (760 mg, 8.40 mmol, 1.6 eq.) and H_2O_2 (30% in H_2O, 858 µl, 8.40 mmol, 1.6 eq.) was added sequentially and the solution was stirred over night to warm to rt. Na_2SO_3 (1.32 g, 10.50 mmol, 2.0 eq.) was added and stirring was continued for 45 min. The mixture was diluted with water (40 ml) and pH adjusted to 1-2 using aqueous 1 N $KHSO_4$ solution. The solution was extracted with CH_2Cl_2 (4x50 ml), the combined organic layers were dried (Na_2SO_4) and concentrated affording 702 mg (4.13 mmol, 79%) product as a colorless solid.



(-)-(2*S*,3*R*)-2-allyl-tetrahydro-5-oxofuran-3-carboxylic acid ((-)-261)

Yield: 79%.- $[\alpha]_D^{20}$ = -34.1 (c = 0.512, $CHCl_3$).- m.p. = 72-74 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68-2.45 (m, 2 H, 1'-H), 2.82 (dd, *J* = 18.1, 9.8 Hz, 1 H, 4-H), 2.95 (dd, *J* = 18.1, 8.1 Hz, 1 H, 4-H), 3.20 (ddd, *J* = 9.8, 8.2, 6.8 Hz, 1 H, 3-H), 4.79-4.70 (m, 1 H, 2-H), 5.32-5.18 (m, 2 H, 3'-H), 5.89-5.72 (m, 1 H, 2'-H), 7.60-6.00 (bs, 1 H, OH).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 31.7 (+, 2-C), 38.7 (+, 3-C), 44.0 (-, 1'-C), 80.5 (-, 4-C), 120.3 (+, 2'-C), 130.9 (-, 3'-C), 174.3 (Cq, CO), 175.8 (Cq, COOH).- IR (KBr): $\tilde{\nu}$ = 3439, 3085, 2928, 2593, 1983, 1747, 1643, 1427, 1356, 1234, 1196, 1109, 1059, 975, 918, 862, 670 cm^{-1}.- MS (CI, NH_3): *m/z (%)* = 190.1 (48), 189.1 (10), 188.1 (100) [M + NH_4^+], 172.1 (11), 144.1 (18).

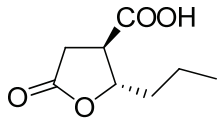


(+)-(2*R*,3*S*)-2-allyl-tetrahydro-5-oxofuran-3-carboxylic acid ((+)-261):

Yield: 81%.- $[\alpha]_D^{20}$ = +29.9 (c = 0.509, $CHCl_3$).- m.p. = 70-72 °C.

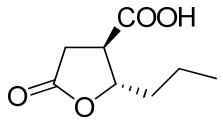
^{1}H NMR and ^{13}C NMR of (+)-**261** identical to (-)-**261**.

Representative procedure for hydrogenation of the allylic double bond:



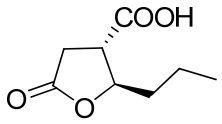
(-)-(2*S*,3*R*)-tetrahydro-5-oxo-2-propylfuran-3-carboxylic acid ((-)-262):

Acid (-)-**261** (502 mg, 2.95 mmol, 1.0 eq.) was dissolved in ethylacetate (20 ml) and Pd/C (5%, 70 mg, 0.0295 mmol, 1 mol%) was added. The apparatus was seal with a septum, flushed with hydrogen and a hydrogen filled balloon was set on top. The mixture was stirred under this hydrogen atmosphere for 24 h, filtered over celite and concentrated affording 486 mg (2.82 mmol, 96%) pure product as a colorless solid.



(-)-(2*S*,3*R*)-tetrahydro-5-oxo-2-propylfuran-3-carboxylic acid ((-)-262):

Yield: 96%.- $[\alpha]_D^{20}$ = -50.2 (c = 0.540, $CHCl_3$).- m.p. = 80-81 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.3 Hz, 3 H, 3´-H), 1.61-1.39 (m, 2 H, 2´-H), 1.83-1.71 (m, 2 H, 1´-H) 2.83 (dd, *J* = 17.8, 9.9 Hz, 1 H, 4-H), 2.99 (dd, *J* = 17.8, 8.2 Hz, 1 H, 4-H), 3.16-3.04 (m, 1 H, 3-H), 4.64 (dt, *J* = 7.3, 5.3 Hz, 1 H, 2-H), 10.00-8.00 (bs, 1 H, OH).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.7 (-, 2´-C), 18.6 (+, 3´-C), 31.9 (+, 2-C), 37.4 (+, 3-C), 45.4 (-, 1'-C), 81.6 (-, 4-C), 174.3 (Cq, CO), 176.3 (Cq, COOH).- IR (KBr): $\tilde{\nu}$ = 3447, 3107, 2960, 2939, 2875, 1749, 1463, 1431, 1402, 1388, 1236, 1195, 1109, 1064, 1010, 861, 669 cm^{-1}.- MS (EI, 70 eV): *m/z (%)* = 129.0 [M-C_3H_7], 173.0 [M+H^+].- HRMS (EI, 70 eV): 173.0814 ($C_8H_{12}O_4$: calc. 173.0814 [M+H^+]).

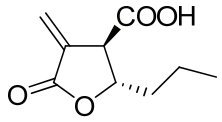


(+)-(2*R*,3*S*)-tetrahydro-5-oxo-2-propylfuran-3-carboxylic acid ((+)-262):

Yield: 98%.- $[\alpha]_D^{20}$ = +49.2 (c = 0.502, $CHCl_3$).- m.p. = 80-81 °C.

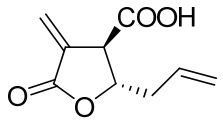
^{1}H NMR and ^{13}C NMR of (+)-**262** identical to (-)-**262**.

Representative procedure for α-methylenation:



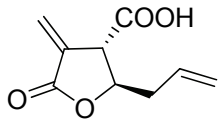
(-)-(2*S*,3*R*)-tetrahydro-4-methylene-5-oxo-2-propylfuran-3-carboxylic acid ((-)-256c):

Under an argon atmosphere acid (-)-**262** (100 mg, 0.587 mmol, 1.0 eq.) was dissolved in methoxymagnesiummethylcarbonate solution (11 ml, 22 mmol, 37.5 eq., 2 N in DMF) and heated for 3 d to 135 °C. After cooling to 0 °C the mixture was carefully acidified with cold 2 N HCl and extracted fast with cold CH_2Cl_2 (4x30 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and concentrated *in vacuo* strictly at rt. The resulting residue was treated under an argon atmosphere with a fresh prepared stock solution (2 ml acetic acid, 3 ml 37% formaldehyde in water, 520 µl N-methylanilin and 100 mg NaOAc) and stirred at rt for 3.5 h. Brine (10 ml + 1 ml conc. HCl) was added and the mixture was extracted with Et_2O (3x20 ml). The combined organic layers were washed with brine (10 ml + 10 drops of conc. HCl). The aqueous layer was extracted with Et_2O (2x20 ml), the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexanes:ethylacetate:acetic acid 7:4:1) afforded 57 mg (0.313 mmol, 53%) product as a white solid.



(-)-(2*S*,3*R*)-2-allyl-tetrahydro-4-methylene-5-oxofuran-3-carboxylic acid ((-)-263)

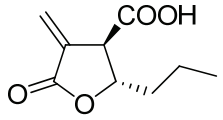
Yield: 53%.- $[\alpha]_D^{20}$ = -10.3 (c = 0.518, $CHCl_3$).- m.p. = 56-57 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.61-2.49 (m, 2 H, 1'-H), 3.74-3.68 (m, 1 H, 3-H), 4.97-4.87 (m, 1 H, 2-H), 5.28-5.17 (m, 2 H, 3'-H), 5.84-5.66 (m, 1 H, 2'-H), 6.04 (d, *J* = 2.5 Hz, 1H, α-CH_2), 6.47 (d, *J* = 3.0 Hz, 1H, α-CH_2), 10.50-9.32 (bs, 1 H, OH).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 39.2 (-, 1´-C), 48.1 (+, 3-C), 77.4 (+, 2-C), 120.5 (-, 3´-C), 126.4 (-, =CH_2), 130.6 (+, 2'-C), 131.9 (Cq, 4-C), 168.0 (Cq, CO), 174.4 (Cq, COOH).- IR (KBr): $\tilde{\nu}$ = 3440, 2085, 2564, 1743, 1660, 1398, 1350, 1255, 1190, 1059, 970, 914, 849, 815, 648 cm^{-1}.- MS (EI, 70 eV): *m/z (%)* = 140.9 (100) [M-C_3H_5], 182.0 [M^+].- HRMS (EI, 70 eV): 182.0581 ($C_9H_{10}O_4$, calc.: 182.0579 [M^+]).



(+)-(2*R*,3*S*)-2-allyl-tetrahydro-4-methylene-5-oxofuran-3-carboxylic acid ((+)-263))

Yield: 56%.- $[\alpha]_D^{20}$ = +7.3 (c = 0.479, $CHCl_3$).- m.p. = 56-57 °C.

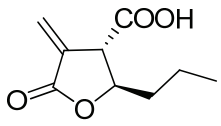
^{1}H NMR and ^{13}C NMR of (+)-**263** identical to (-)-**263**.



(-)-(2*S*,3*R*)-tetrahydro-4-methylene-5-oxo-2-propylfuran-3-carboxylic acid ((-)-265c))

Yield: 53%.- $[\alpha]_D^{20}$ = -5.2 (c = 0.512, $CHCl_3$).- m.p. = 60-61 °C.- ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H, 3´-H), 1.51-1.33 (m, 2 H, 2´-H), 1.75-1.59 (m, 2 H, 1´-H), 3.59-3.53 (m, 1H, 3-H), 4.86-4.71 (m, 1 H, 2-H), 5.96 (d, *J* = 2.47 Hz, 1H, α-CH_2), 6.39 (d, *J* = 3.0 Hz, 1H, α-CH_2), 11.06-10.75 (bs, 1 H, OH).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.6 (+, 3´-C), 17.1 (-, 2´-C), 36.7 (-, 1´-C), 48.6 (+, 3-C), 77.9 (+, 2-C), 125.0 (-, =CH_2), 131.5 (Cq, 4-C), 167.6 (Cq, CO), 173.3 (Cq, COOH).- IR (KBr): $\tilde{\nu}$ = 3440, 2964, 1742, 1660, 1394, 1303, 1254, 1220, 1182, 1098, 1015, 956, 859, 813, 711, 648 cm^{-1}.- MS (CI, NH_3): *m/z (%)* =

141.0 (100) [M-C_3H_7], 155.1 (24.4) [M-C_2H_5], 184.1 [M^+].- HRMS (EI, 70 eV): 184.0735 ($C_9H_{12}O_4$: calc. 184.0736 [M^+]).



(+)-(2*R*,3*S*)-tetrahydro-4-methylene-5-oxo-2-propylfuran-3-carboxylic acid ((+)-265c)

Yield: 63%.- $[\alpha]_D^{20}$ = +6.1 (c = 0.489, $CHCl_3$).- m.p. = 62-63 °C.

^{1}H NMR and ^{13}C NMR of (+)-**265c** identical to (-)-**265c**.

12. Appendix

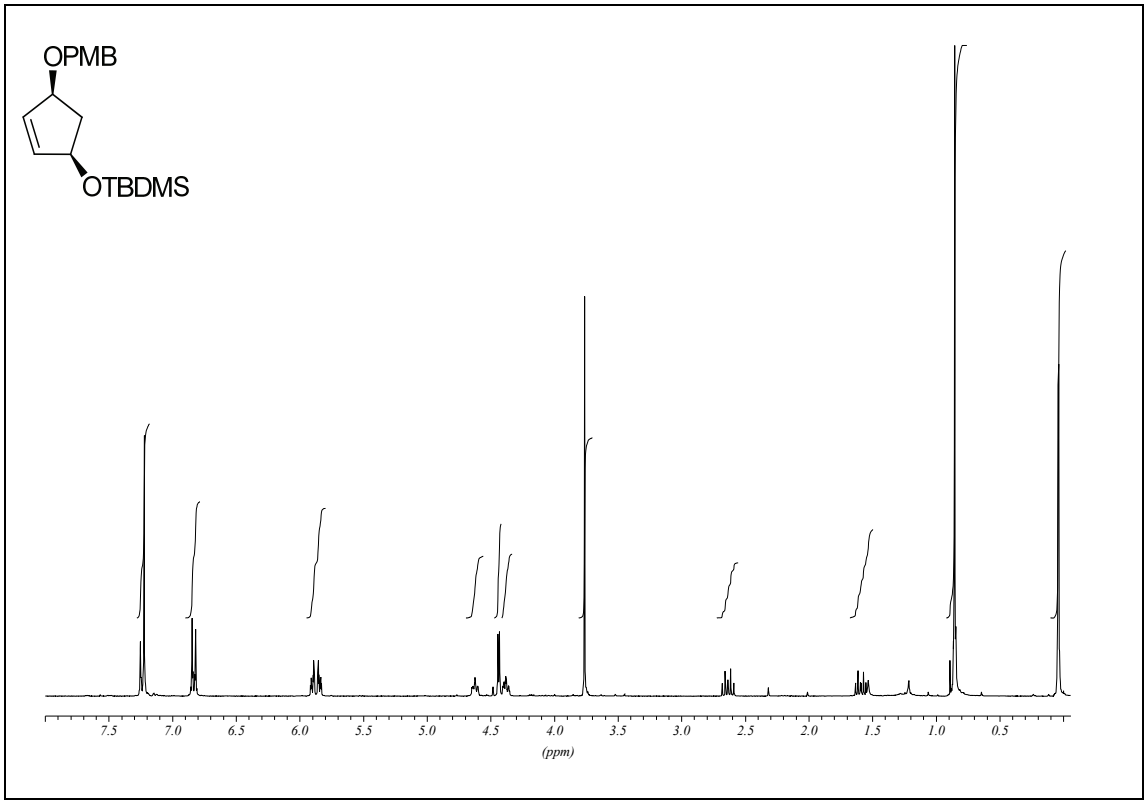
12.1 NMR - spectra

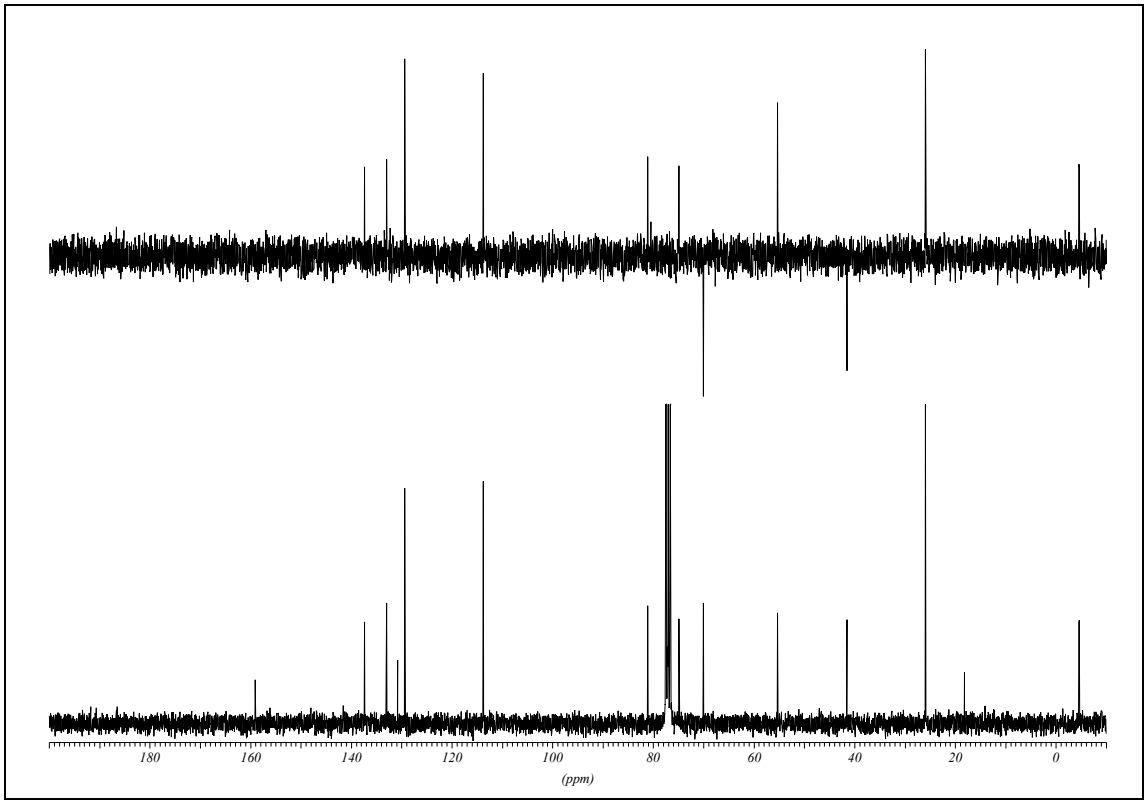
^{1}H-NMR spectra - upper image

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

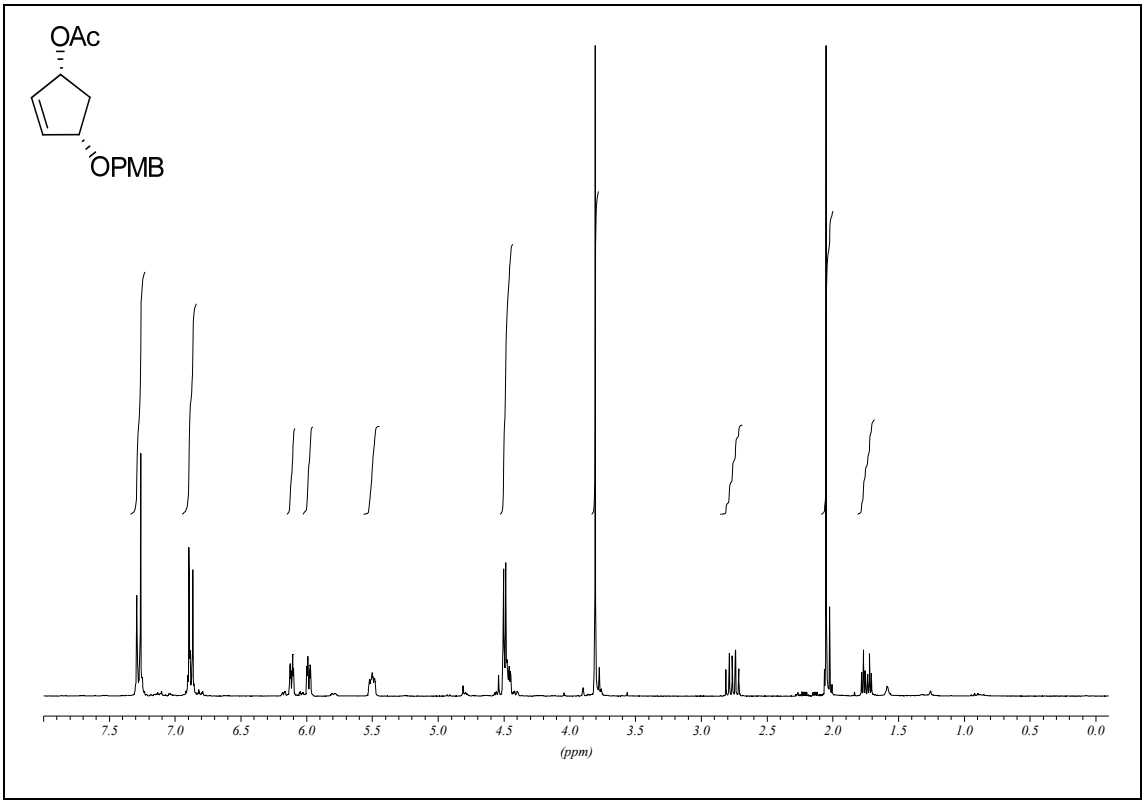
Solvents, if not stated otherwise: $CDCl_3$

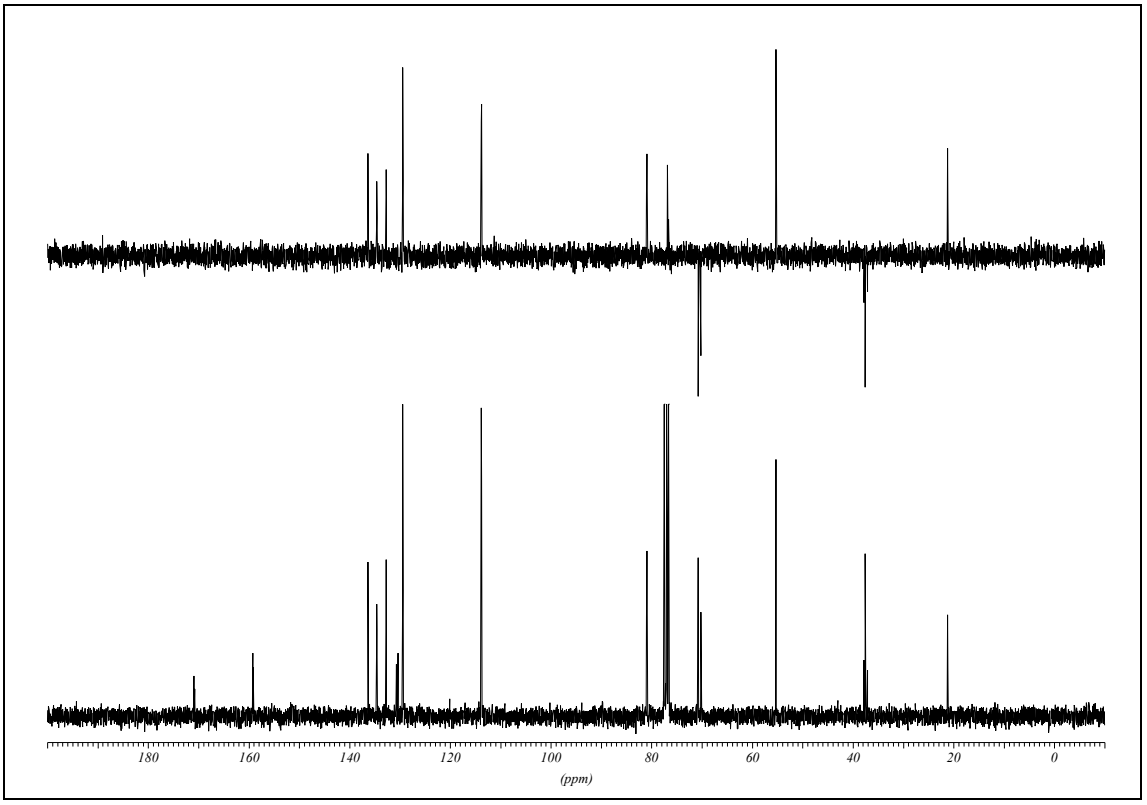
((1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enyloxy)(*tert*-butyl)dimethylsilane ((+)-141)



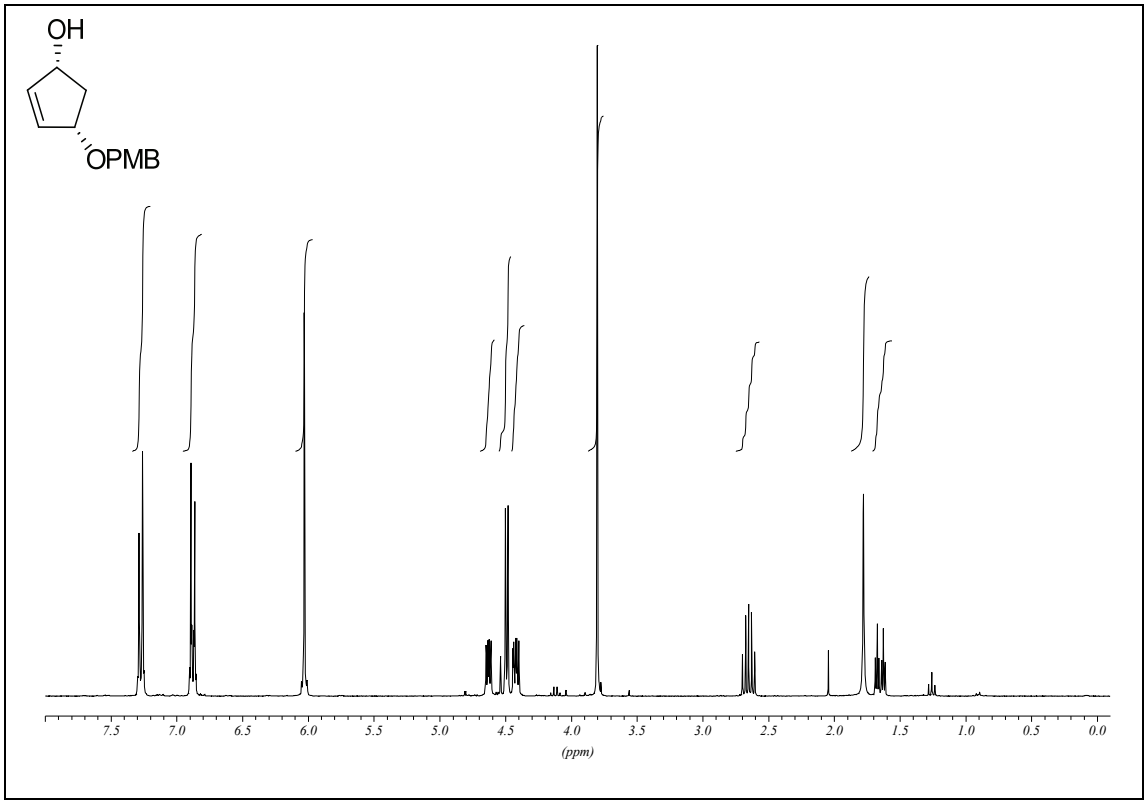


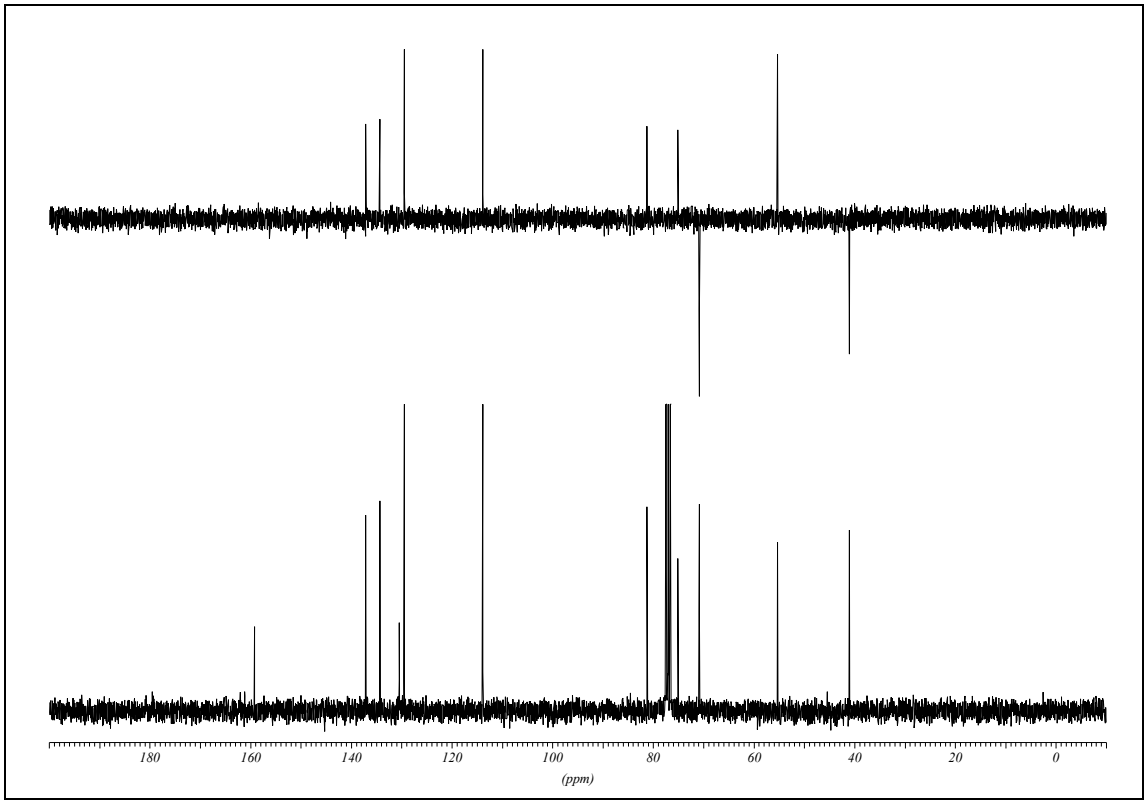
(1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enyl acetate ((+)-144)



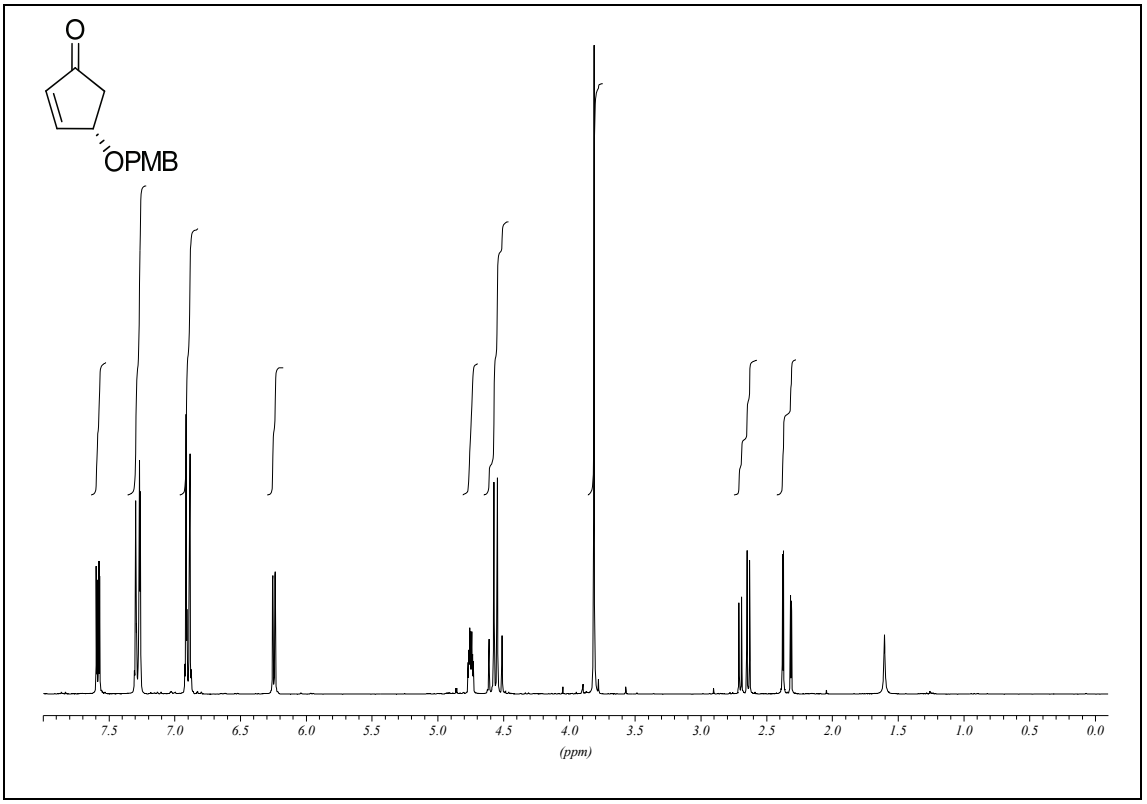


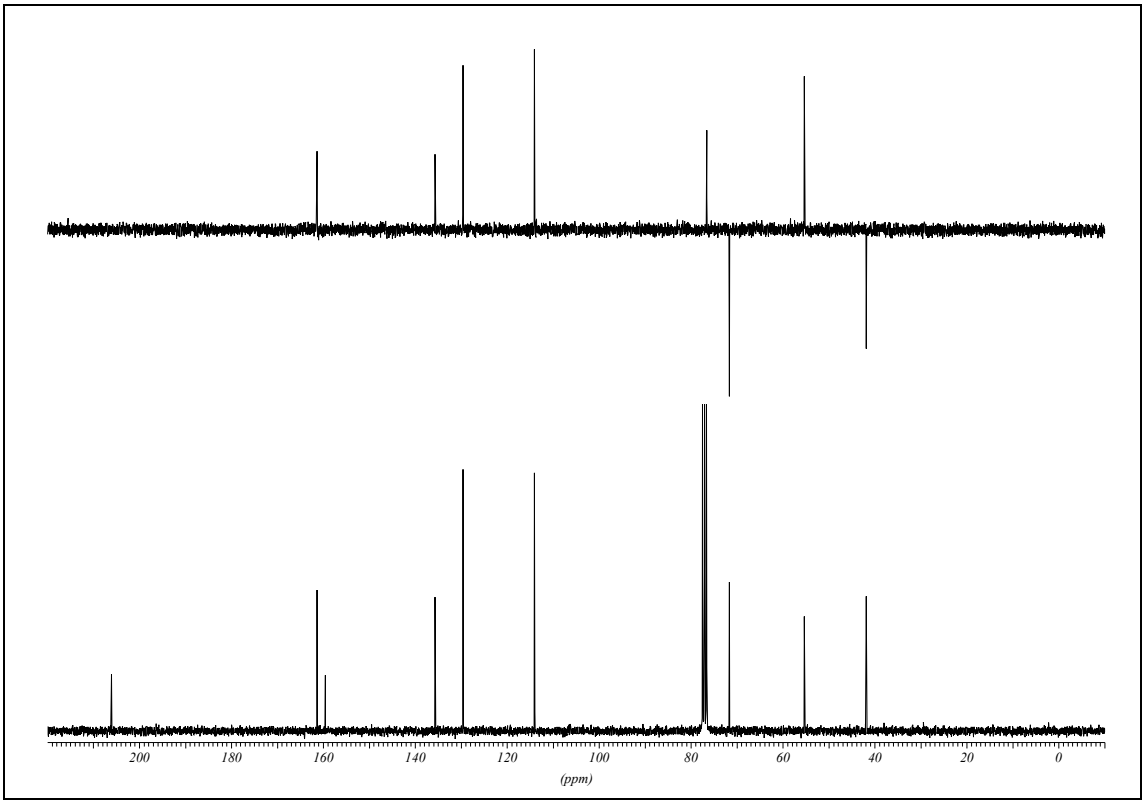
(1*R*,4*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enol ((-)-142)



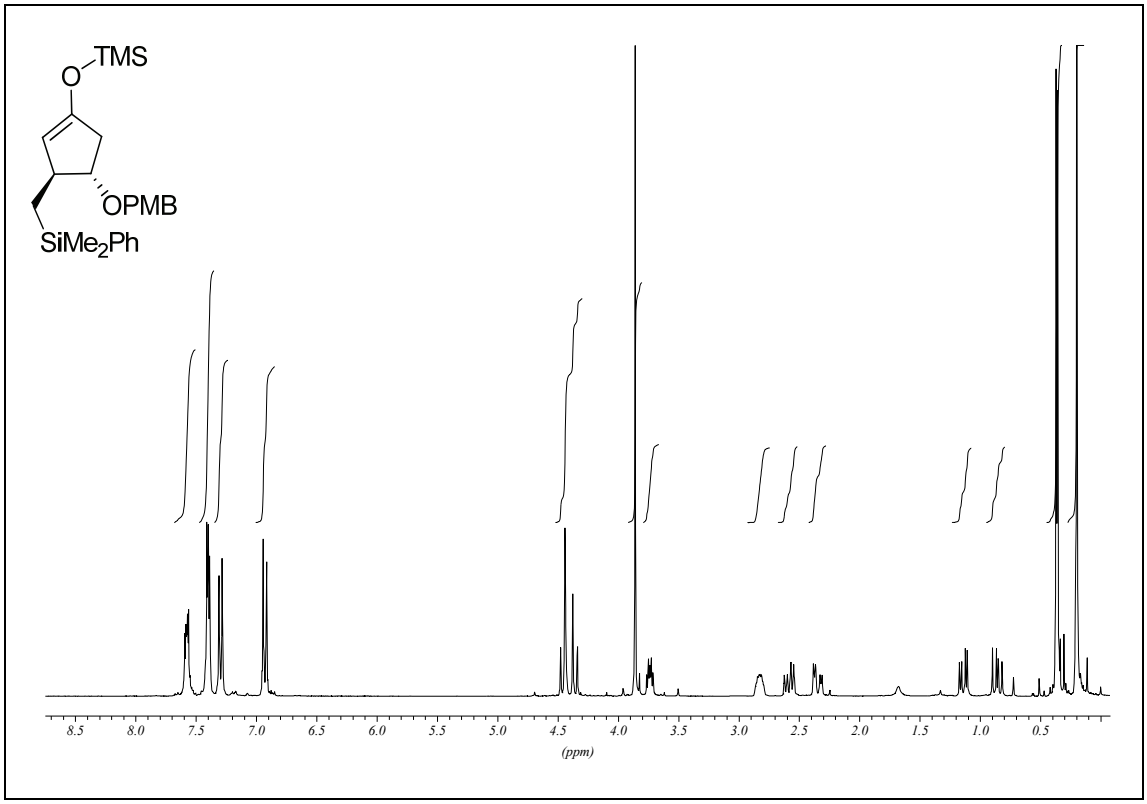


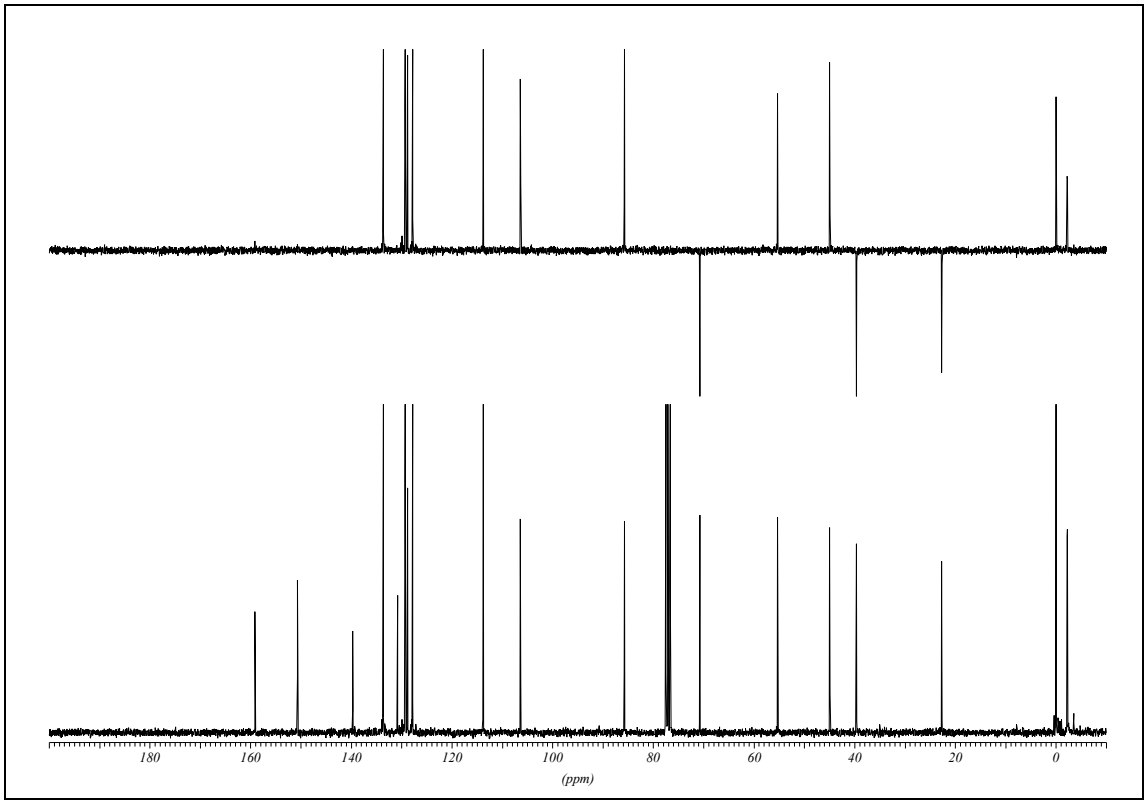
(*S*)-4-(*p*-methoxybenzyloxy)cyclopent-2-enone ((-)-145)



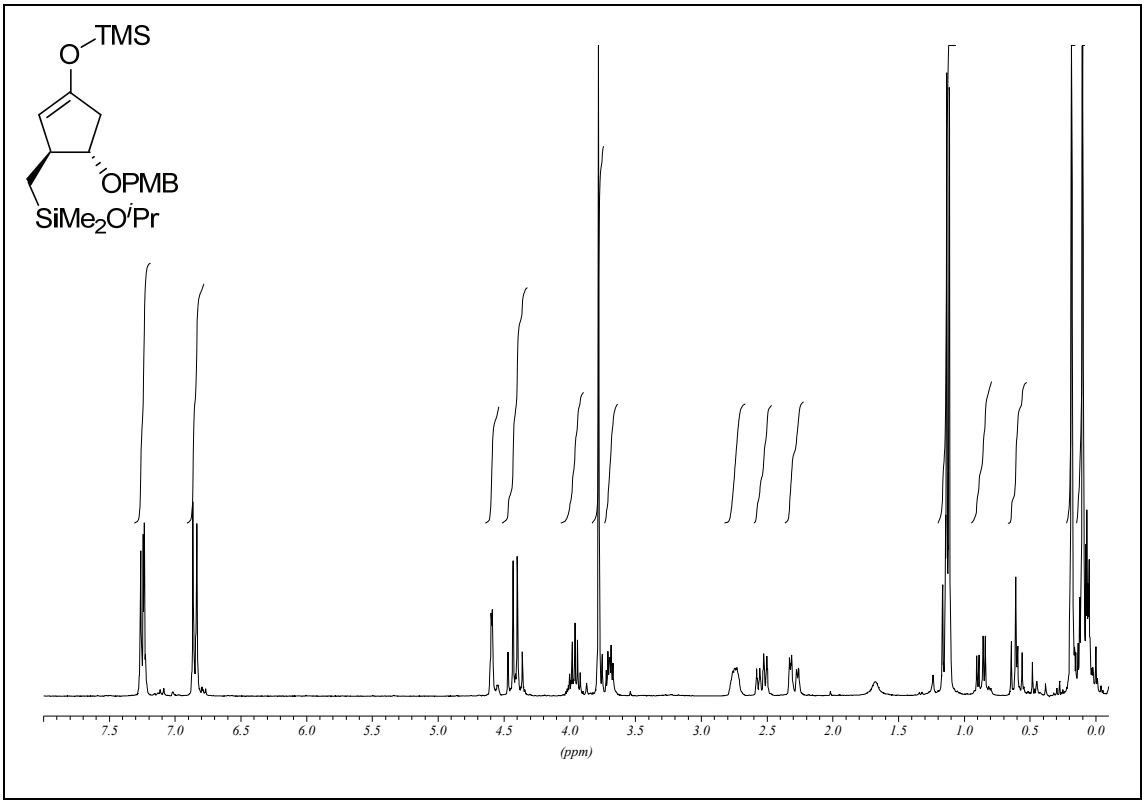


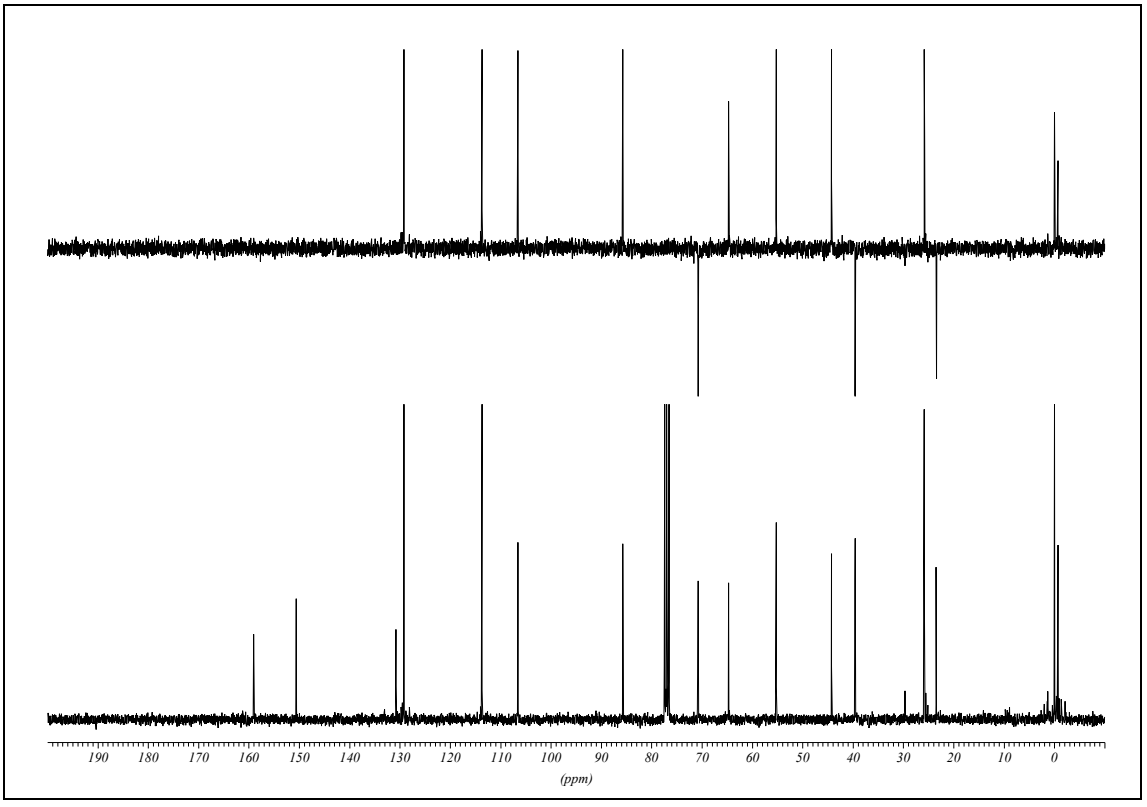
((3*S*,4*S*)-3-((dimethyl(phenyl)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopent-1-enyloxy) trimethylsilane (150)



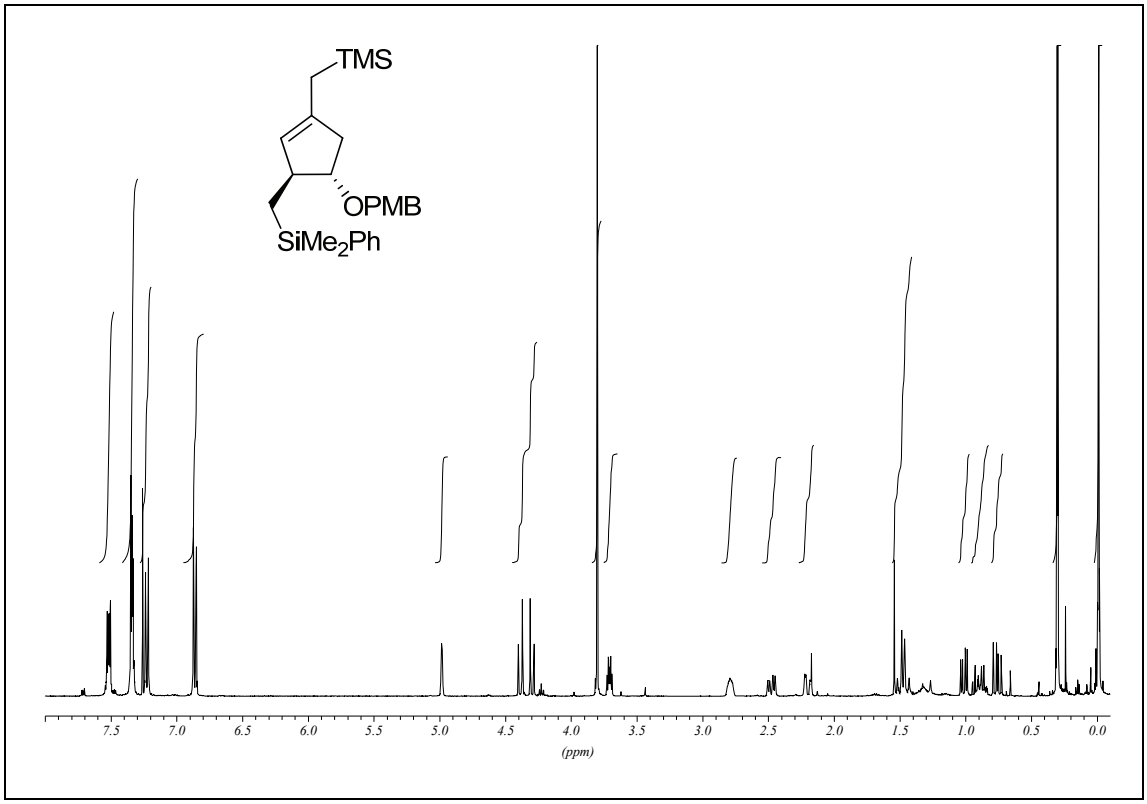


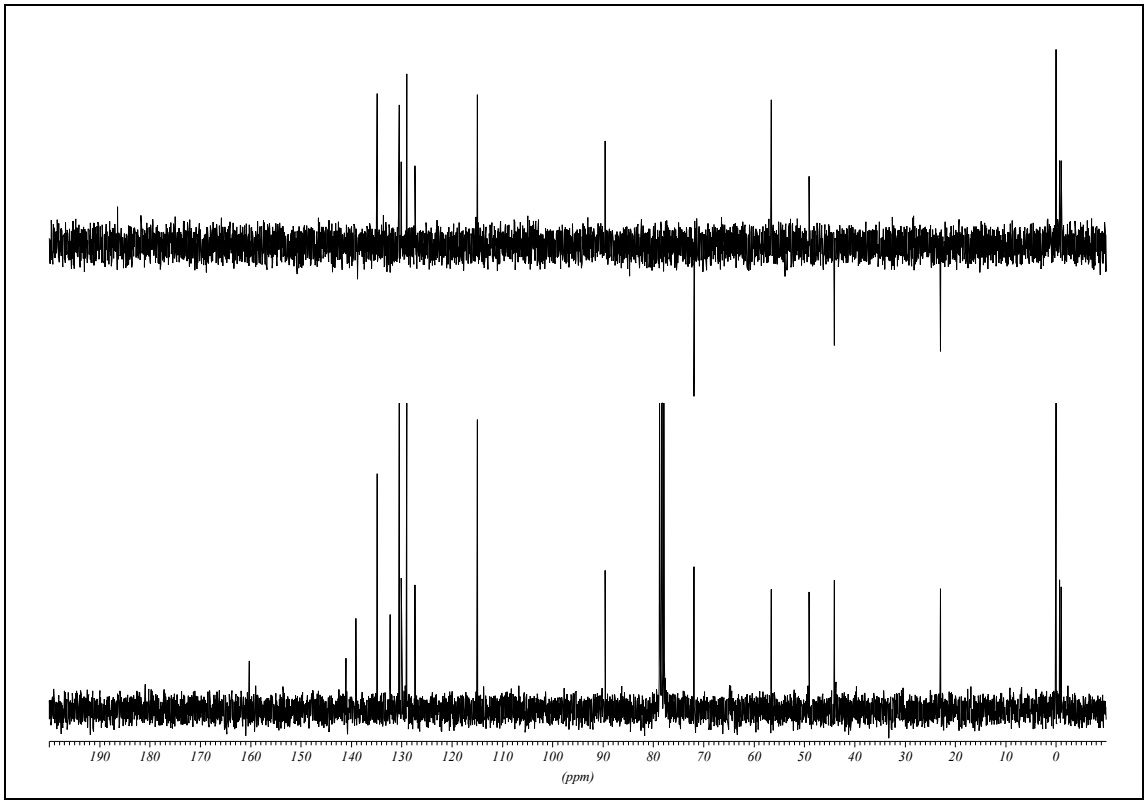
iso-propoxy(((1_S_,5_S_)-5-(_p_-methoxybenzyloxy)-3-(trimethylsilyloxy)cyclopent-2-enyl) methyl)dimethylsilane (151)



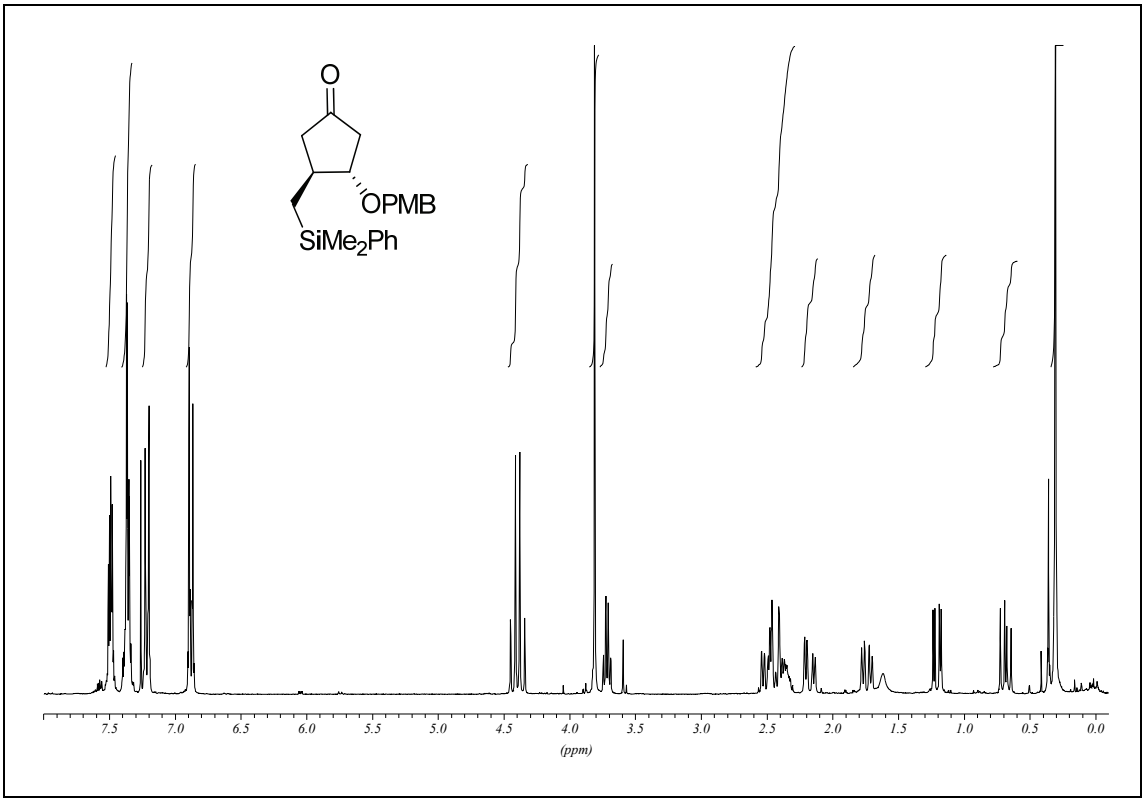


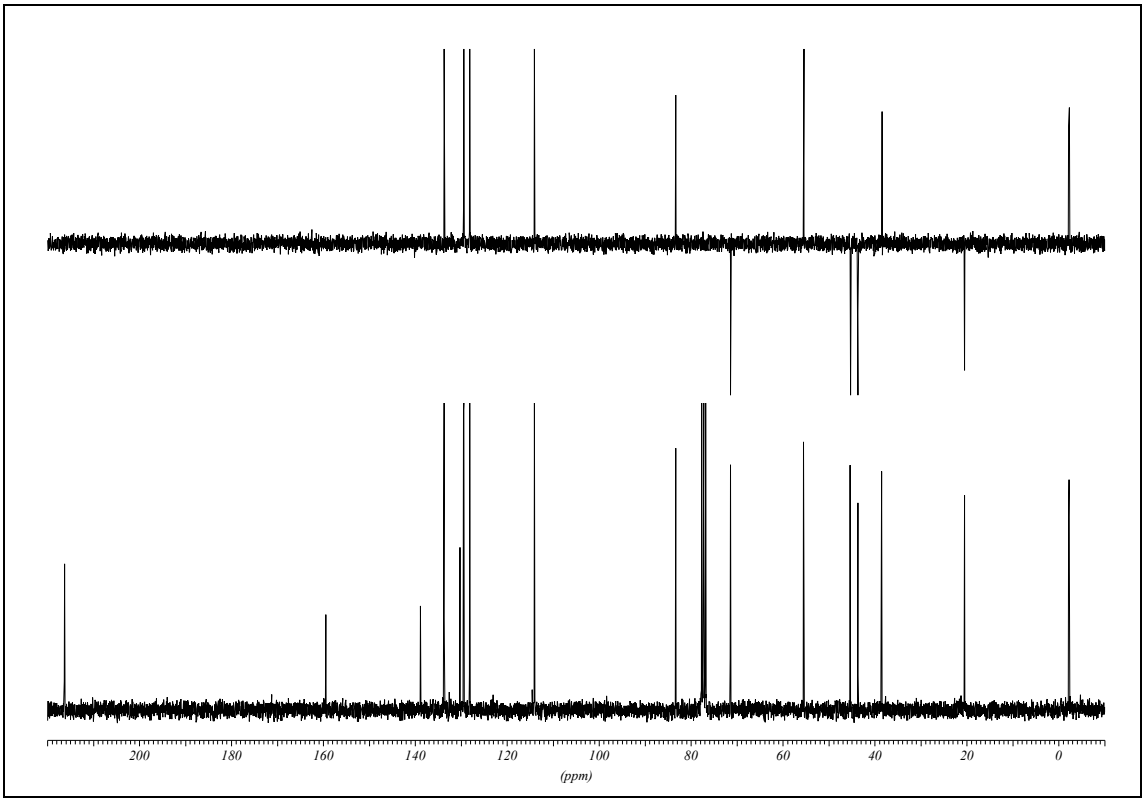
1-((((1*S*,5*S*)-5-(*p*-methoxybenzyloxy)-3-((trimethylsilyl)methyl)cyclopent-2-enyl)methyl) dimethylsilyl)benzene (152)



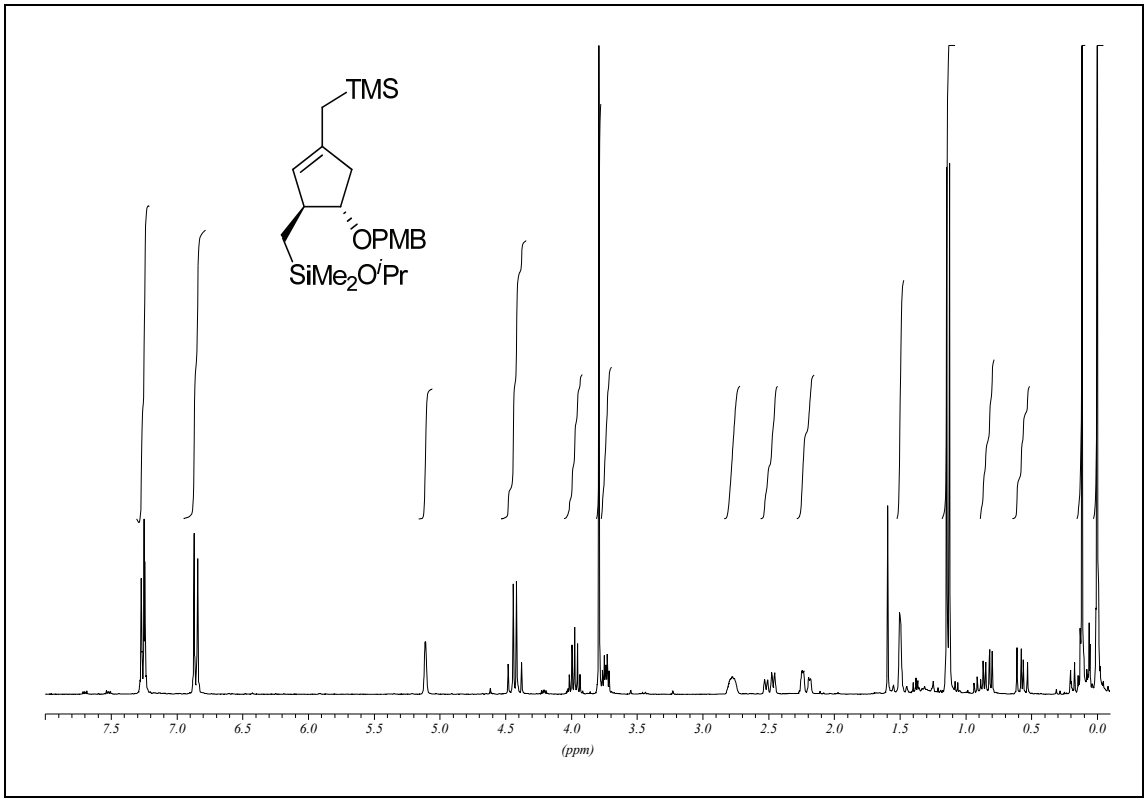


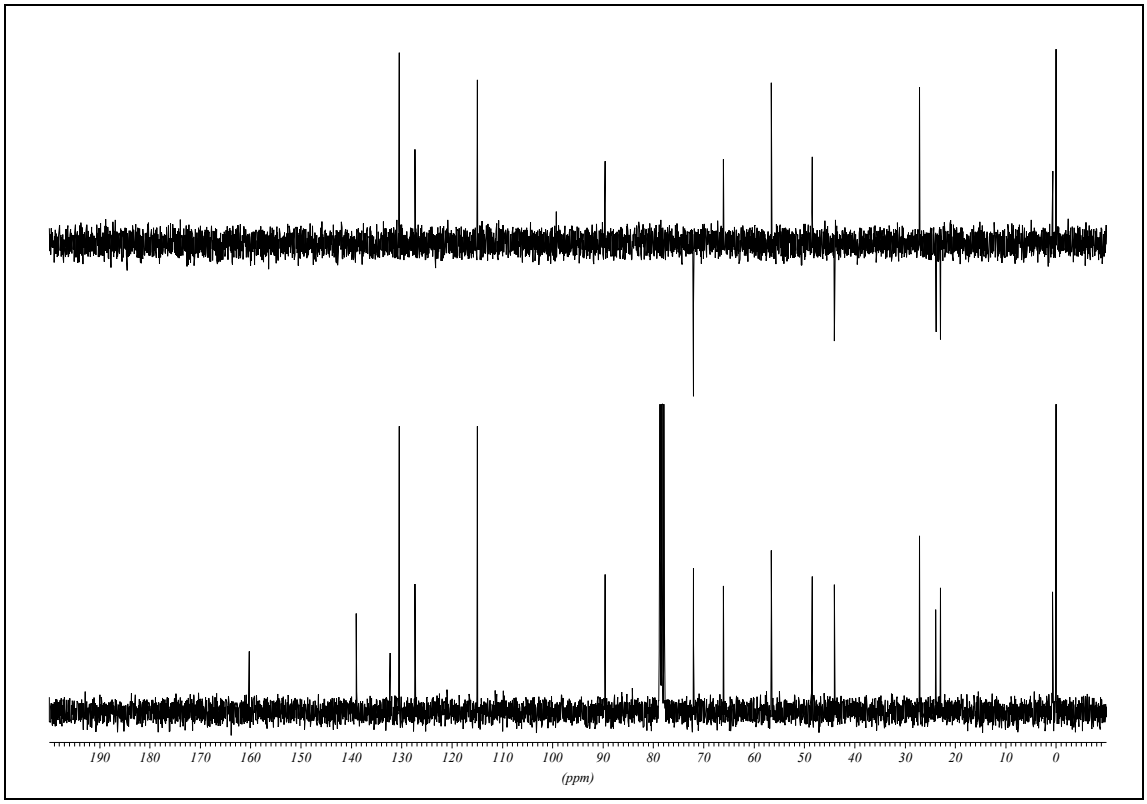
(3*S*,4*S*)-3-(*p*-methoxybenzyloxy)-4-((dimethyl(phenyl)silyl)methyl)cyclopentenone (154)



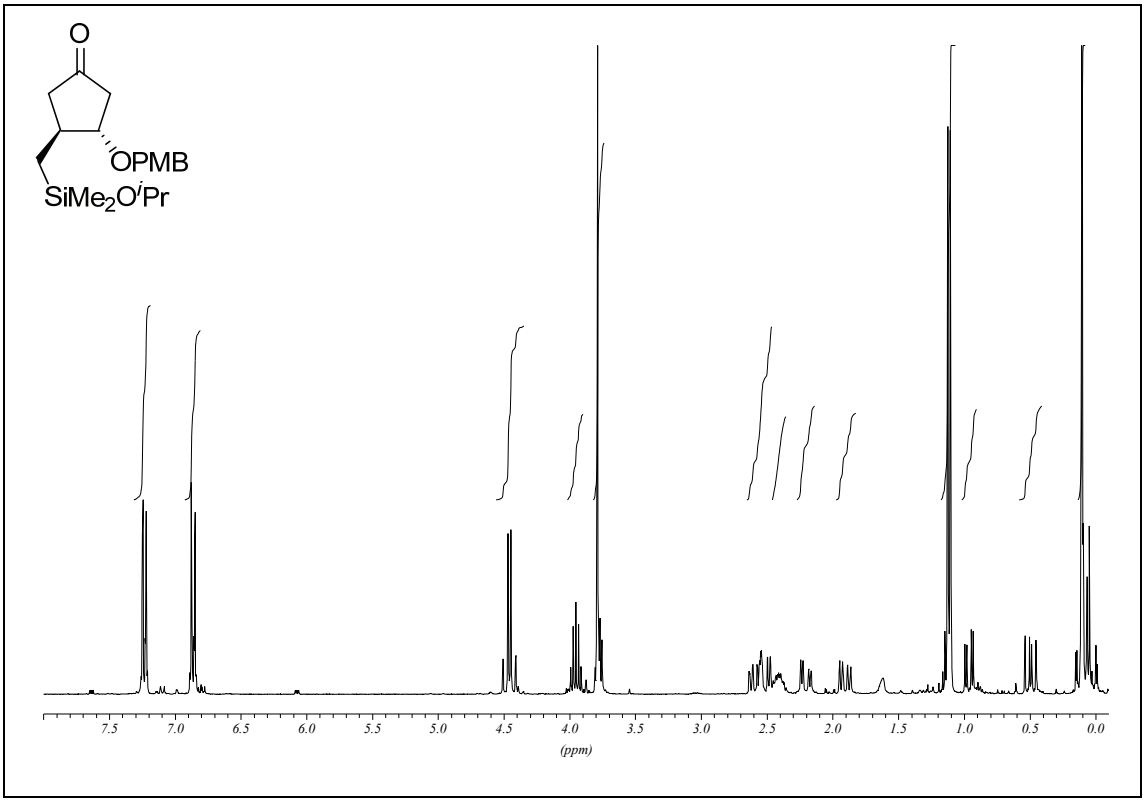


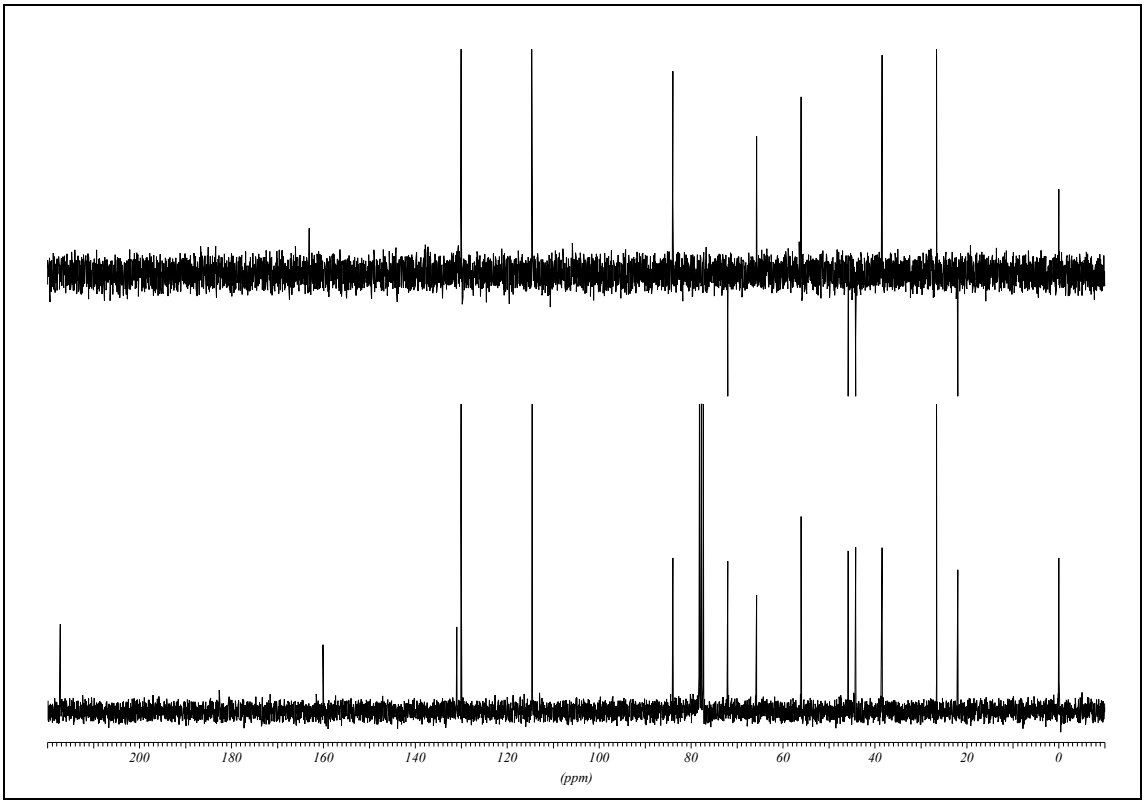
(((3*S*,4*S*)-3-((dimethyl(*iso*-propoxy)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopent-1-enyl)methyl)trimethylsilane (153)



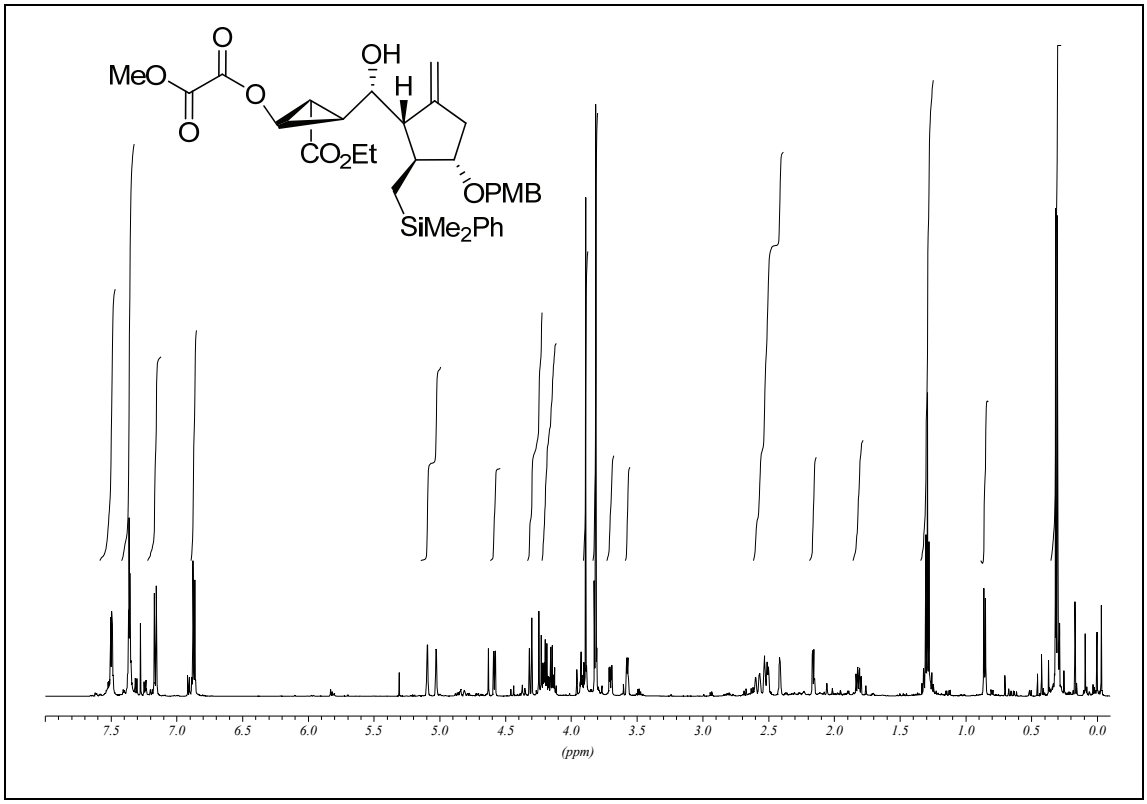


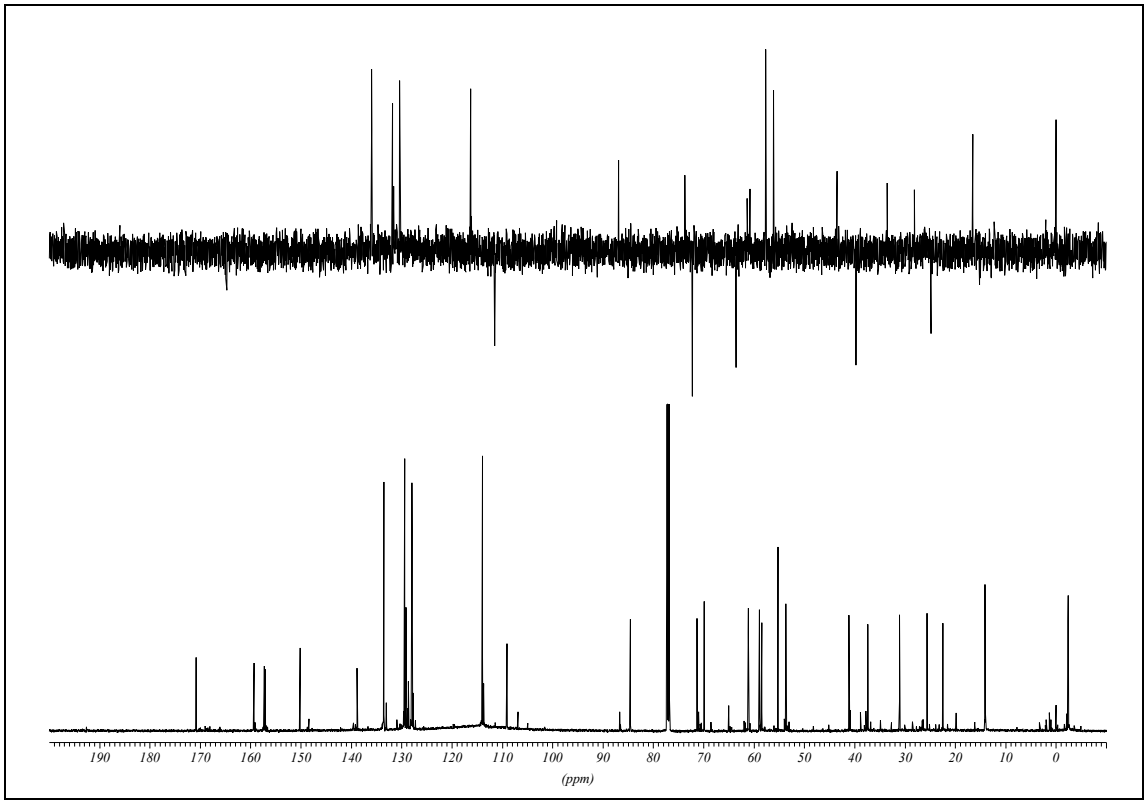
(3*S*,4*S*)-3-((dimethyl(*iso*-propoxy)silyl)methyl)-4-(*p*-methoxybenzyloxy)cyclopentenone (155)



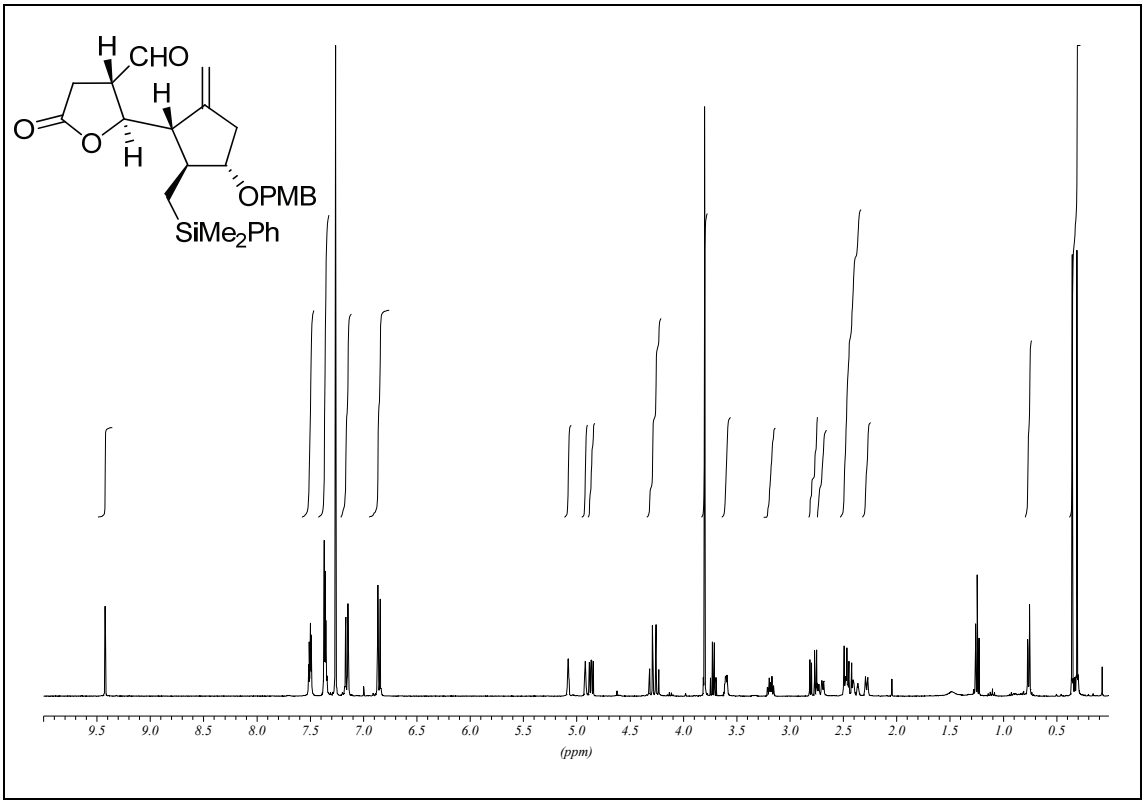


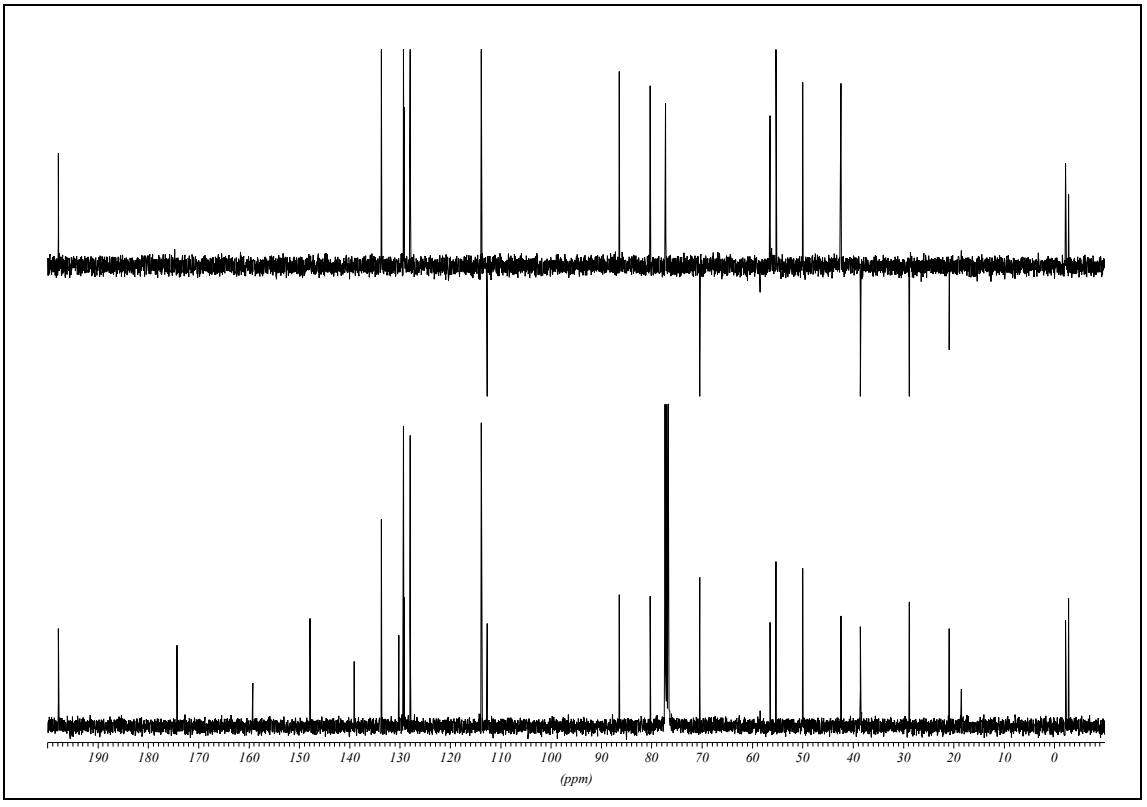
(1*R*,2*S*,3*R*)-2-((*R*)-((1´*S*,2´*S*,3´*S*)-2-((dimethyl(phenyl)silyl)methyl)-3-(*p*-methoxy-benzyloxy)-5´-methylenecyclopentyl)(hydroxy)methyl)-3-(ethoxycarbonyl)cyclopropyl methyl oxalate (171)



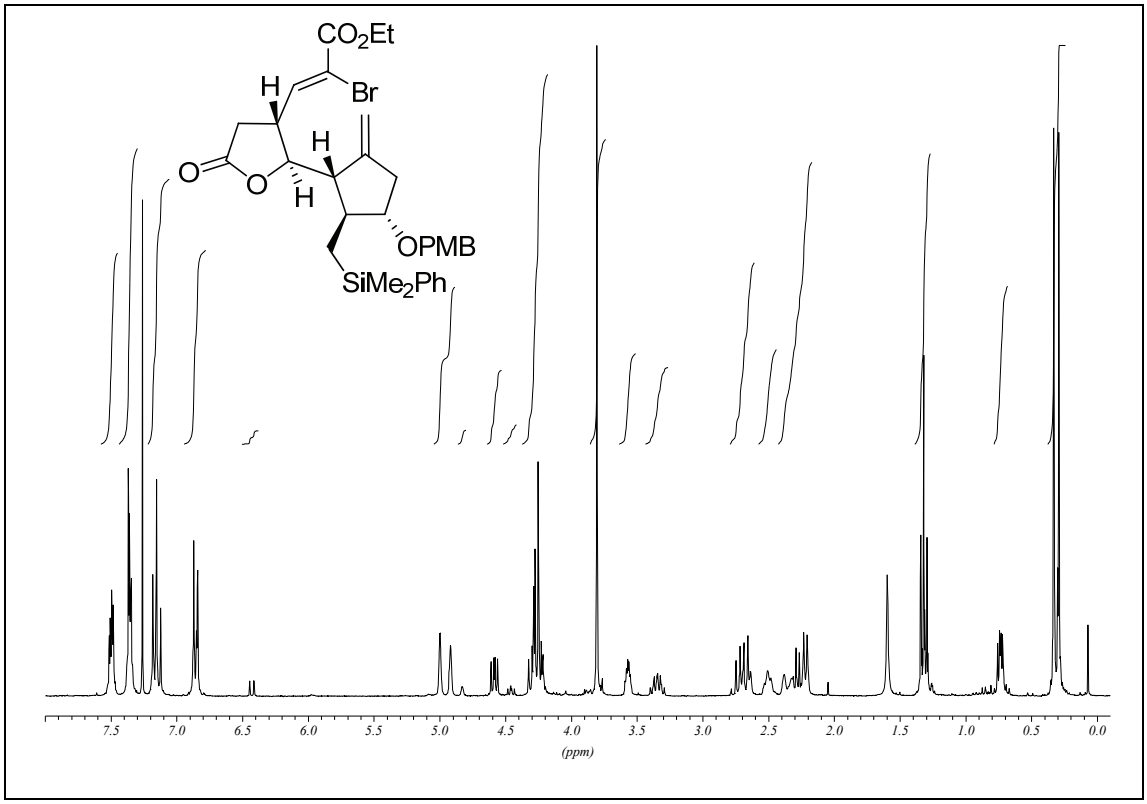


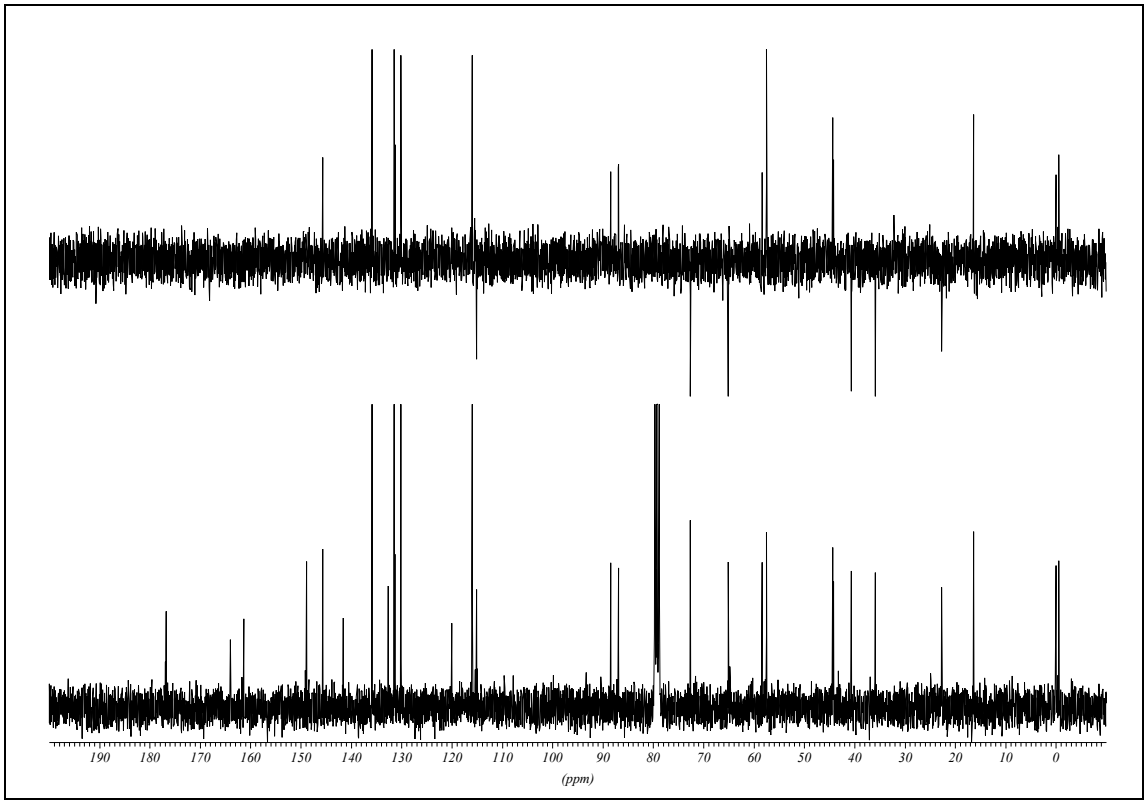
(2*R*,3*S*)-2-((1´*S*,2´*S*,3´*S*)-3´-(*p*-methoxybenzyloxy)-2´-((dimethyl(phenyl)silyl)methyl)-5´-methylenecyclopentyl)-tetrahydro-5-oxofuran-3-carbaldehyde (175)



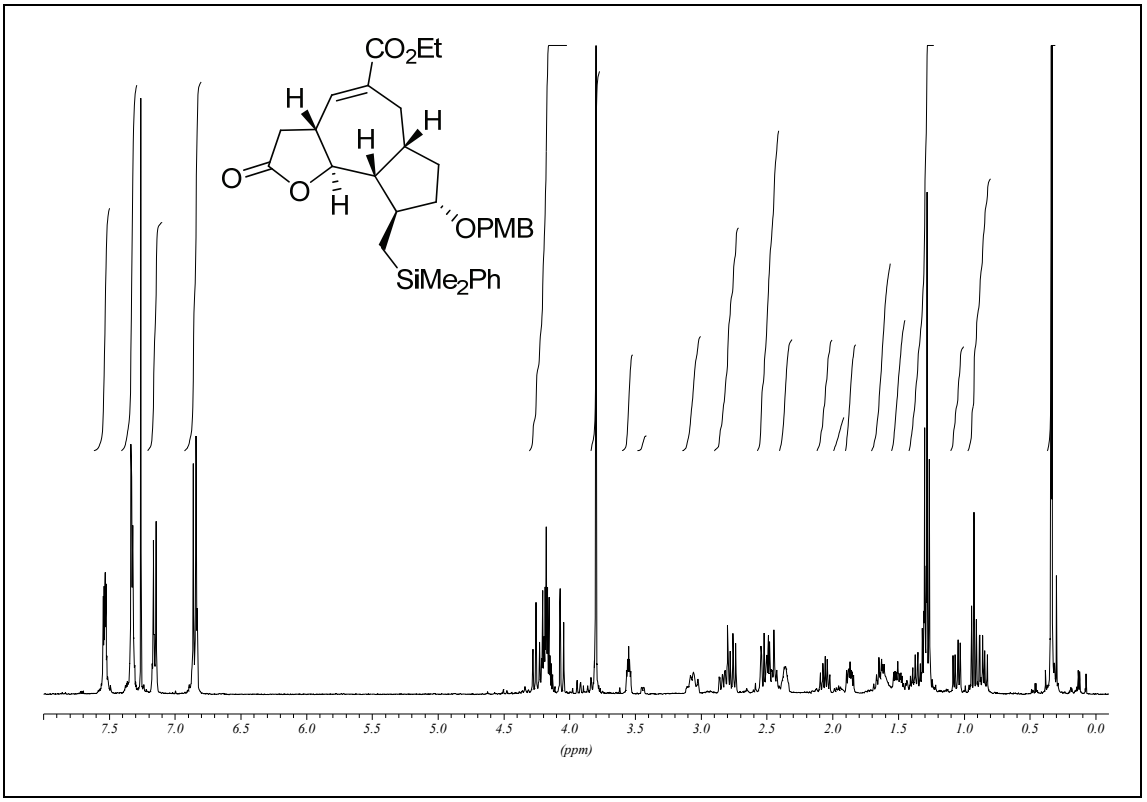


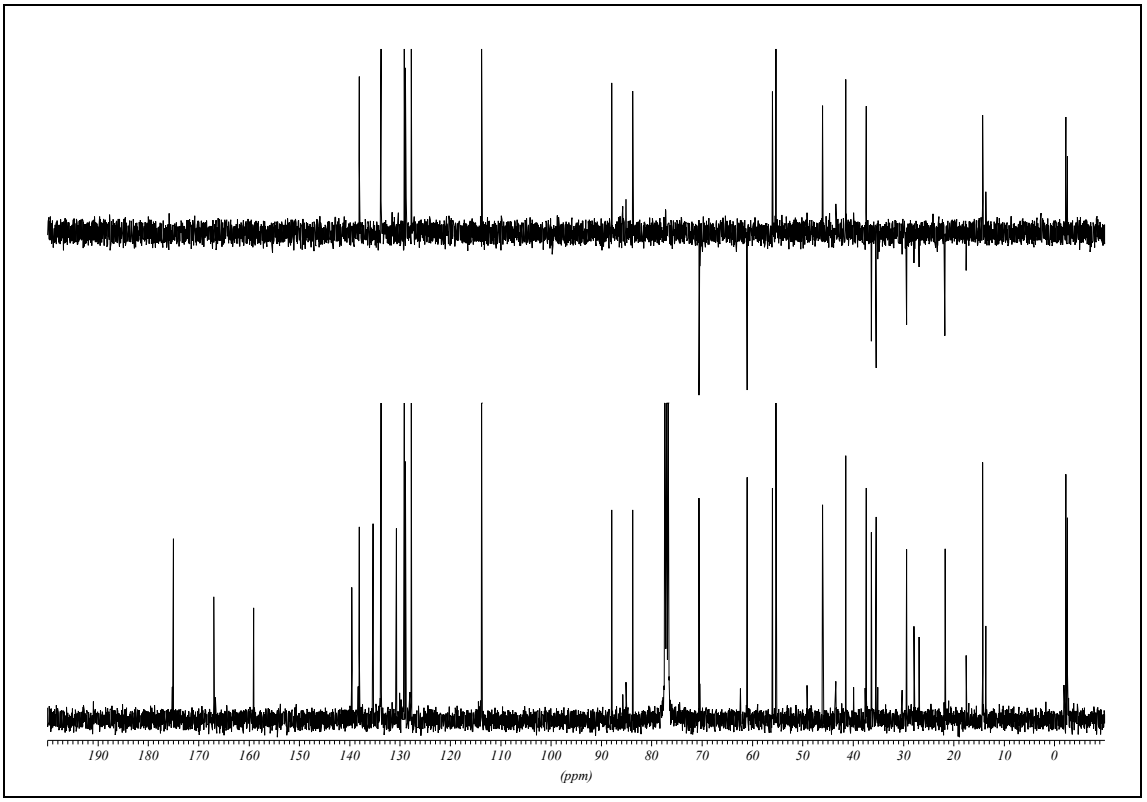
(*E/Z*)-ethyl 2-bromo-3-((2′*S*,3′*R*)-2′-((1′′*S*,2′′*S*,3′′*S*)-2′′-((dimethyl(phenyl)silyl) methyl)-3′′-(*p*-methoxybenzyloxy)-5′′-methylenecyclopentyl)-5′-oxo-tetrahydrofuran-3′-yl)acrylate (183), *E/Z* = 17:83



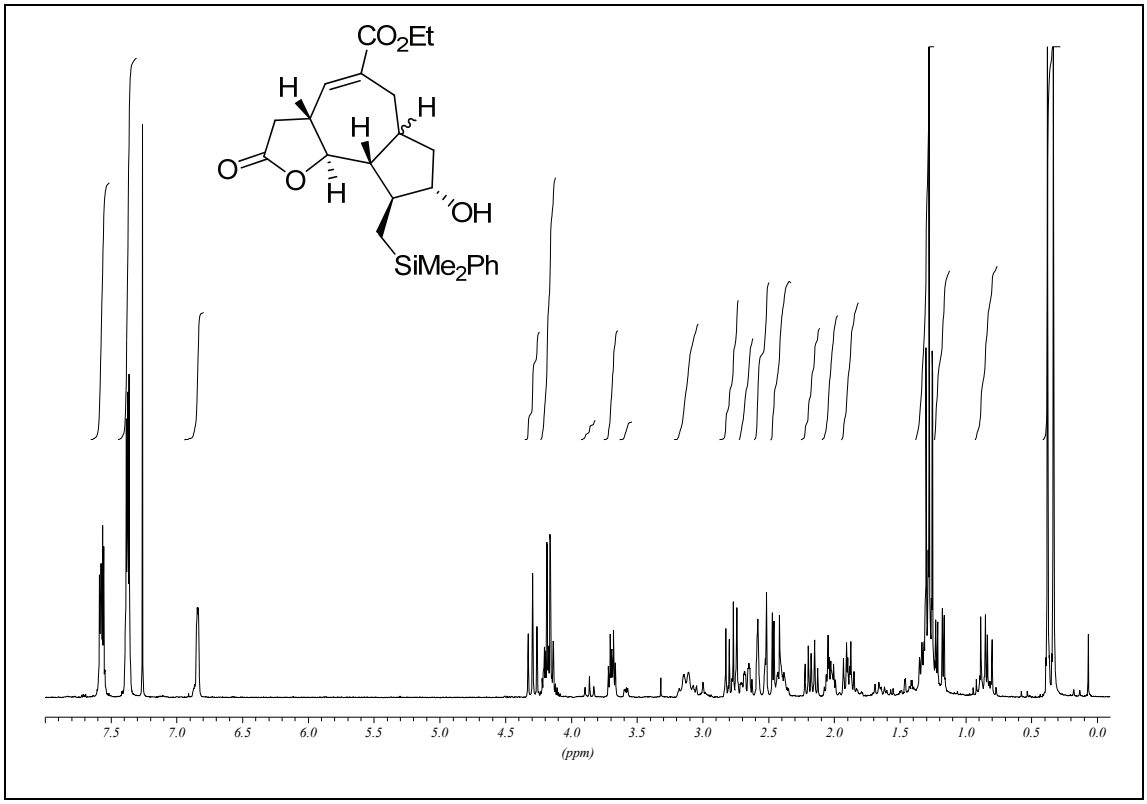


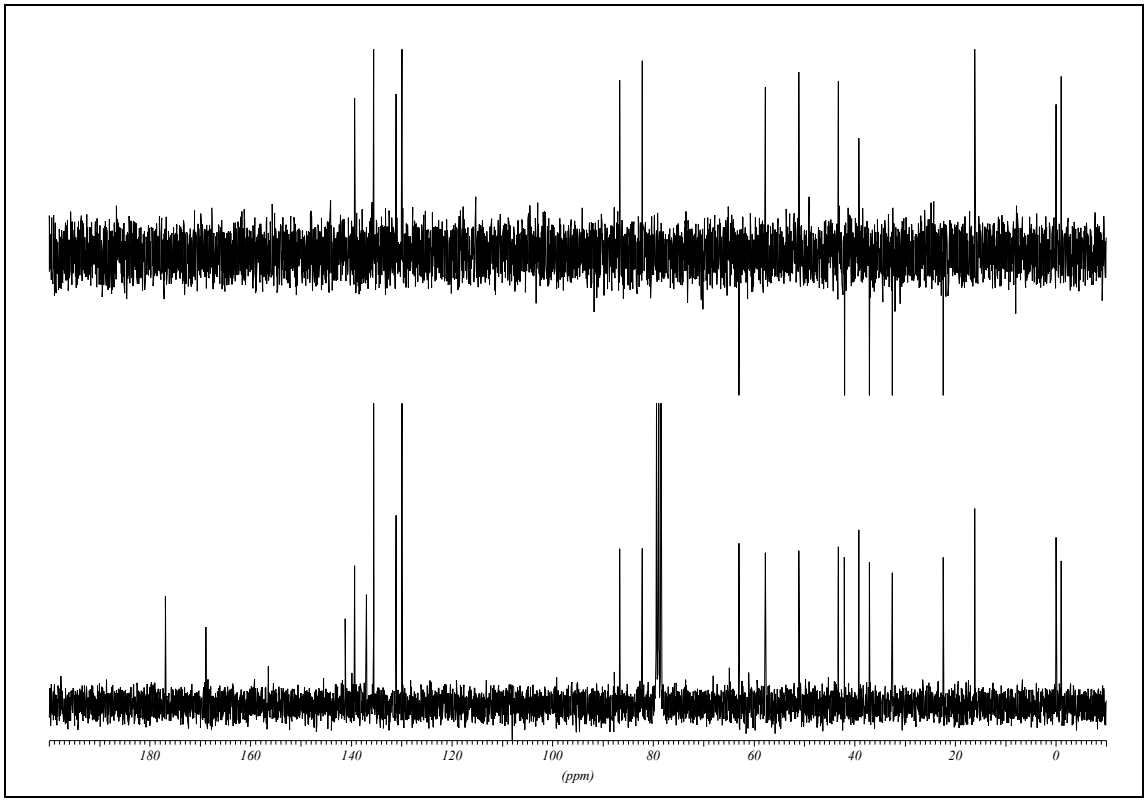
(3a*R*,8*S*,9*S*,9a*R*,9b*S*,*E*)-ethyl 9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,6,6a,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-5-carboxylate (184),
dr = 87:13



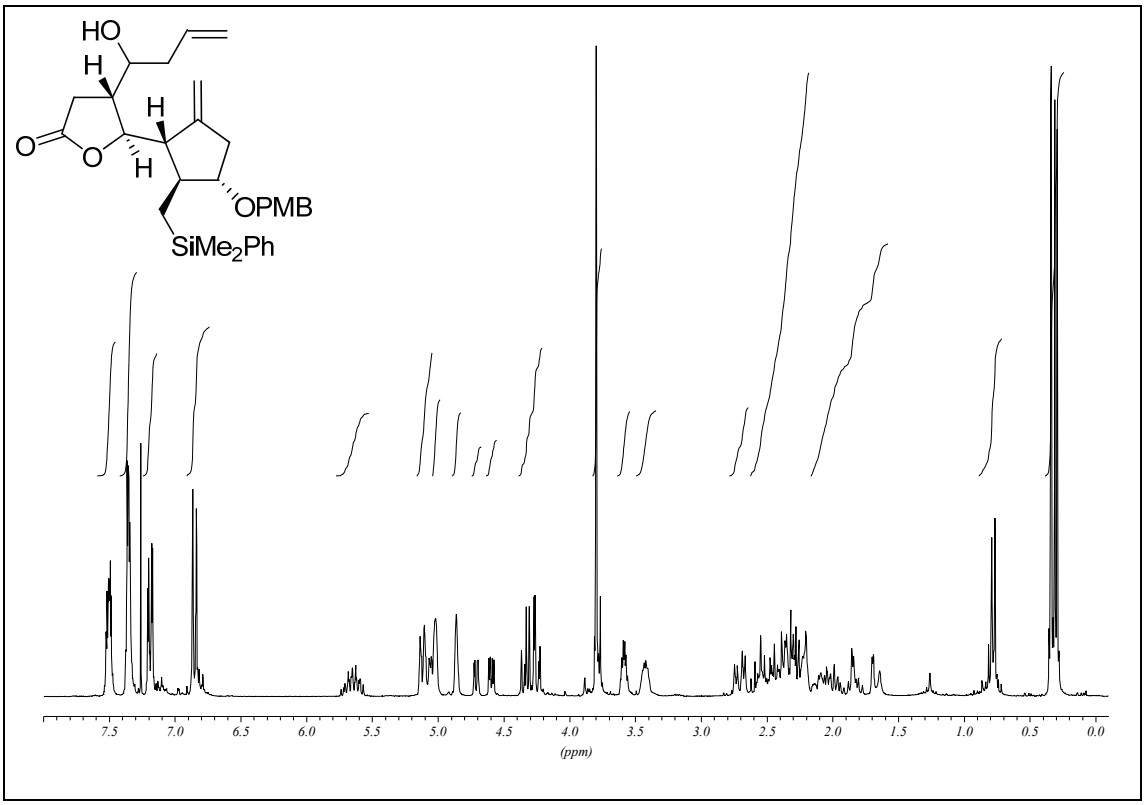


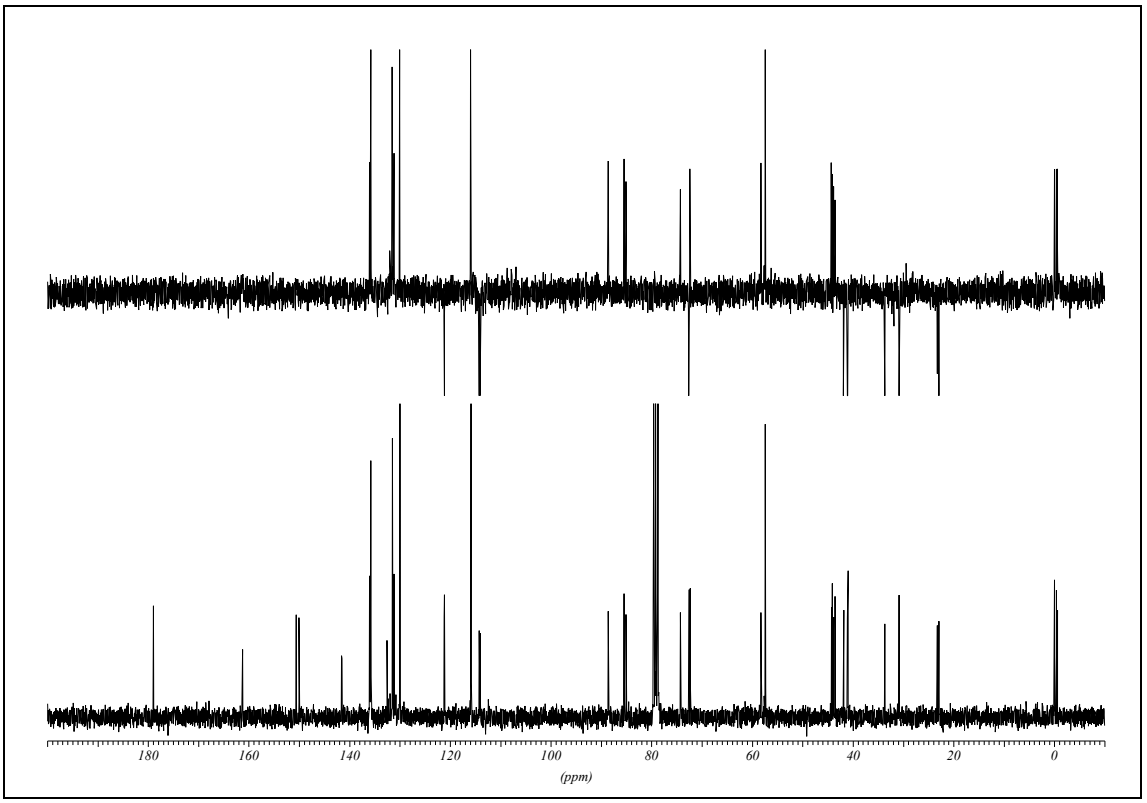
(3a*R*,8*S*,9*S*,9a*R*,9b*S*,*E*)-ethyl 9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-2-oxo-2,3,3a,6,6a,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-5-carboxylate (185), *dr* = 87:13



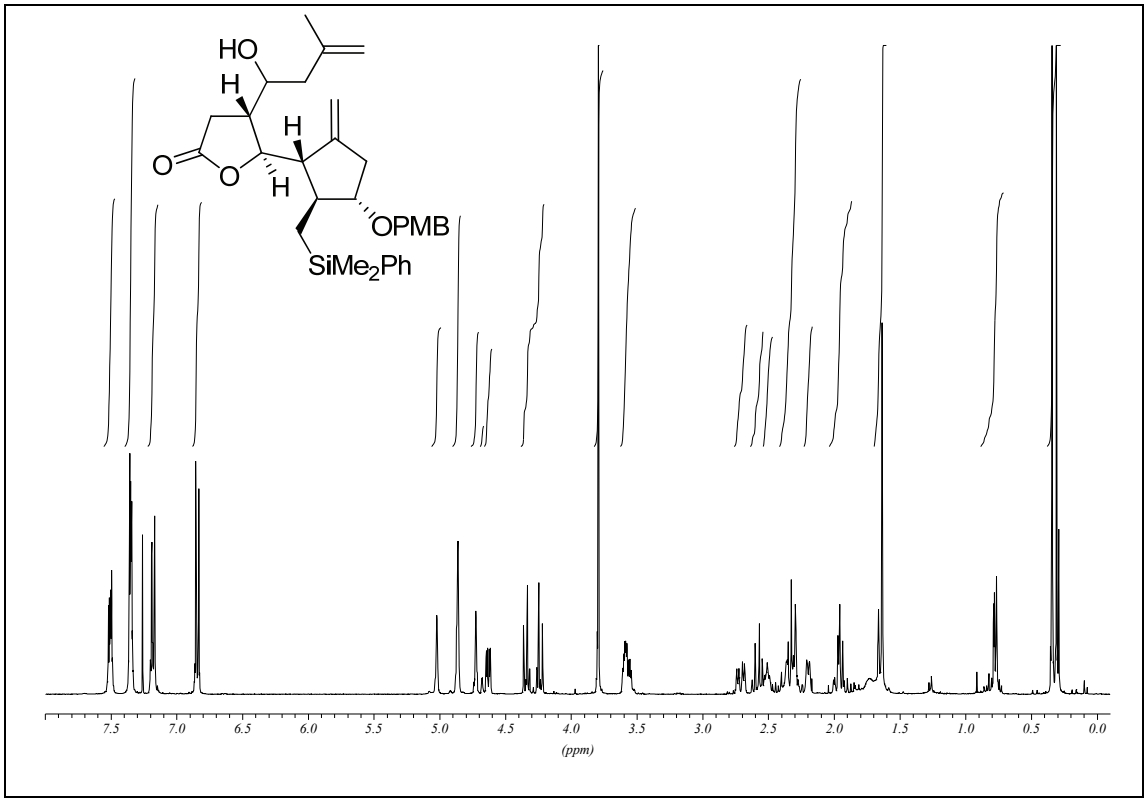


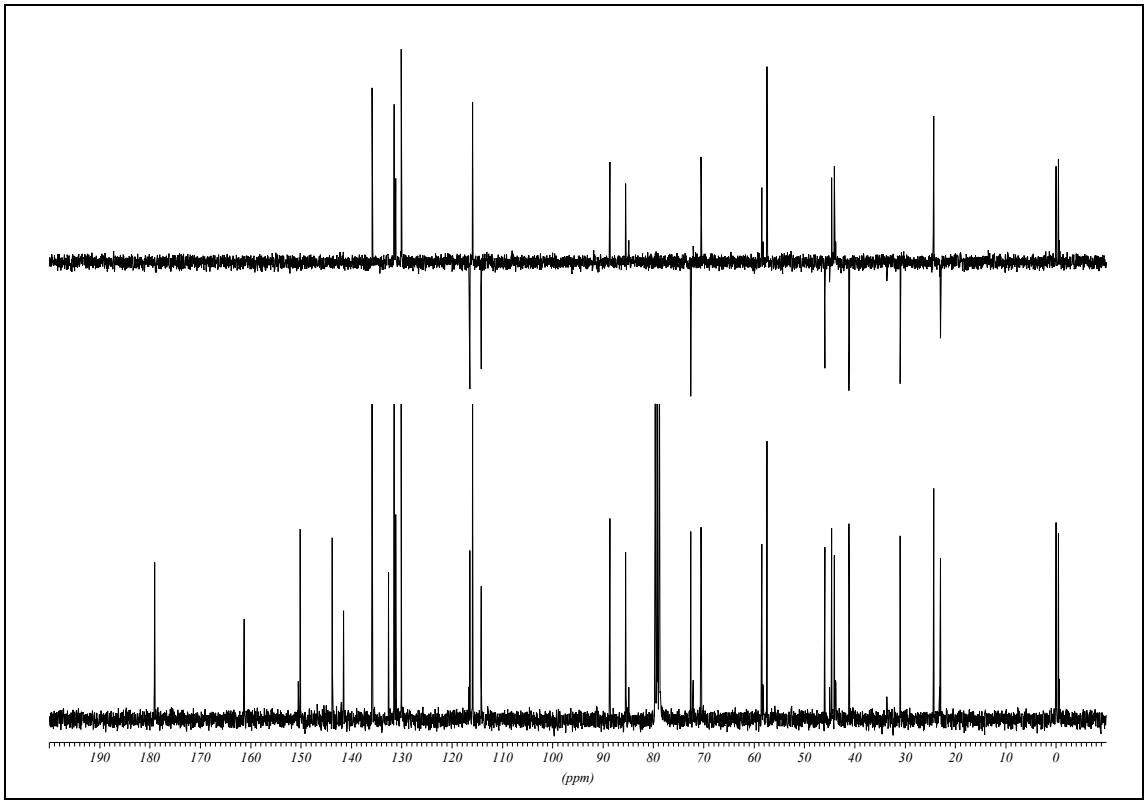
(4*R/S*,5*R*)-5-((1*S*,2*S*,3*S*)-2-((dimethyl(phenyl)silyl)methyl)-3-(*p*-methoxybenzyloxy)-5-methylenecyclopentyl)-4-(1-hydroxybut-3-enyl)dihydrofuran-2(3H)-one (195), *dr* = 50:50



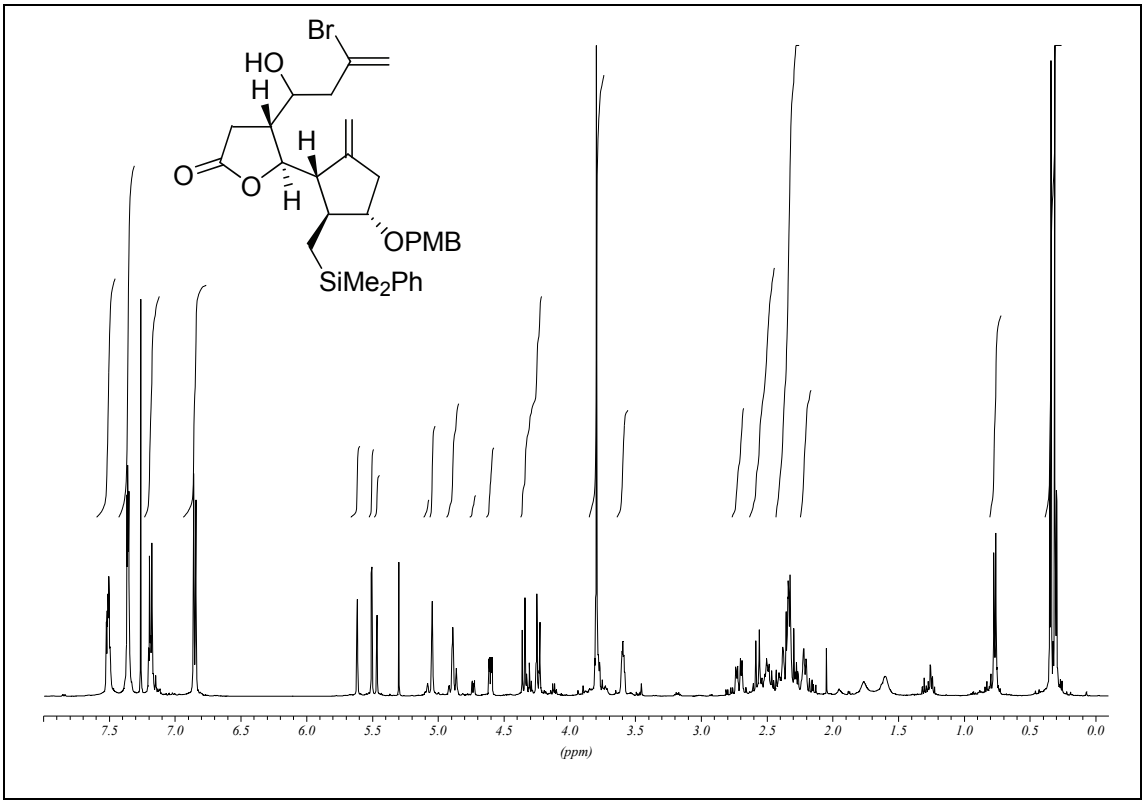


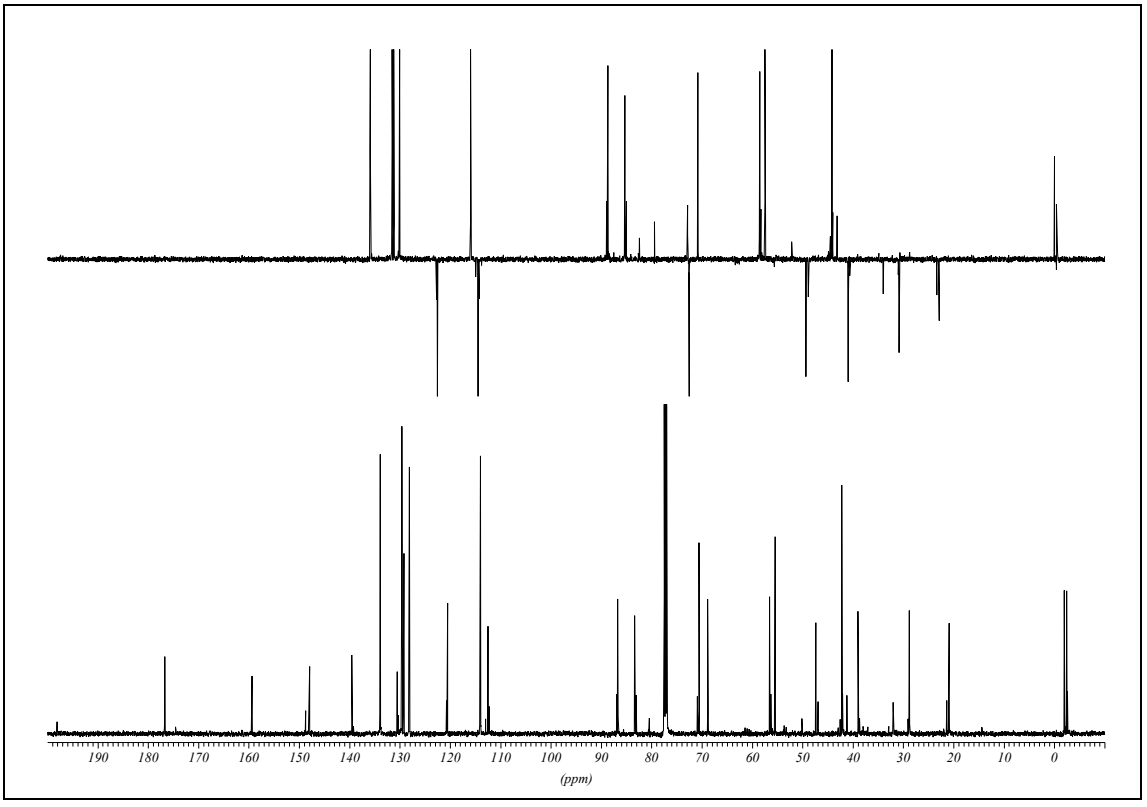
(4*R/S*,5*R*)-5-((1´*S*,2´*S*,3´*S*)-3´-(*p*-methoxybenzyloxy)-2´-((dimethyl(phenyl)silyl)methyl)-5´-methylenecyclopentyl)-dihydro-4-(1´´*R/S*-hydroxy-3´´-methylbut-3´´-enyl)furan-2(3H)-one (196), *dr* = 80:20



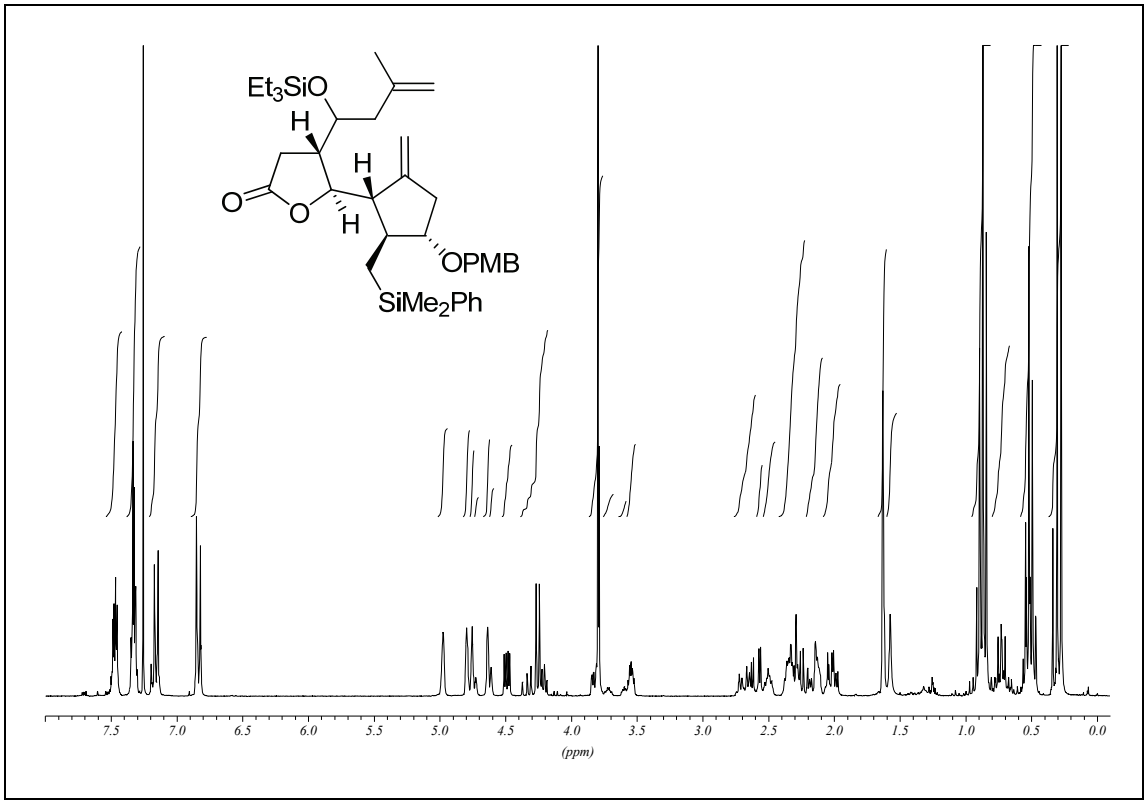


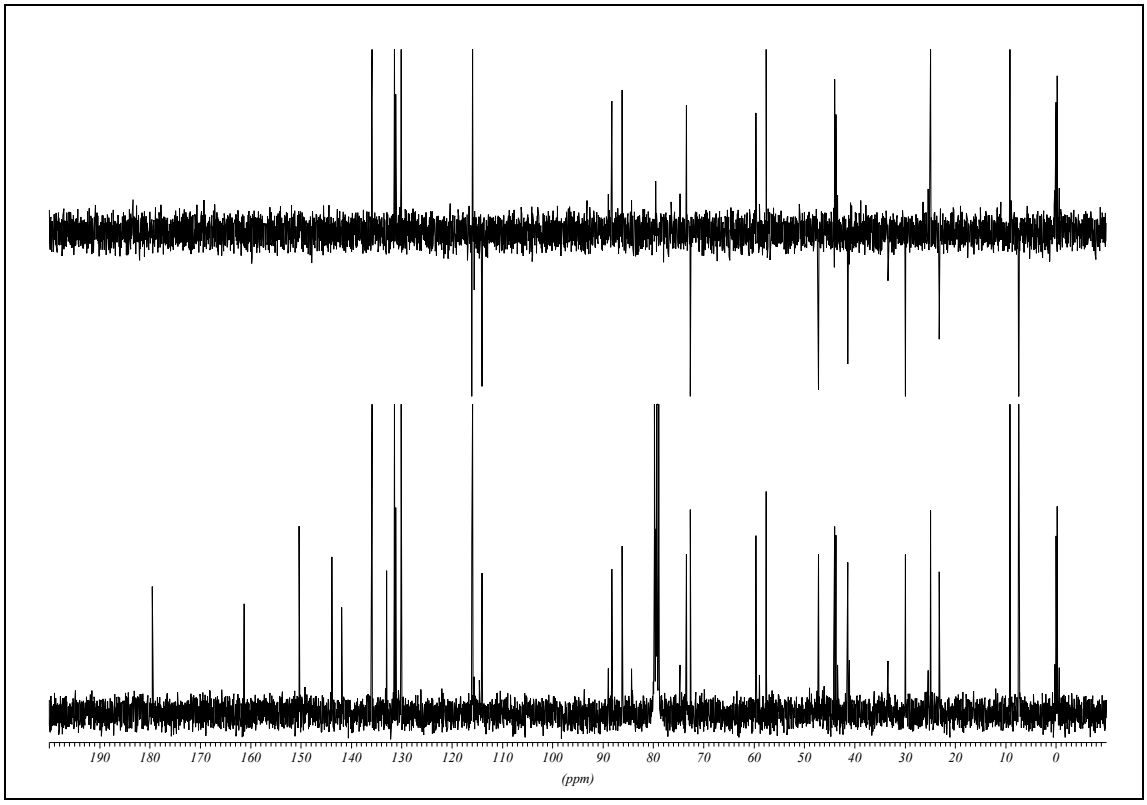
(4*R/S*,5*R*)-4-(3´-bromo-1´-hydroxybut-3-enyl)-5-((1´´*S*,2´´*S*,3´´*S*)-2´´-((dimethyl(phenyl) silyl)methyl)-3´´-(*p*-methoxybenzyloxy)-5´´-methylenecyclopentyl)-dihydrofuran-2(3H)-one (197), *dr* = 78:22



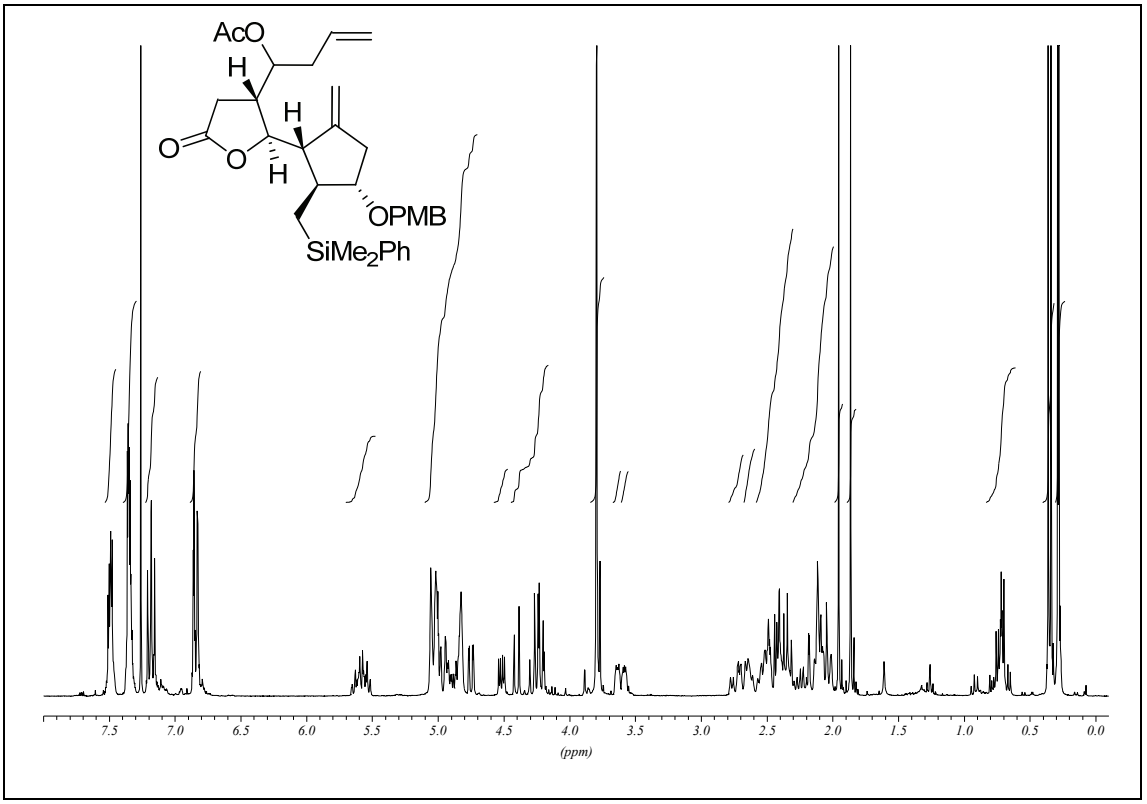


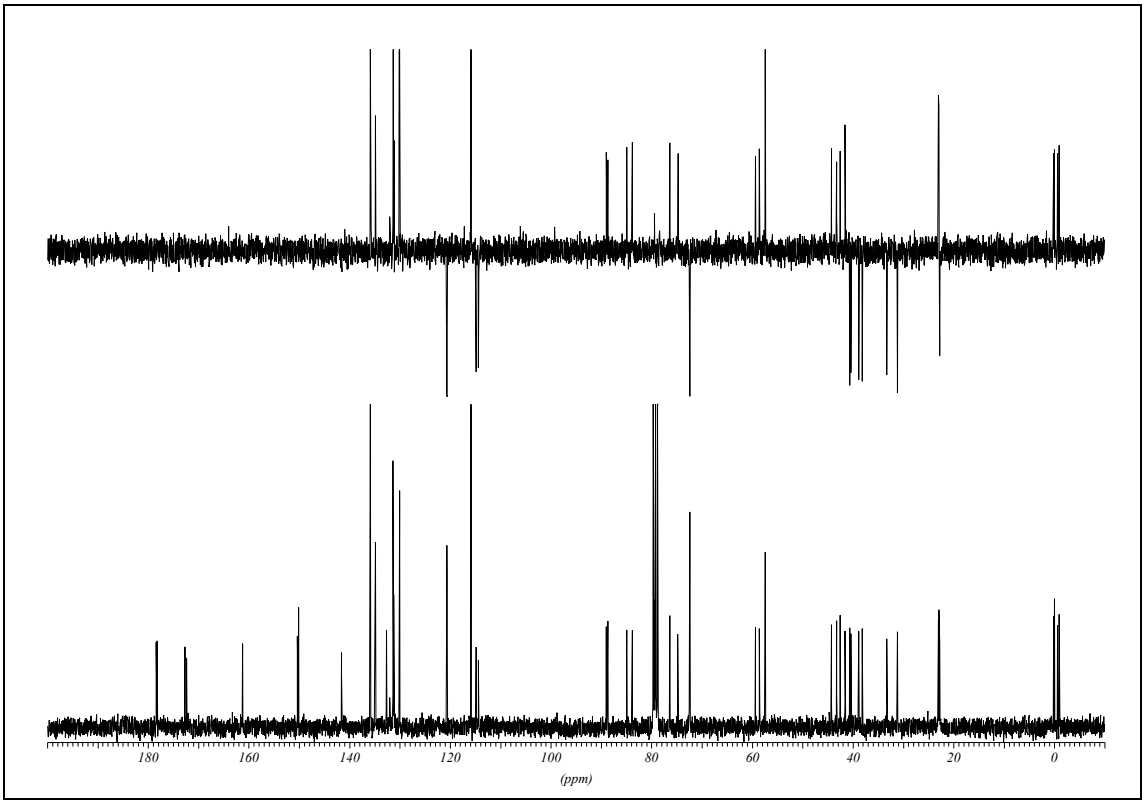
(4*S*,5*R*)-5-((1´*S*,2´*S*,3´*S*)-3´-(*p*-methoxybenzyloxy)-2´-((dimethyl(phenyl)silyl)methyl)-5´-methylenecyclopentyl)-dihydro-4-(1´´*R/S*-triethylsilanyloxy-3´´-methylbut-3´´-enyl) furan-2(3H)-one (198a), *dr* = 80:20



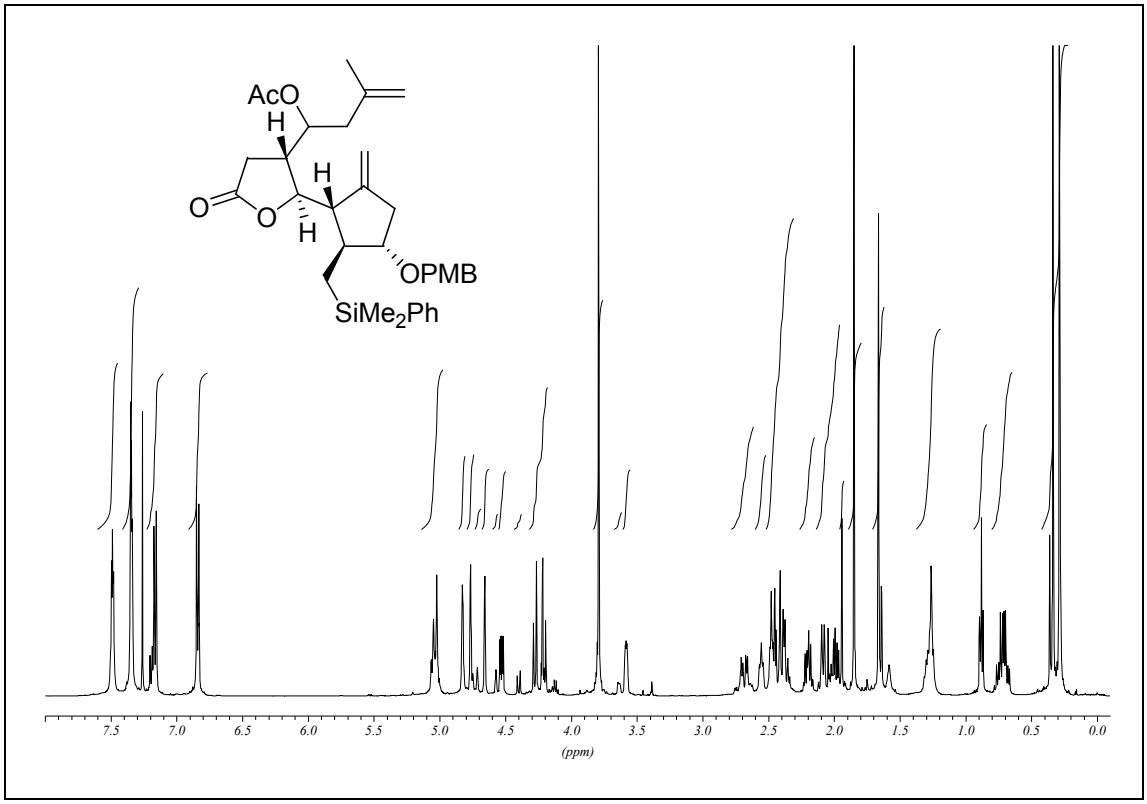


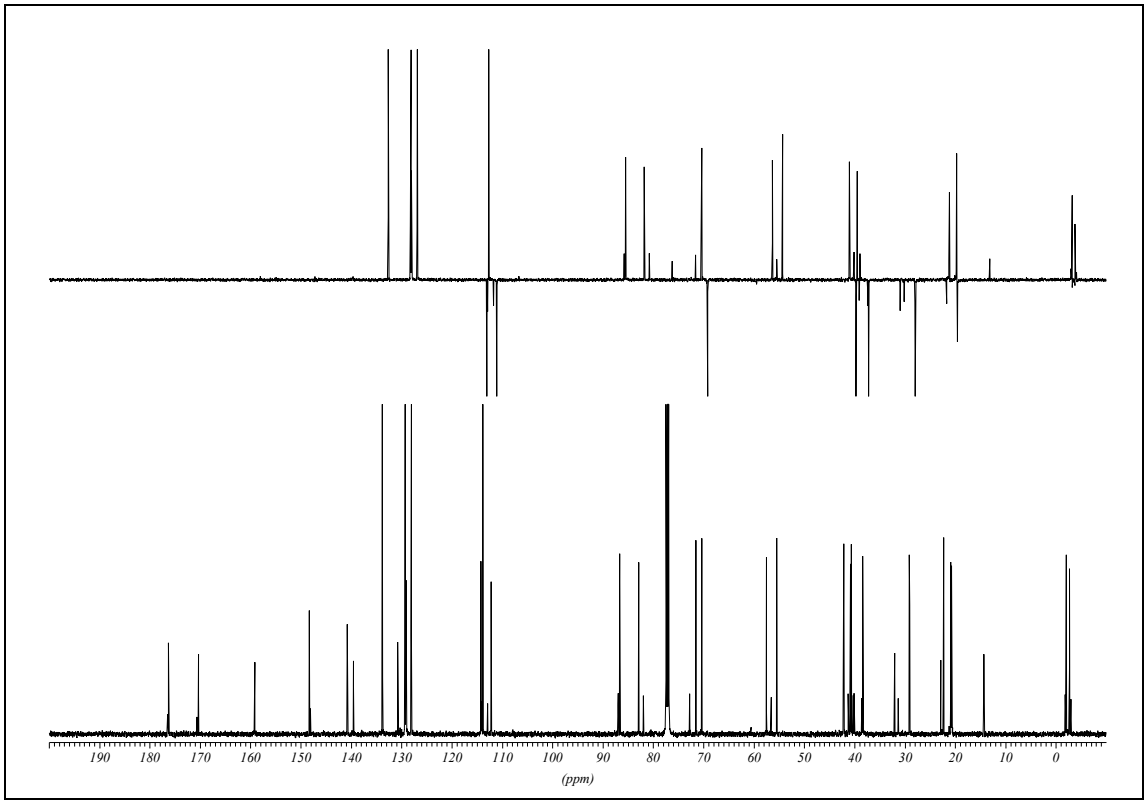
1(*R/S*)-((2*R*,3*R*)-2-((1*S*,2*S*,3*S*)-2-((dimethyl(phenyl)silyl)methyl)-3-(*p*-methoxybenzyl oxy)-5-methylenecyclopentyl)-5-oxotetrahydrofuran-3-yl)but-3-enyl acetate (198b), *dr* = 50:50



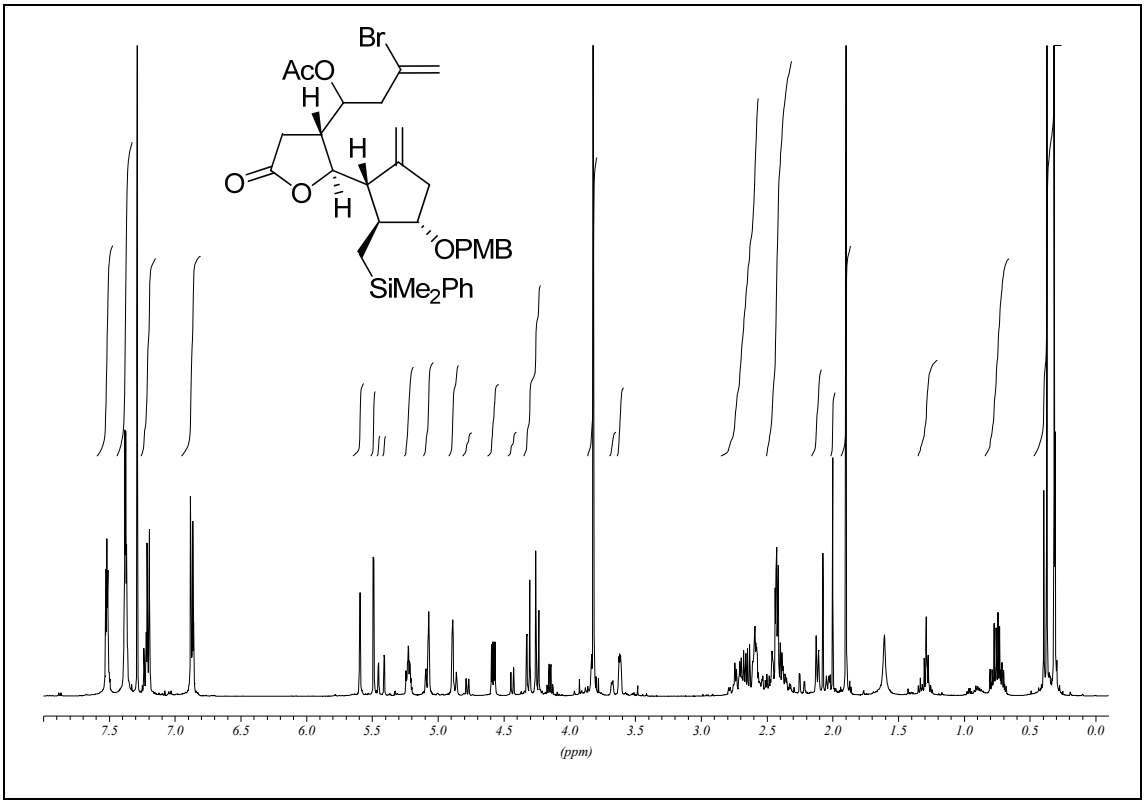


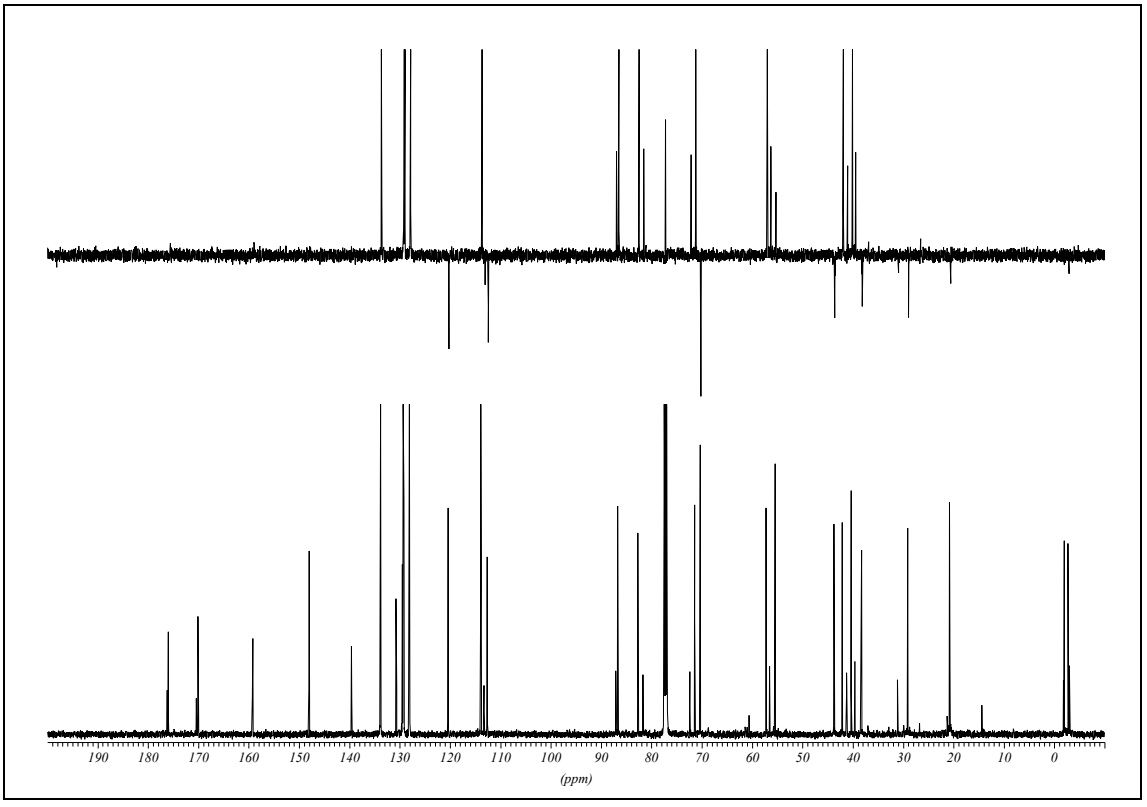
1-((2′*R*,3′*R*)-2′-((1′′*S*,2′′*S*,3′′*S*)-2′′-((dimethyl(phenyl)silyl)methyl)-3′′-(*p*-methoxybenzyloxy)-5′′-methylenecyclopentyl)-5′-oxo-tetrahydrofuran-3′-yl)-3-methylbut-3-enyl acetate (198c), *dr* = 80:20



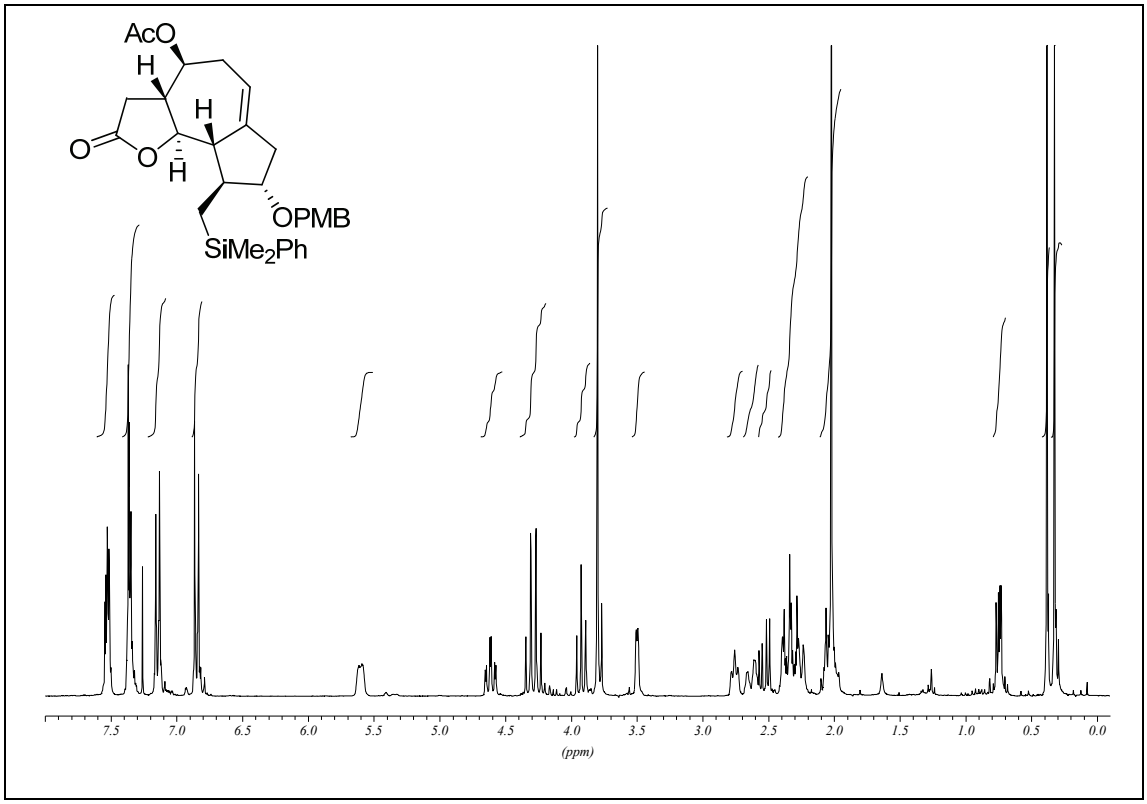


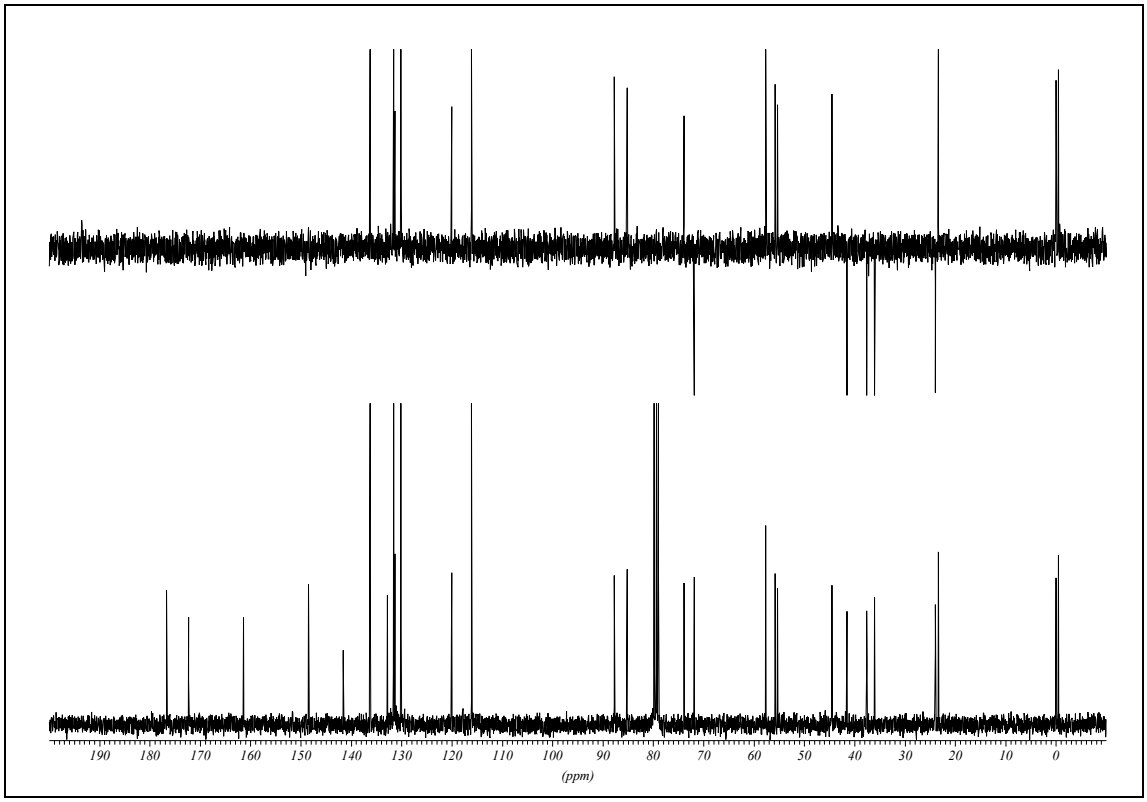
3-bromo-1(*R/S*)-((2´*R*,3´*R*)-2´-((1´´*S*,2´´*S*,3´´*S*)-2´´-((dimethyl(phenyl)silyl)methyl)-3´´-(*p*-methoxybenzyloxy)-5´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (198d), *dr* = 75:25



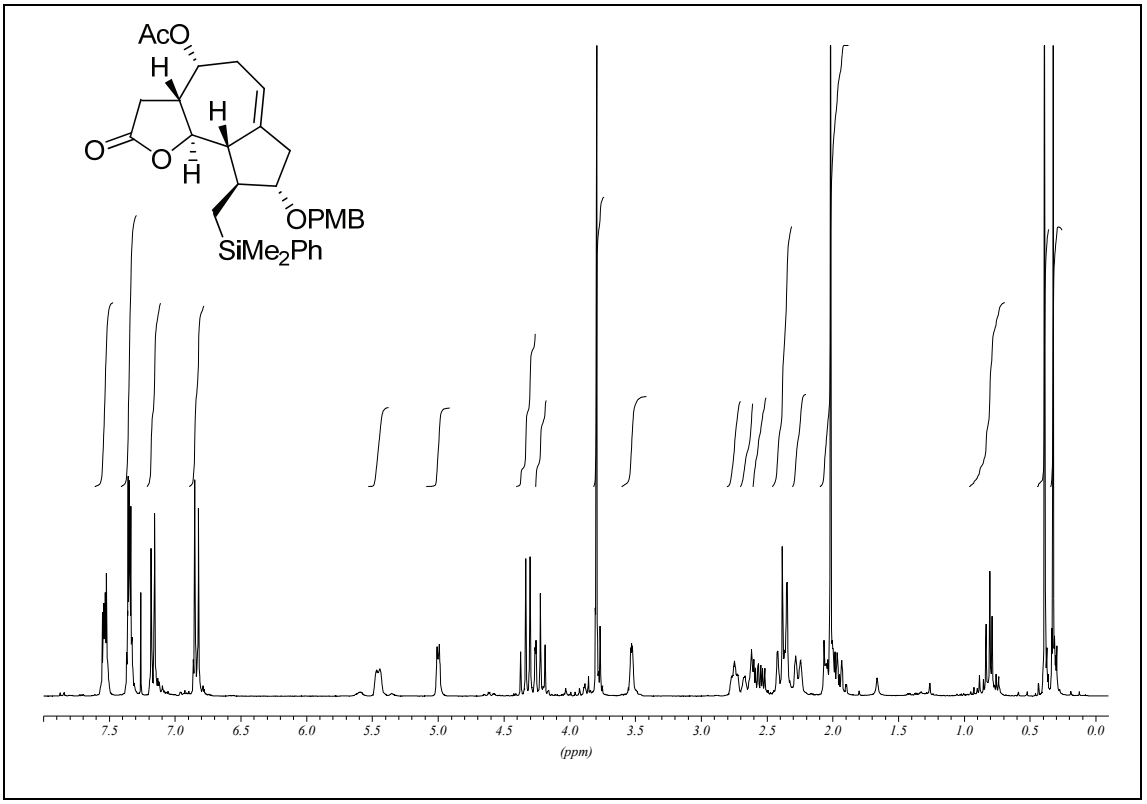


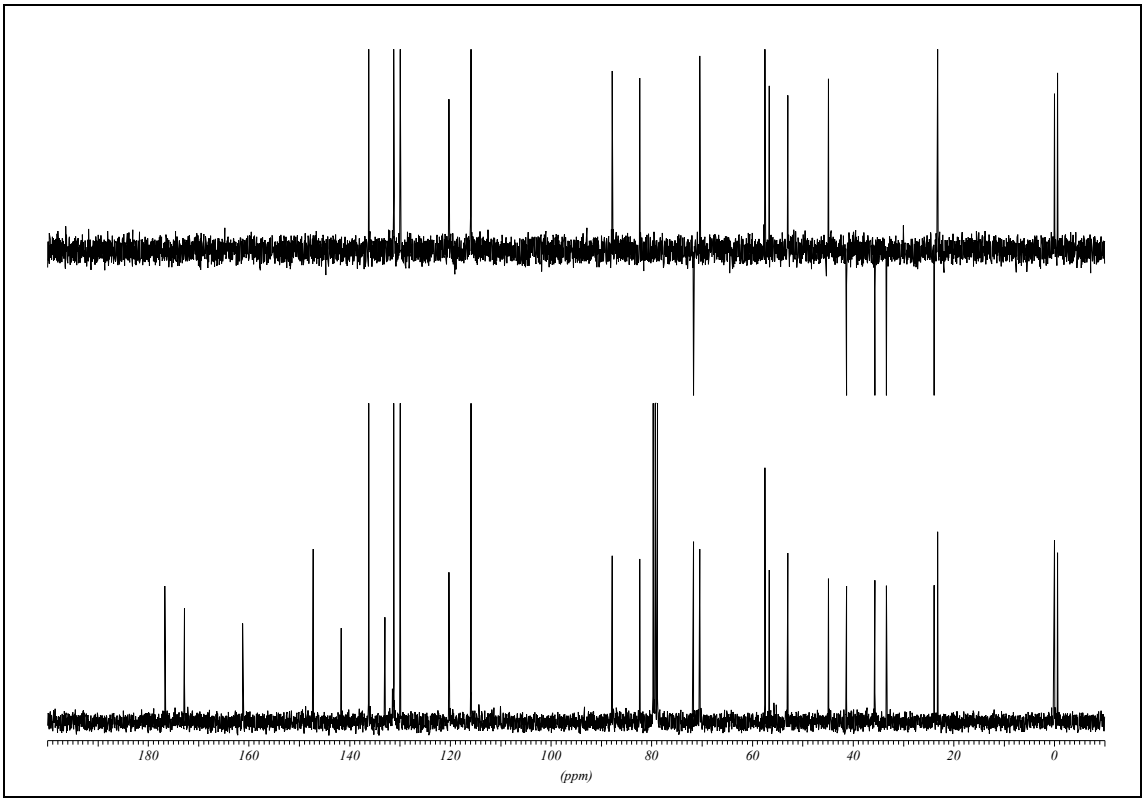
(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*S*-199a)



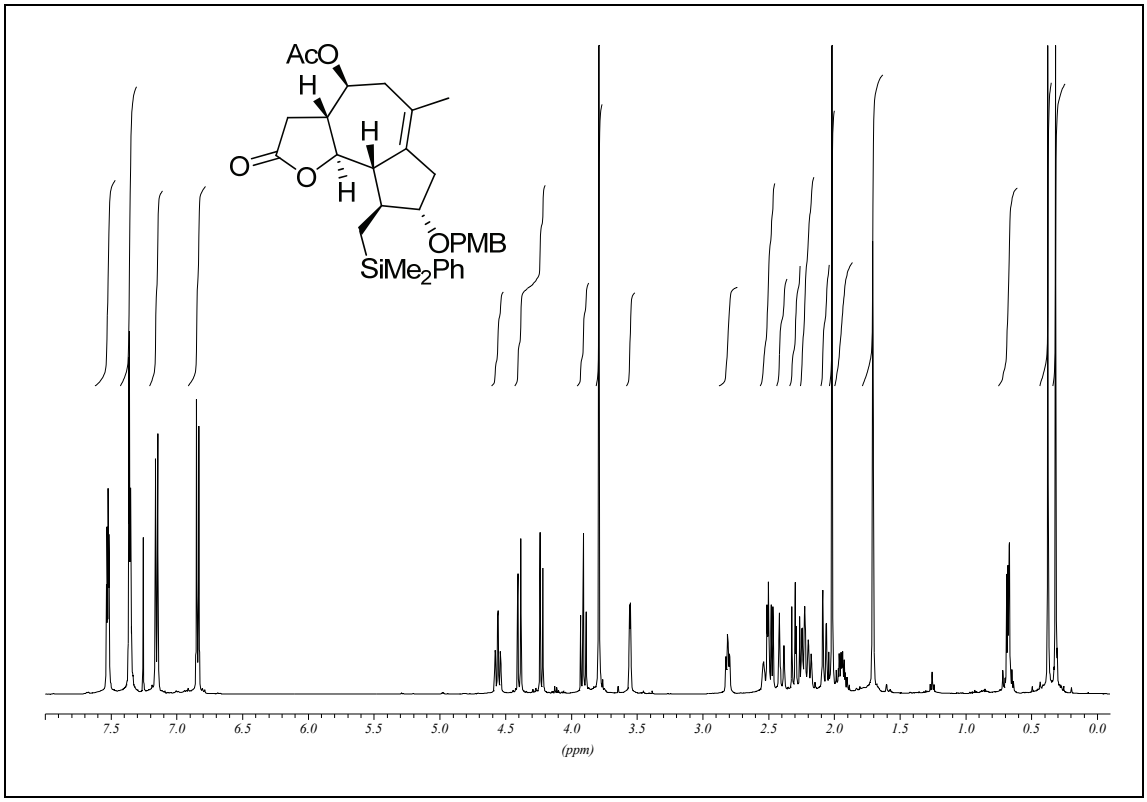


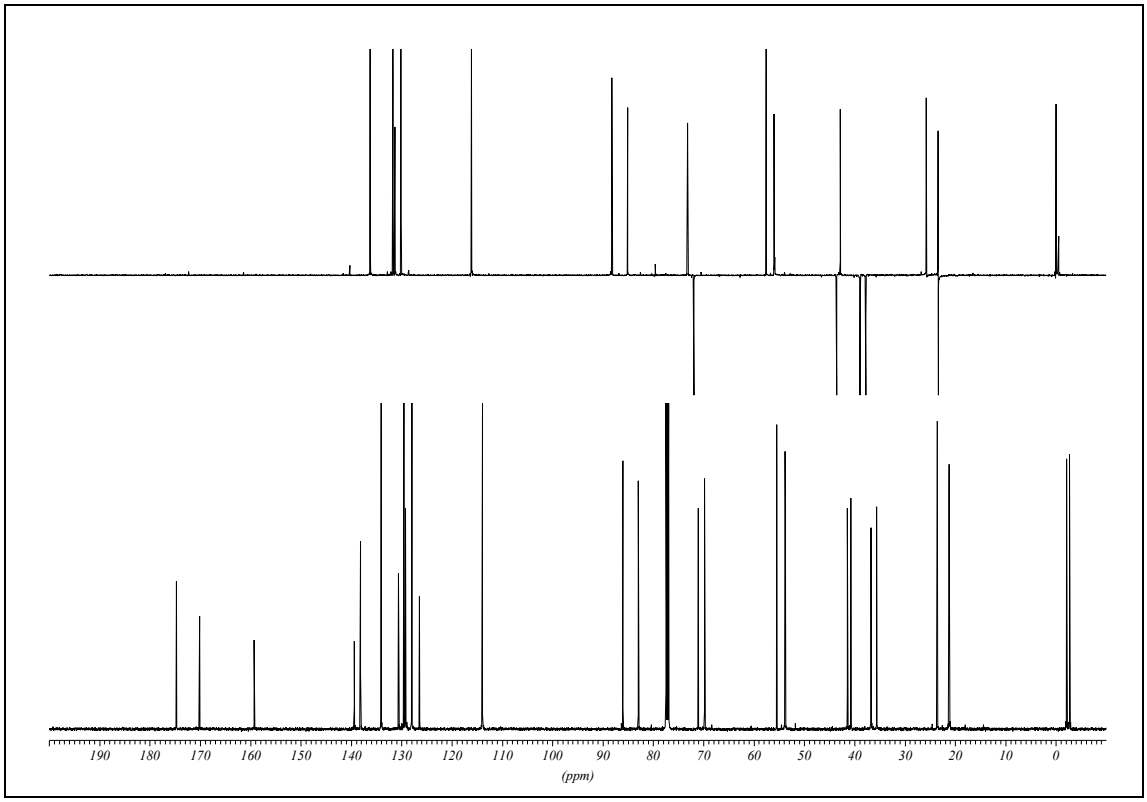
(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*R*-199a)



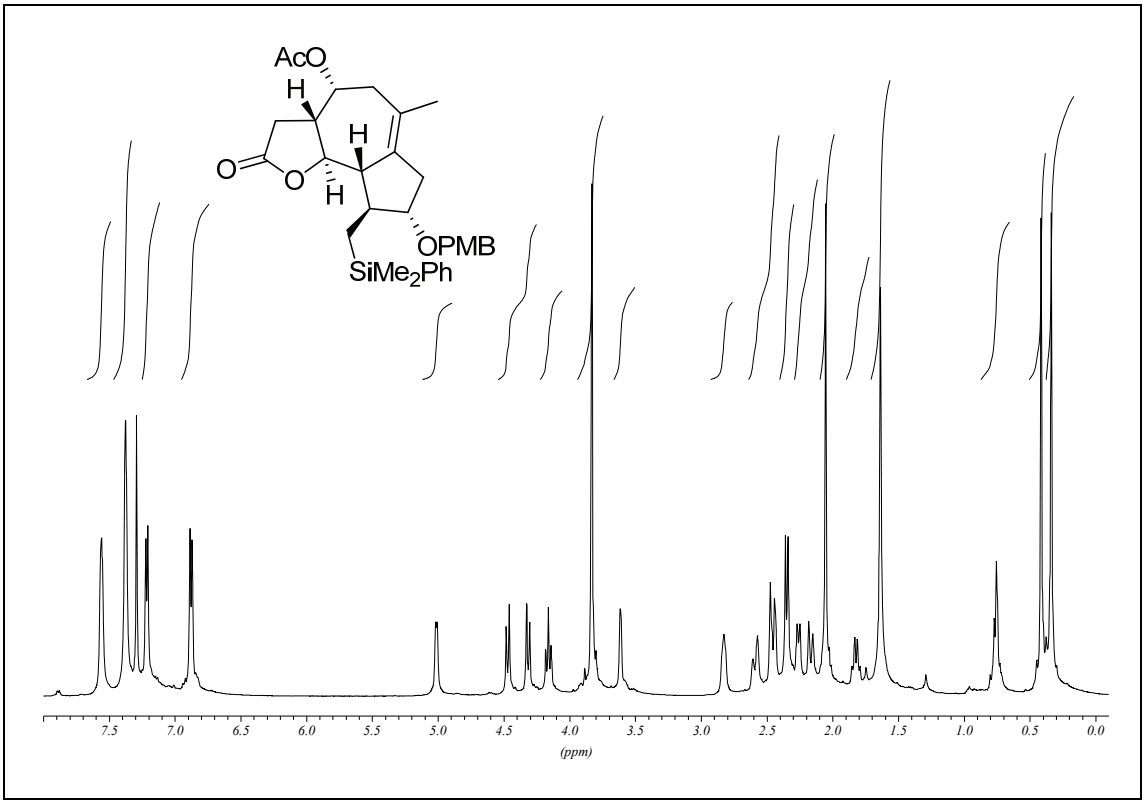


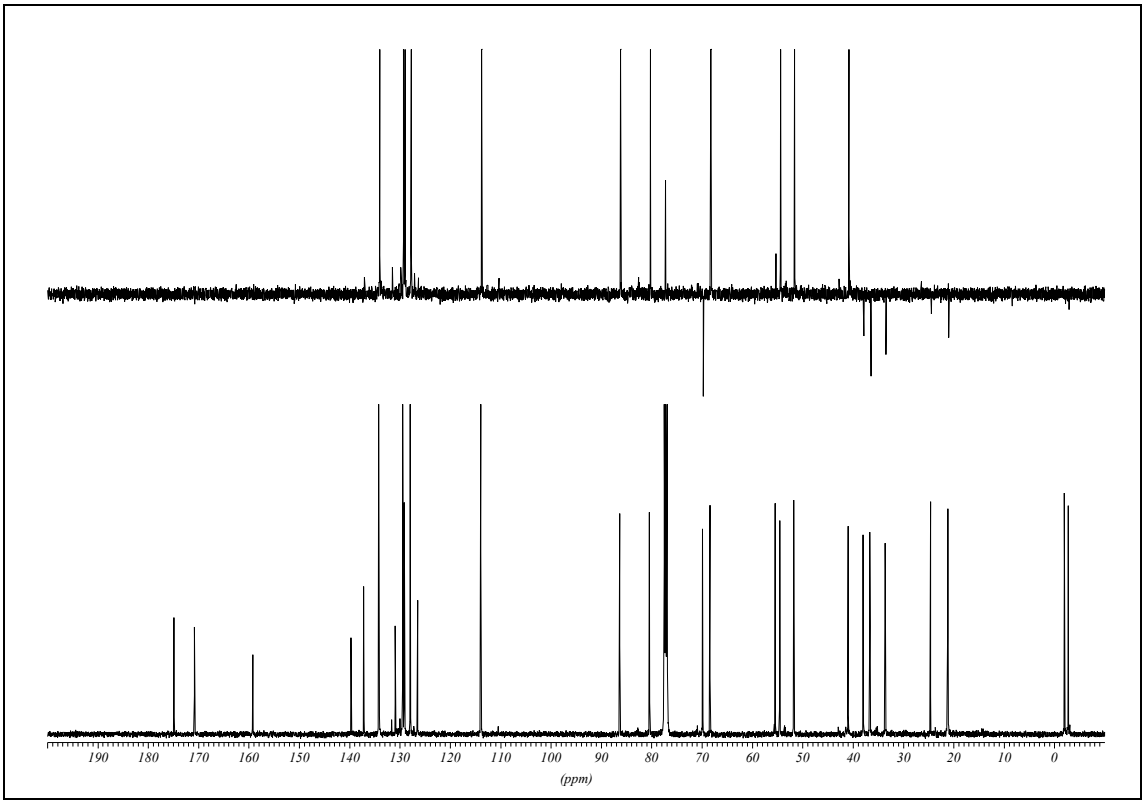
(3a*R*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*S*-**199b)**



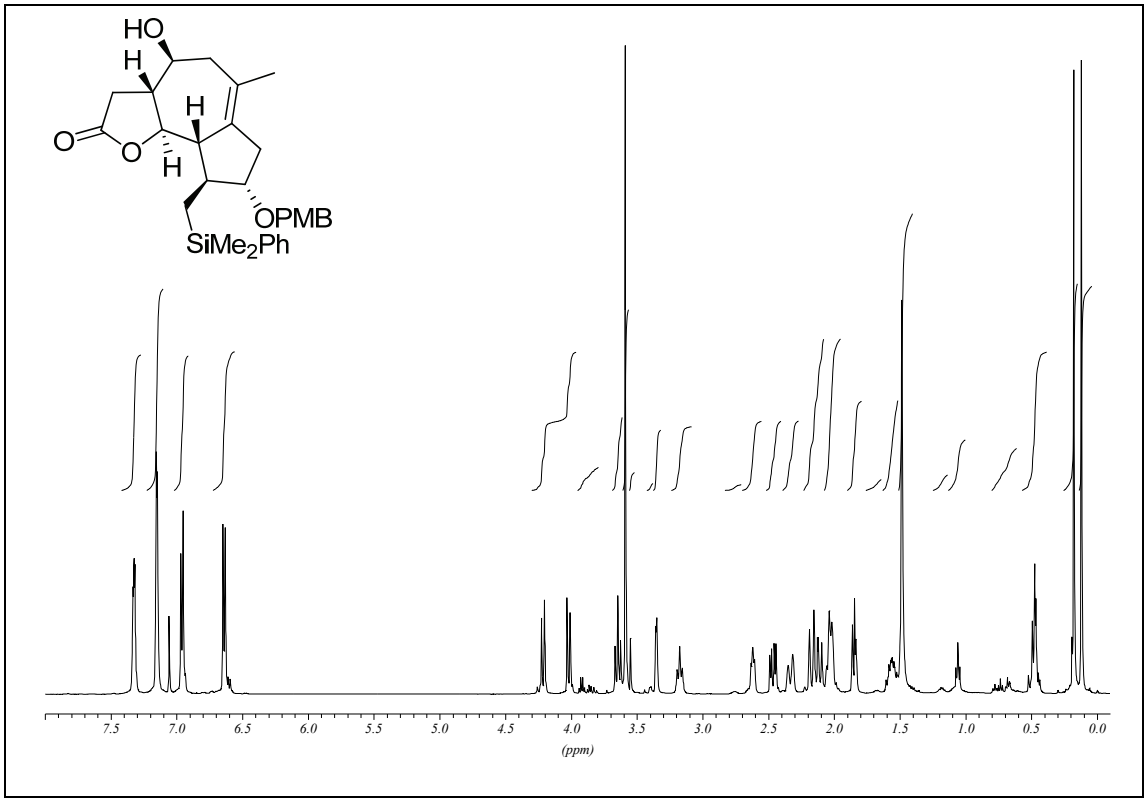


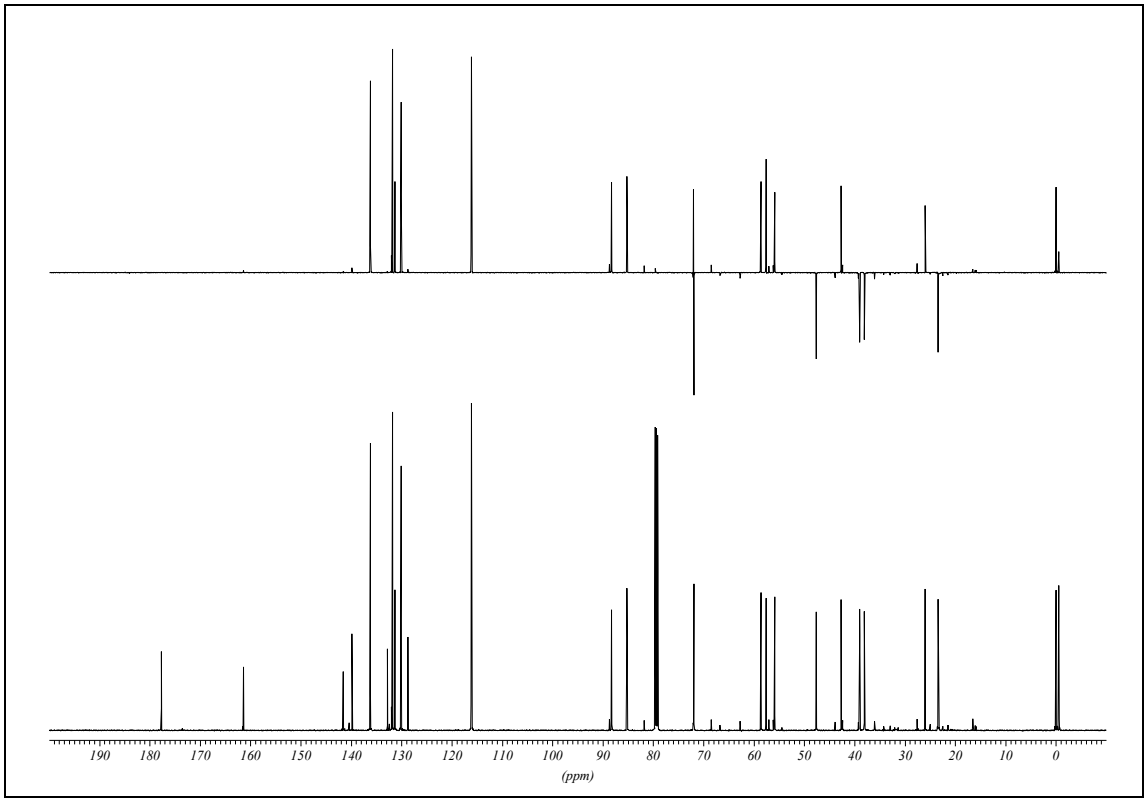
(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (4*R*-199b)



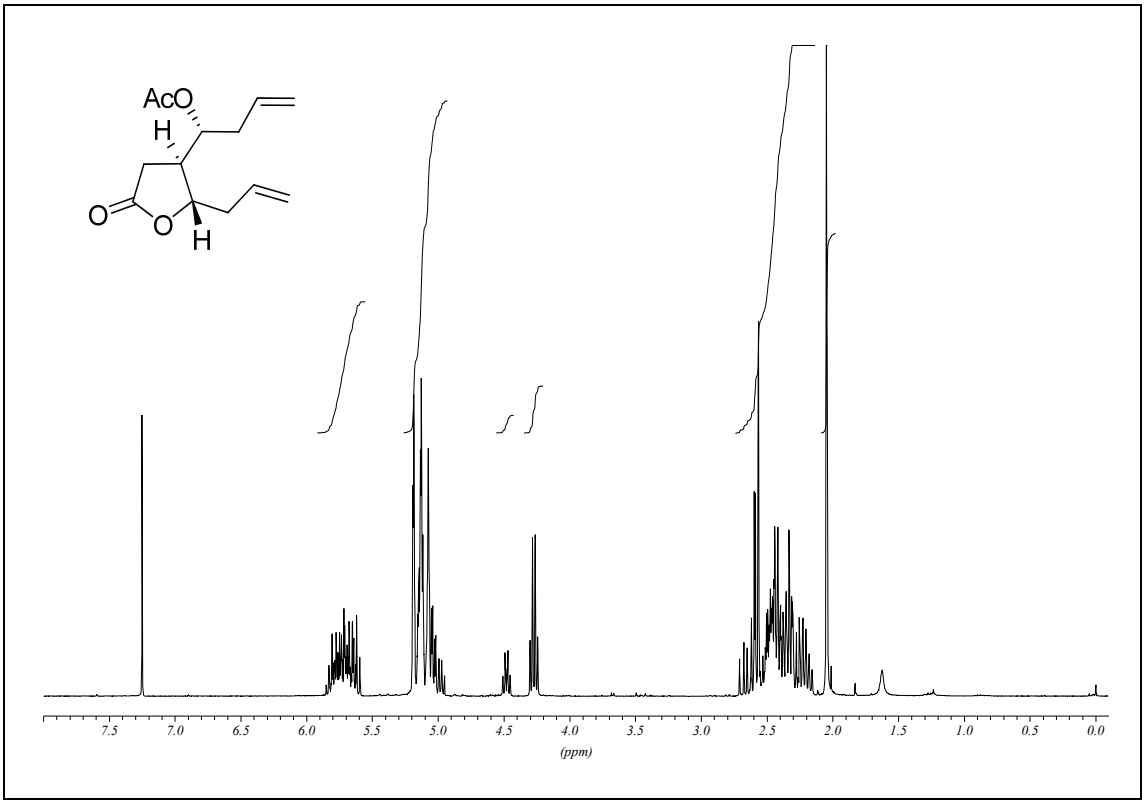


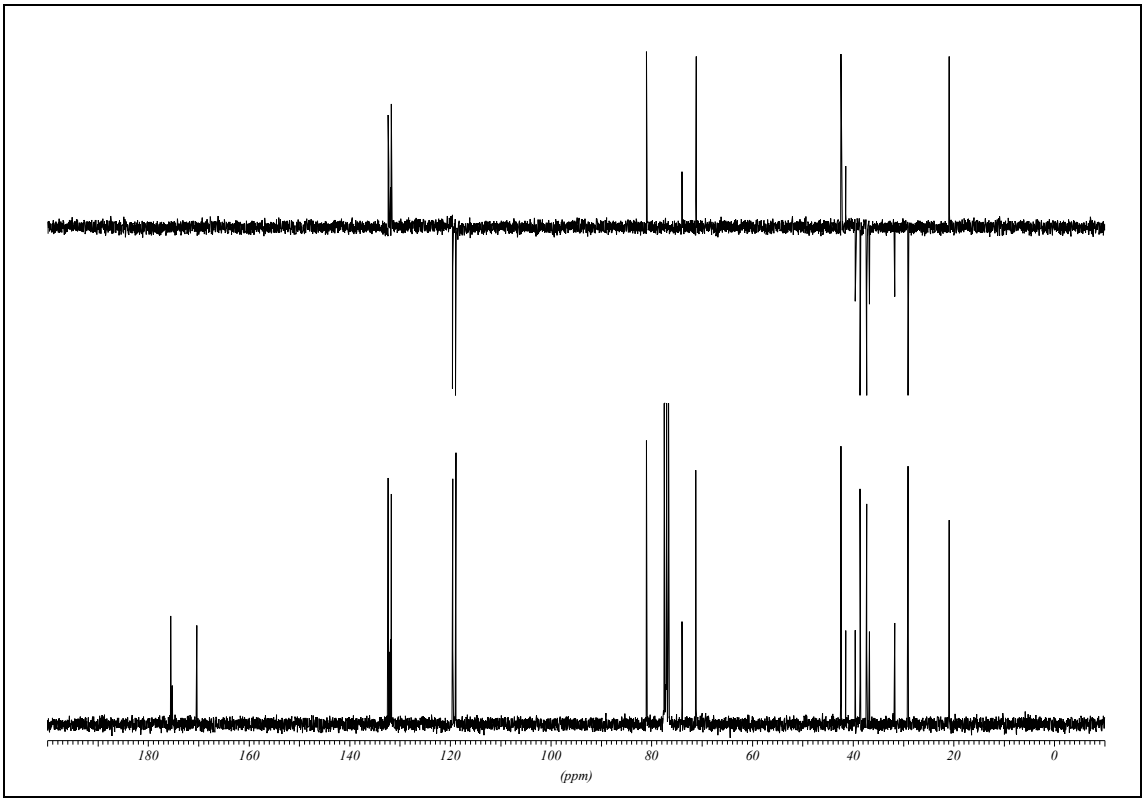
(3a*R*,4*R*/*S*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-4-hydroxy-8-(*p*-methoxybenzyloxy)-6-methyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one (199c)
dr = 80:20



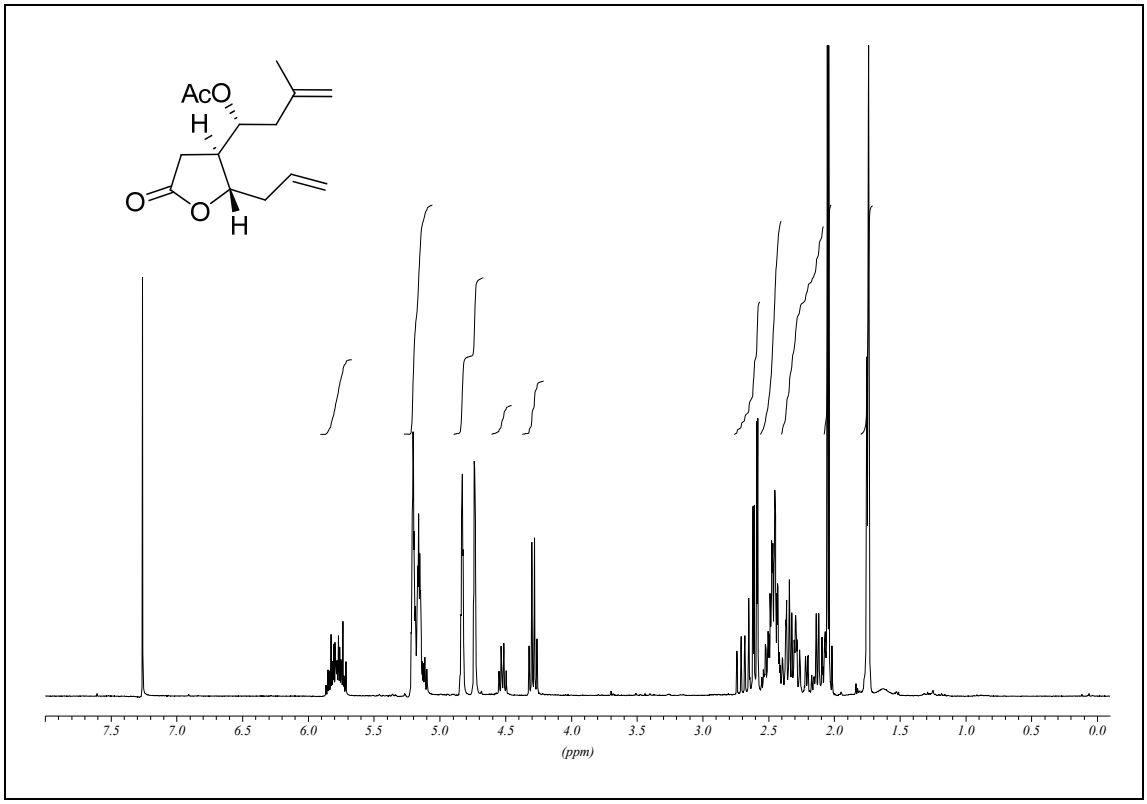


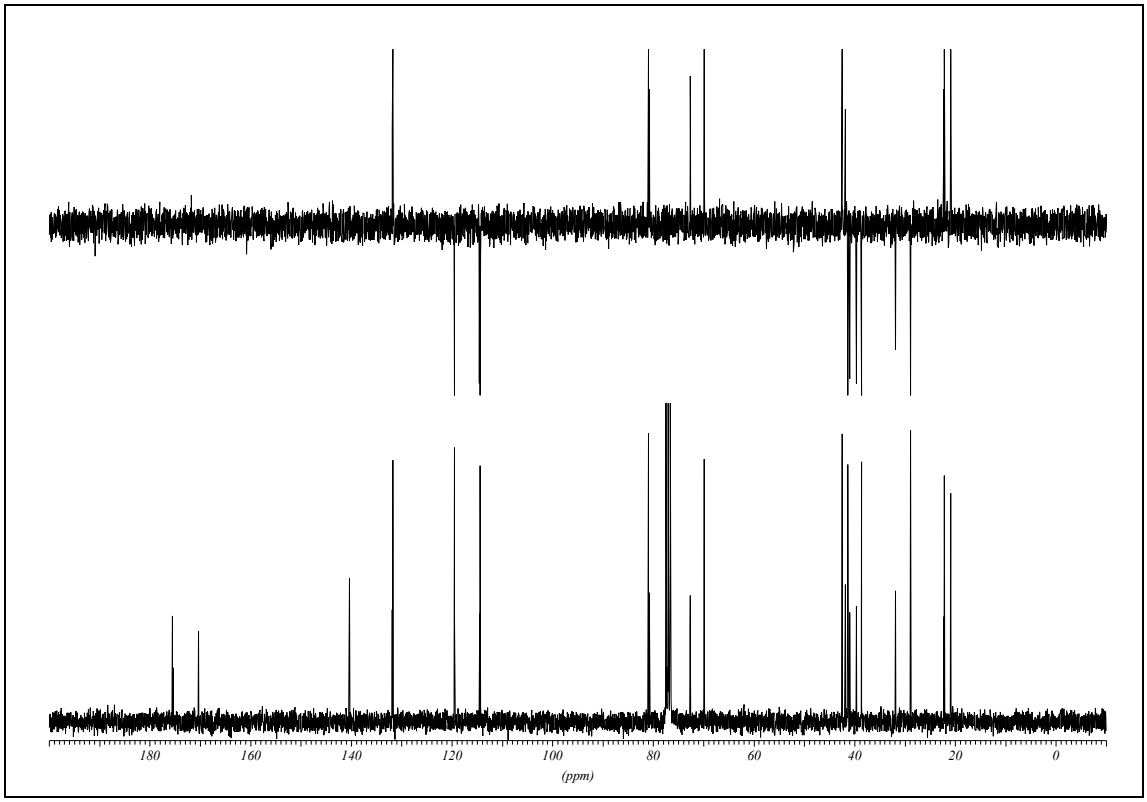
1-((2´*S*,3´*S*)-2´-allyl-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (213a), *dr* = 73:27



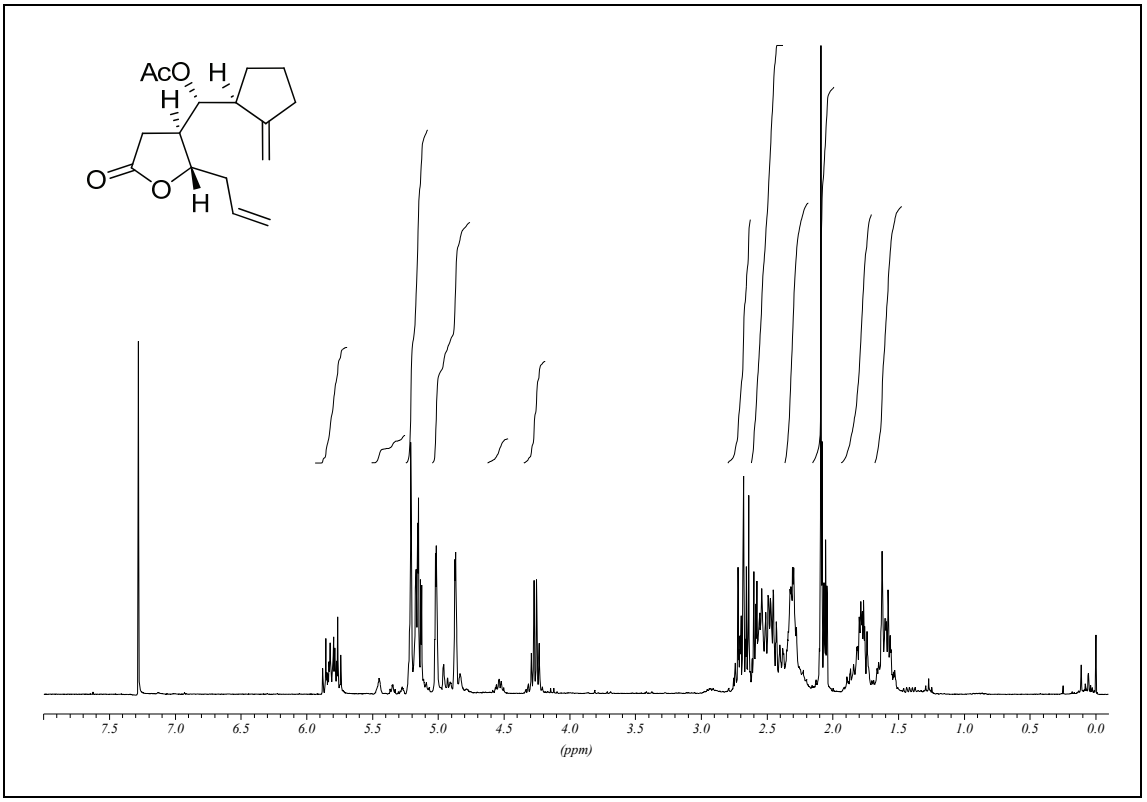


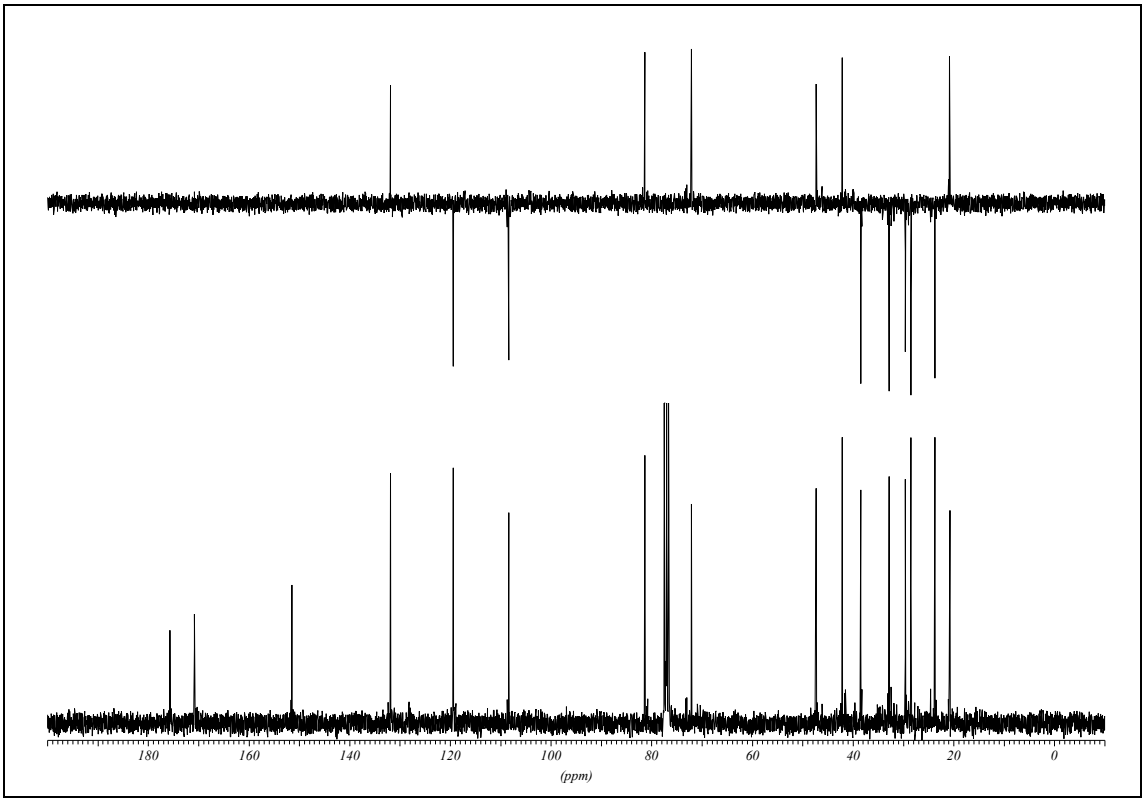
1-((2´S,3´*R*)-2´-allyl-5´-oxo-tetrahydrofuran-3´-yl)-3-methylbut-3-enyl acetate (213b), *dr* = 67:33



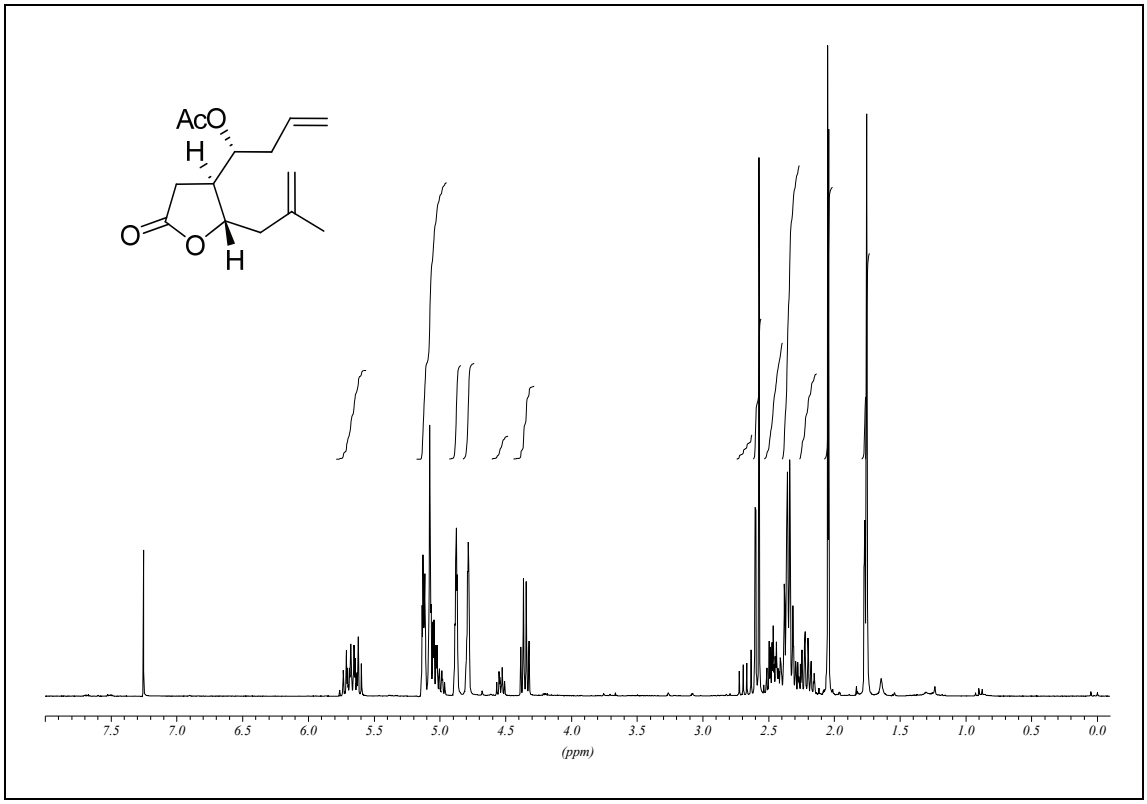


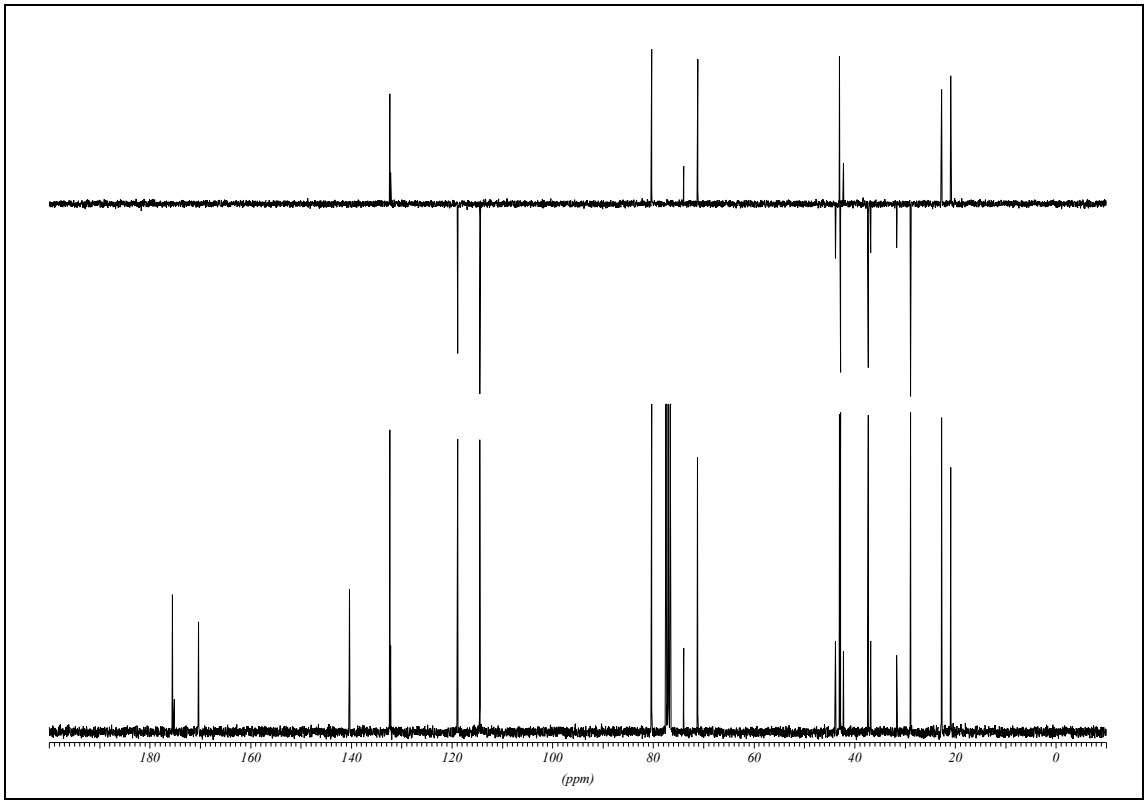
((2´*S*,3´*R*)-2´-allyl-5´-oxo-tetrahydrofuran-3´-yl)(2-methylenecyclopentyl)methyl acetate (213c), *dr* = 82:18:0:0



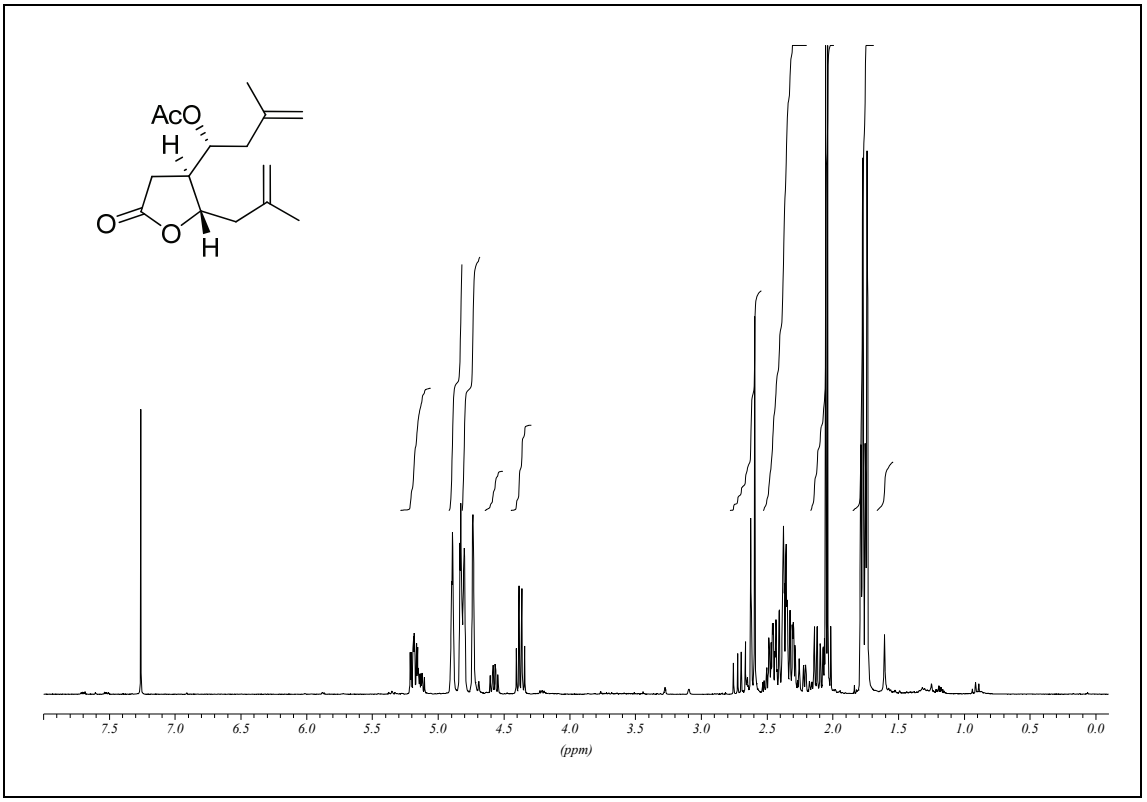


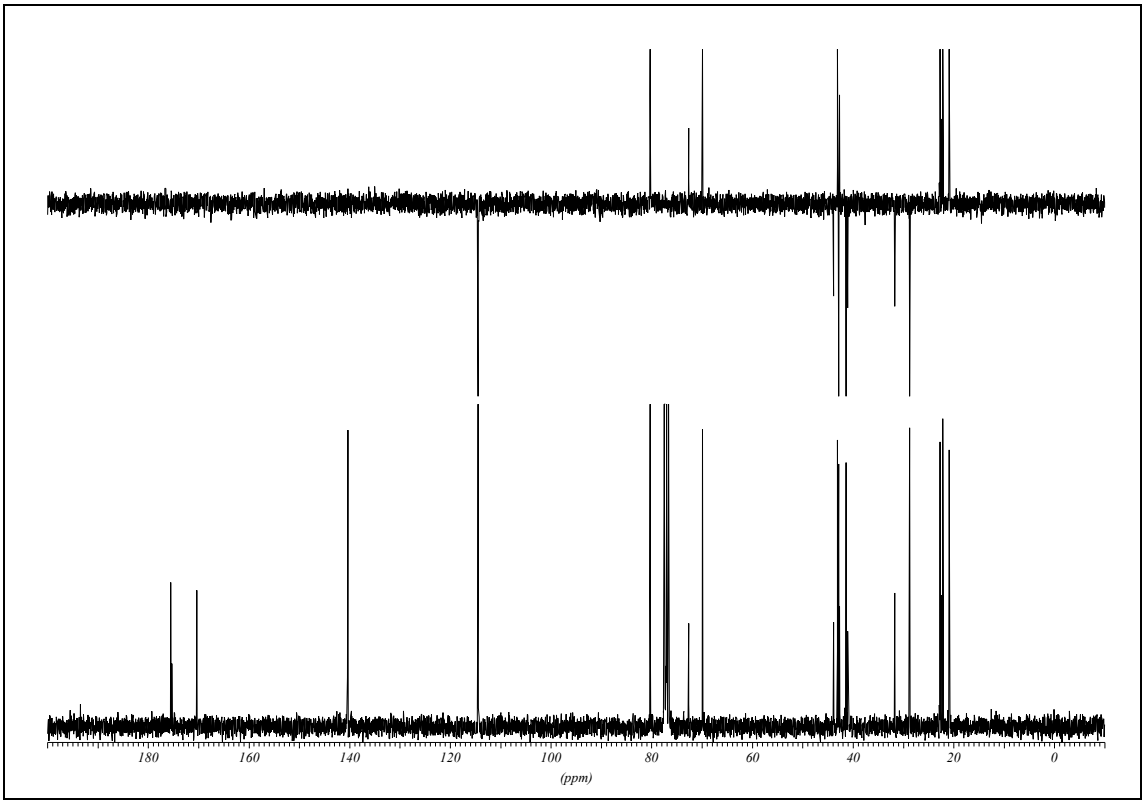
1-((2´*S*,3´*S*)-2´-(2´´-methylallyl)-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (213d), *dr* = 77:23



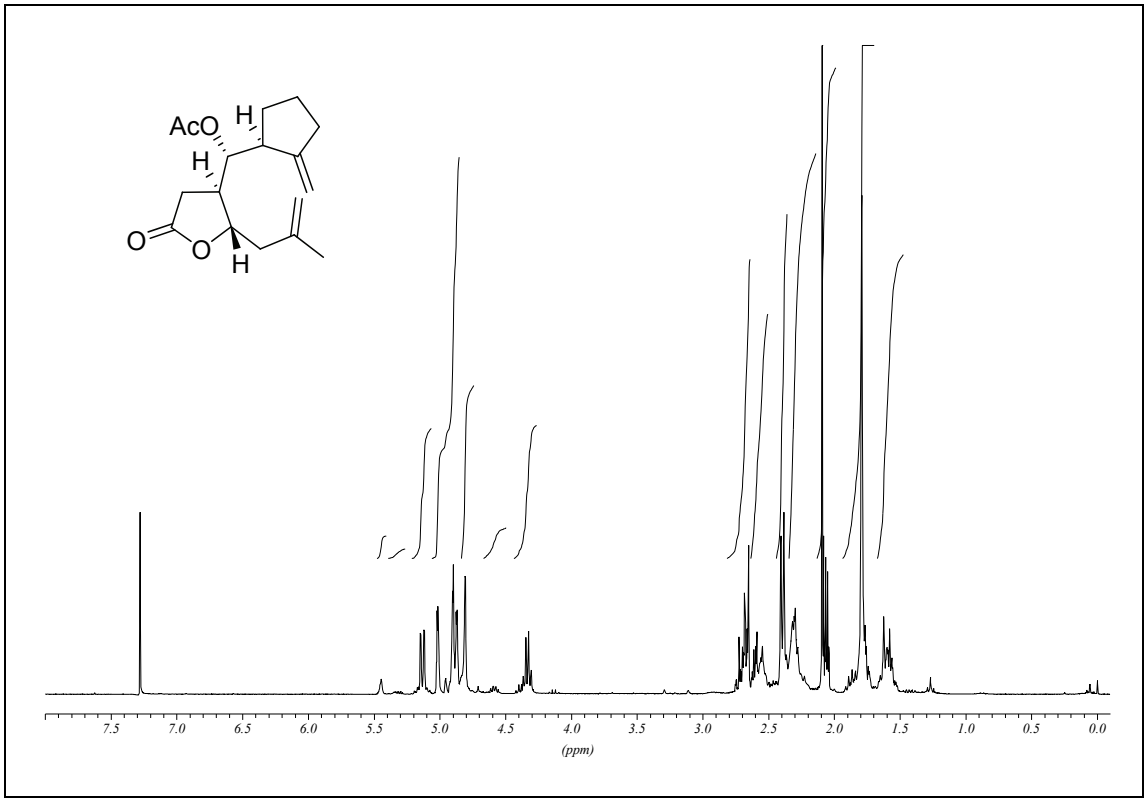


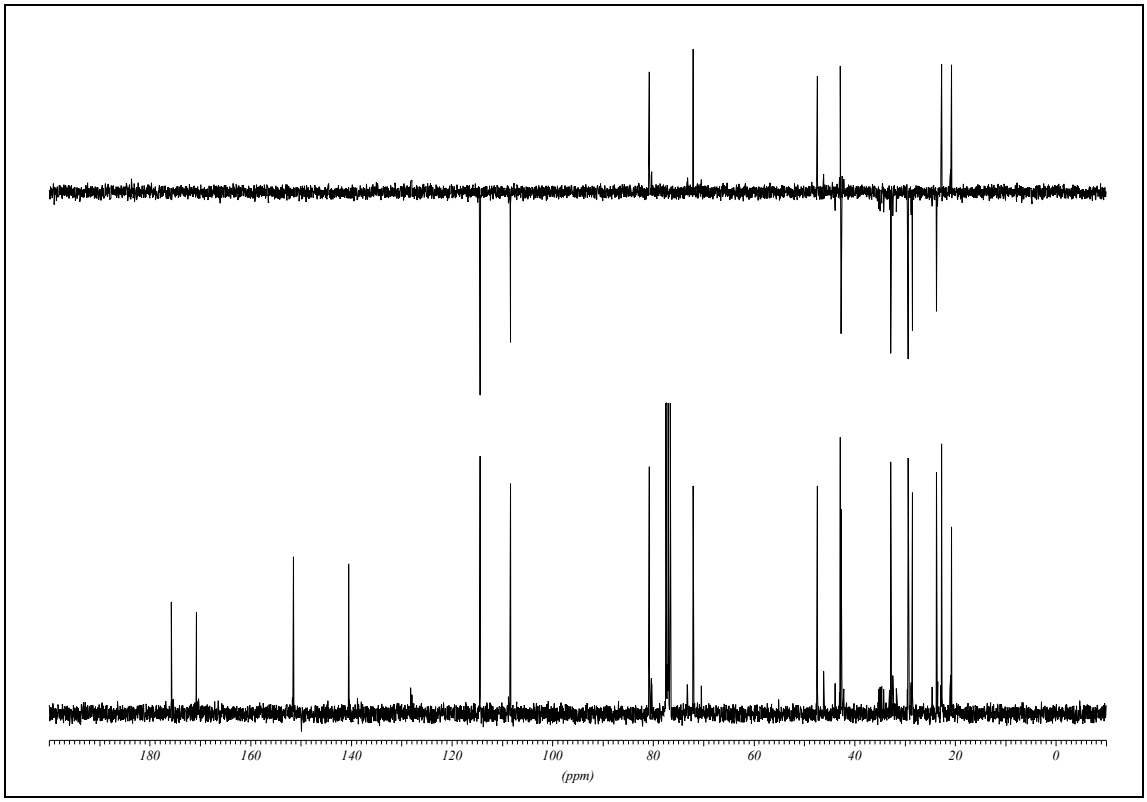
3-methyl-1-((2´*S*,3´*S*)-2´-(2´´-methylallyl)-5´-oxo-tetrahydrofuran-3´-yl)but-3-enyl acetate (213e), *dr* = 70:30



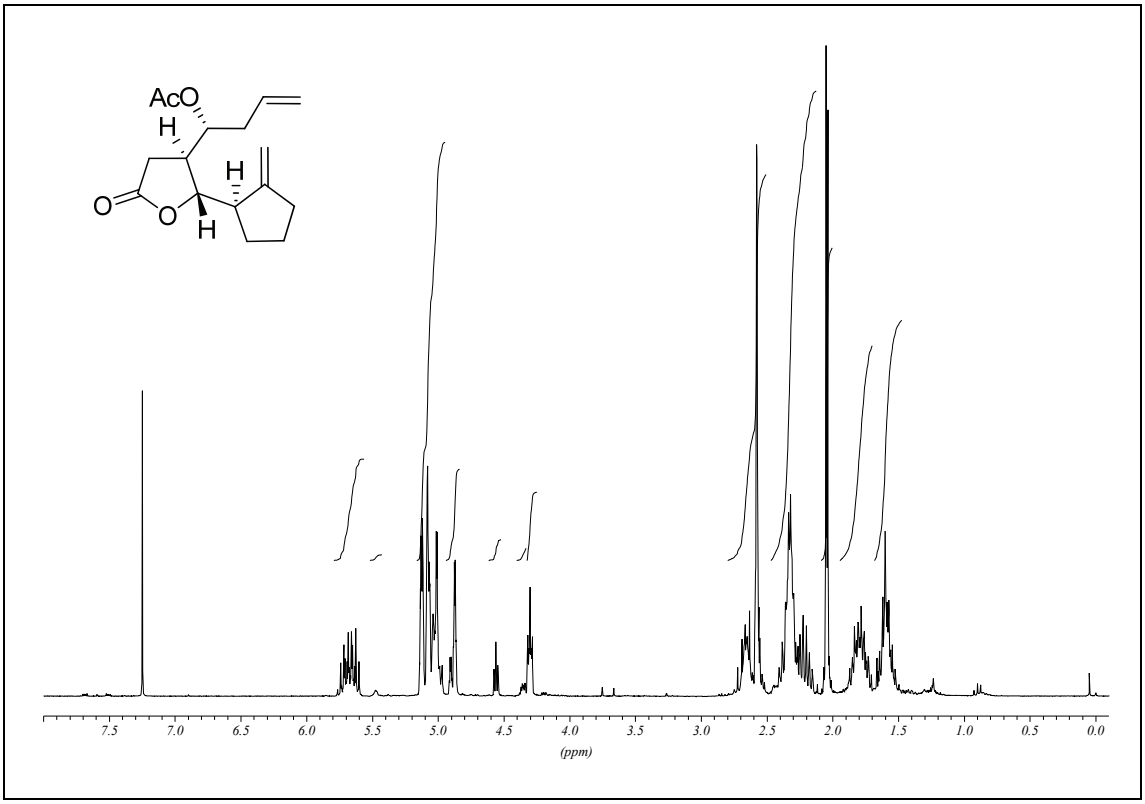


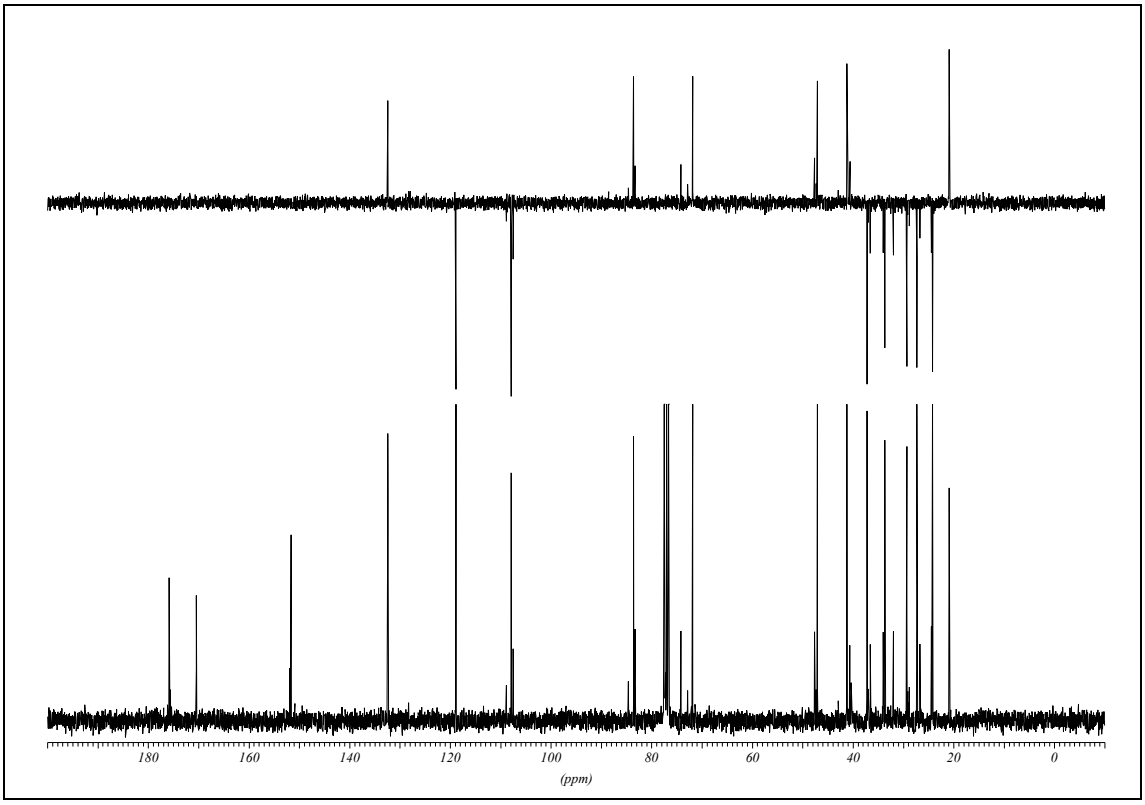
((2′*S*,3′*R*)-2′-(2′′-methylallyl)-5′-oxo-tetrahydrofuran-3′-yl)(2-methylenecyclopentyl) methyl acetate (213f), *dr* = 79:21:0:0



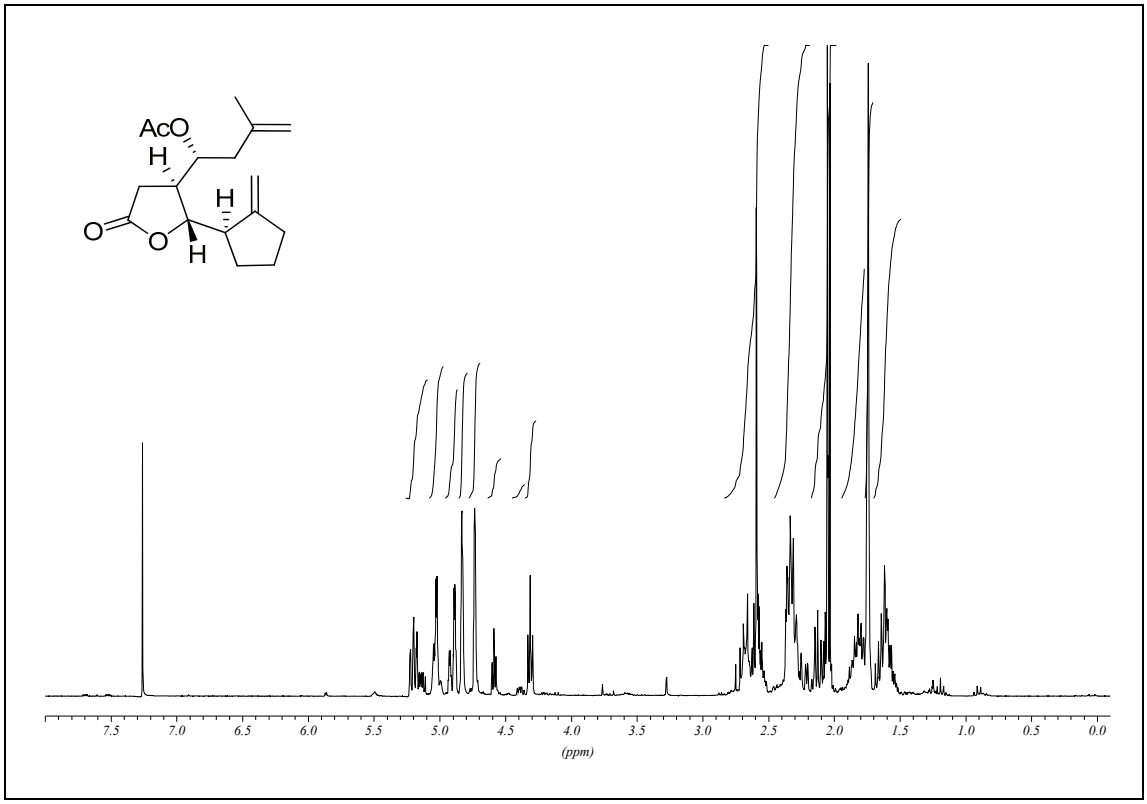


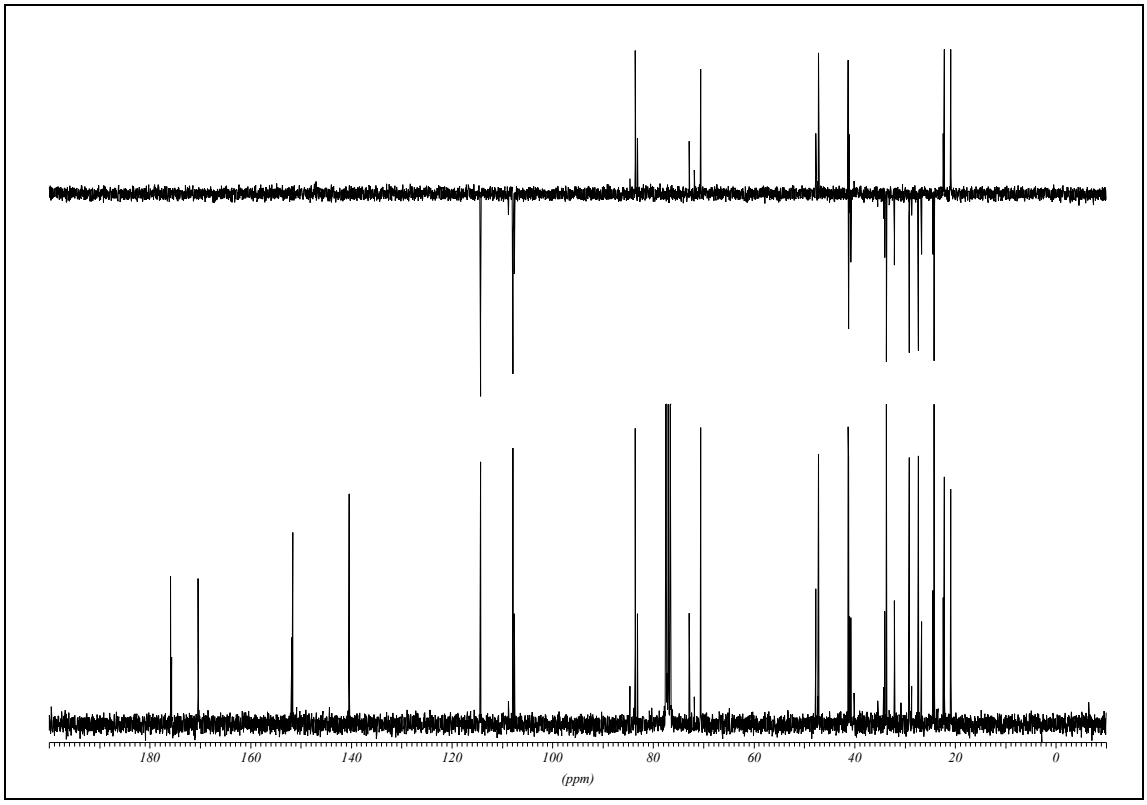
1-((2´*S*,3´*S*)-2´-(2´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3-yl)but-3-enyl acetate (213g), *dr* = 80:20



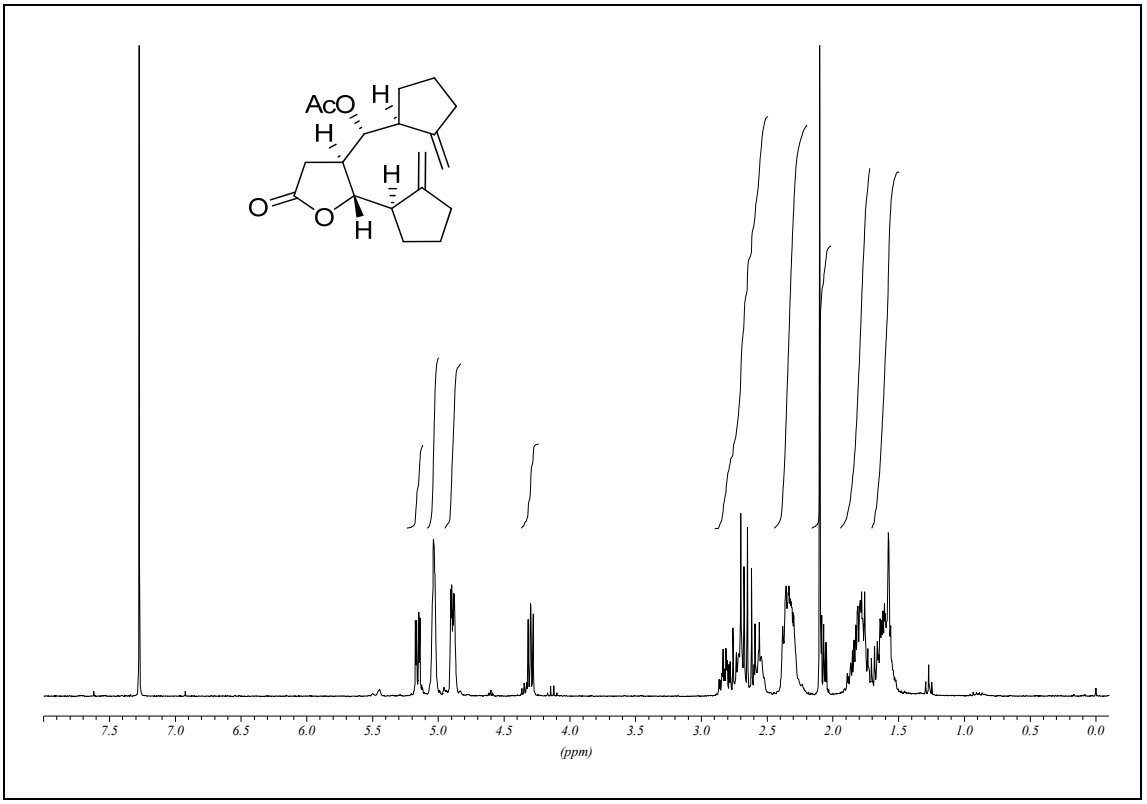


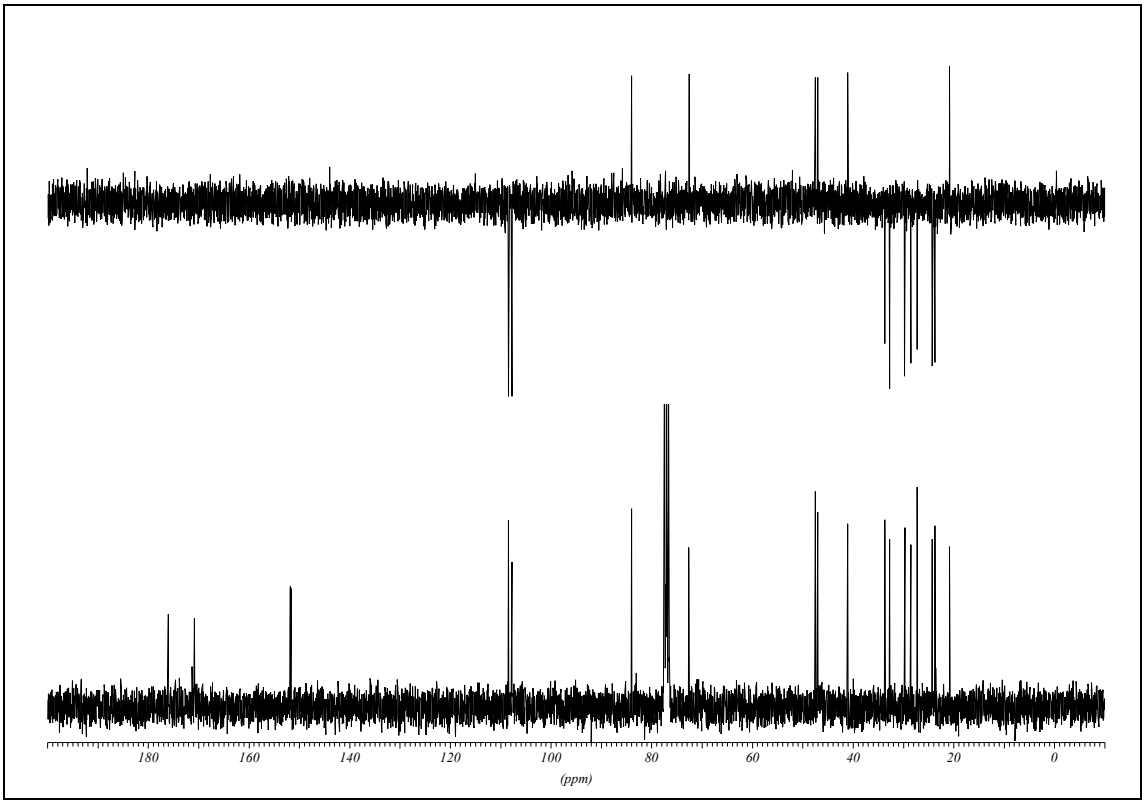
3-methyl-1-((2′*S*,3′*S*)-2′-(2′′-methylenecyclopentyl)-5′-oxo-tetrahydrofuran-3′-yl)but-3-enyl acetate (213h), *dr* = 70:30



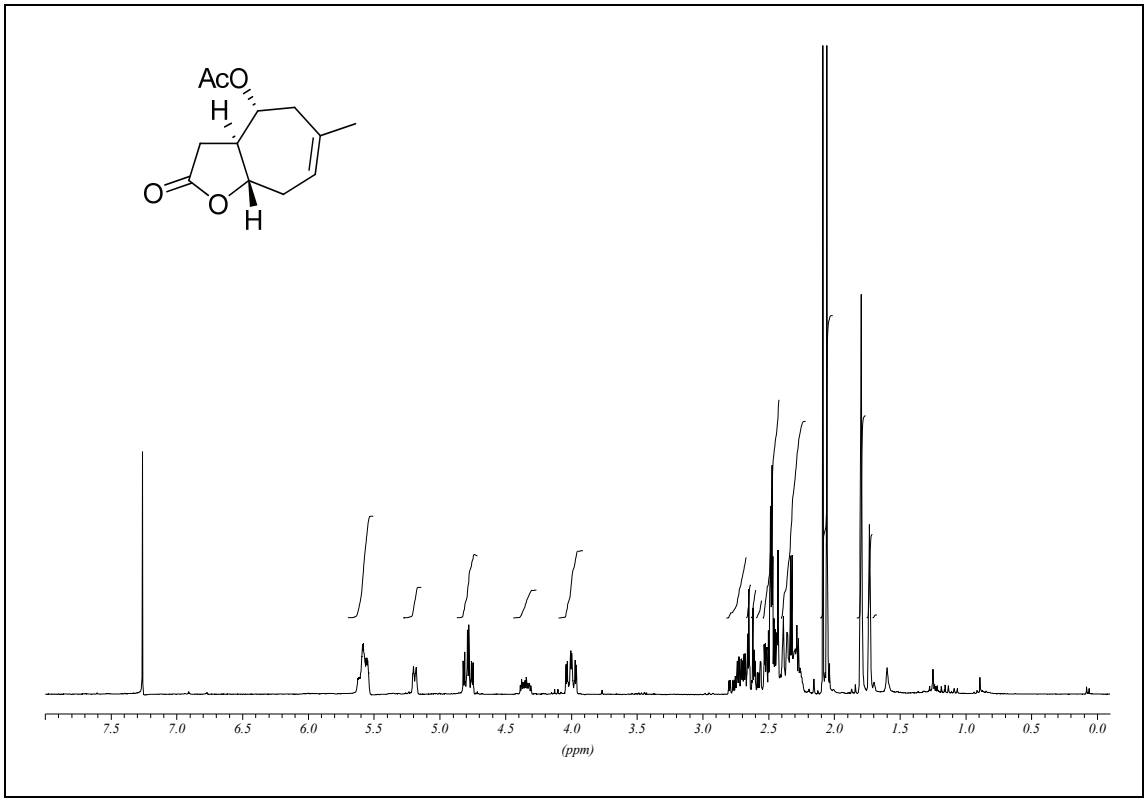


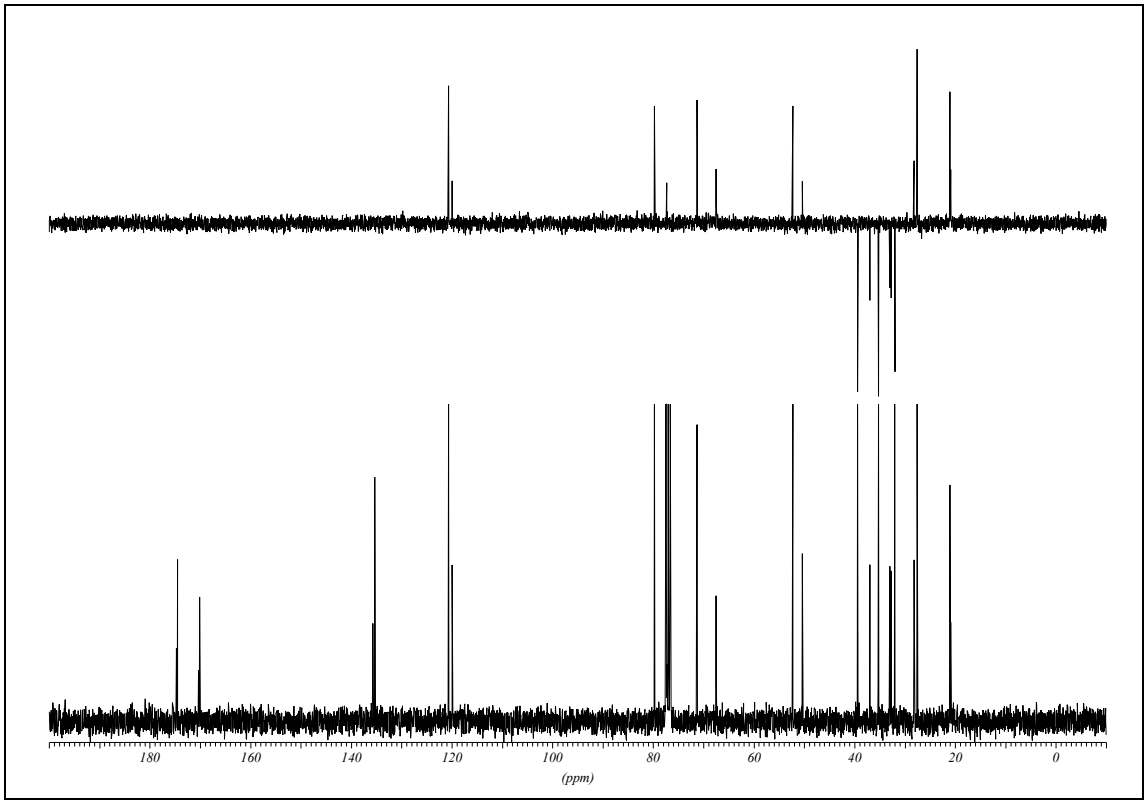
(2-methylenecyclopentyl)((2´*S*,3´*S*)-2´-(2´´-methylenecyclopentyl)-5´-oxo-tetrahydrofuran-3´-yl)methyl acetate (213i), *dr* = 99:1:0:0



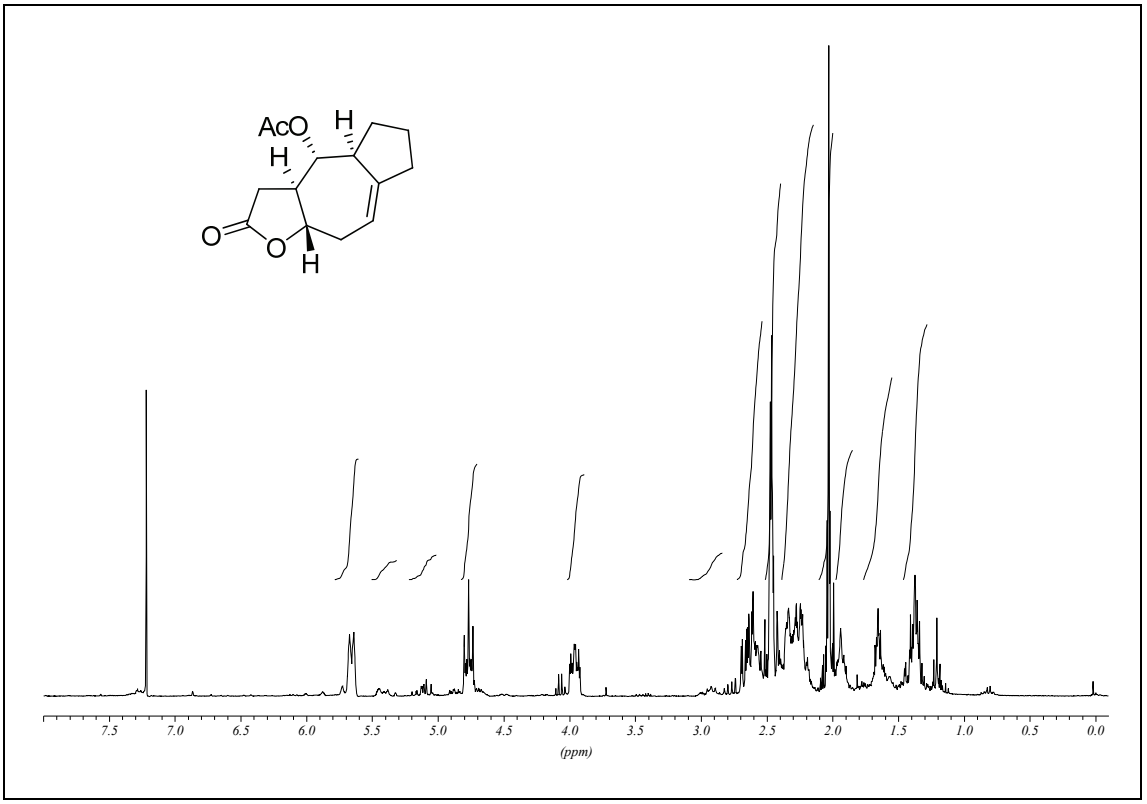


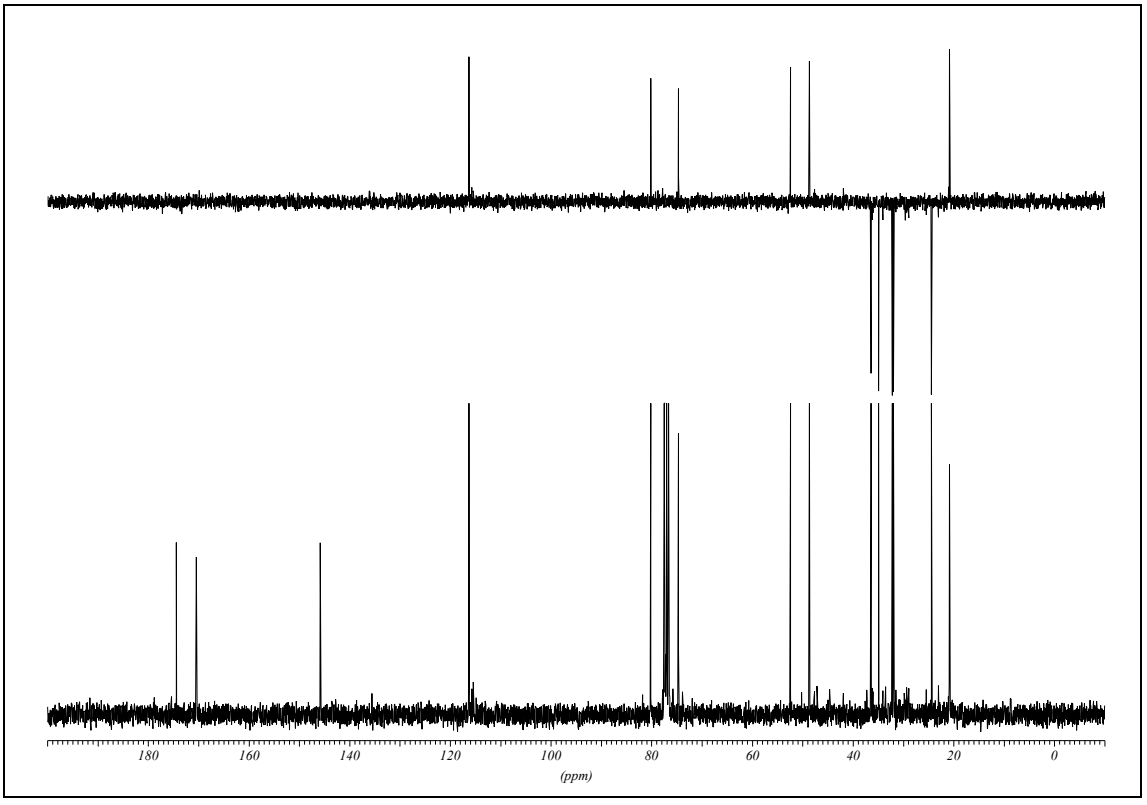
(3a*R*,8a*S*,*Z*)-6-methyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209b), *dr* = 68:32



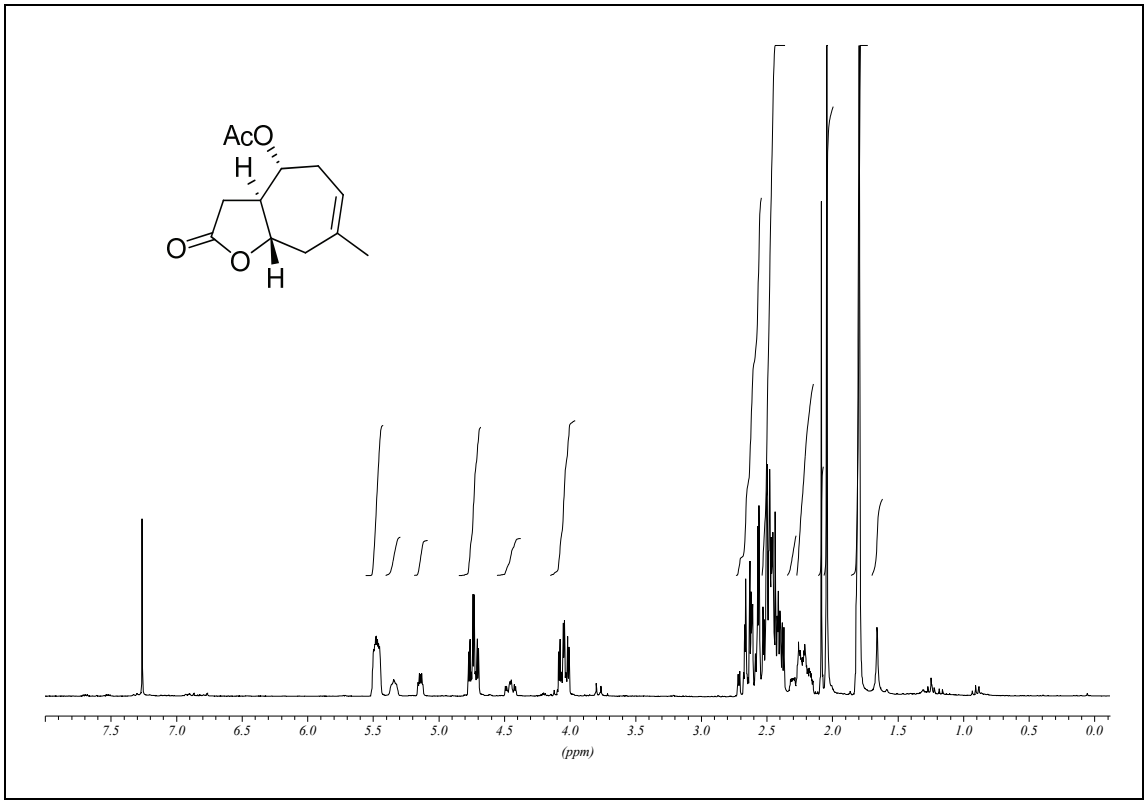


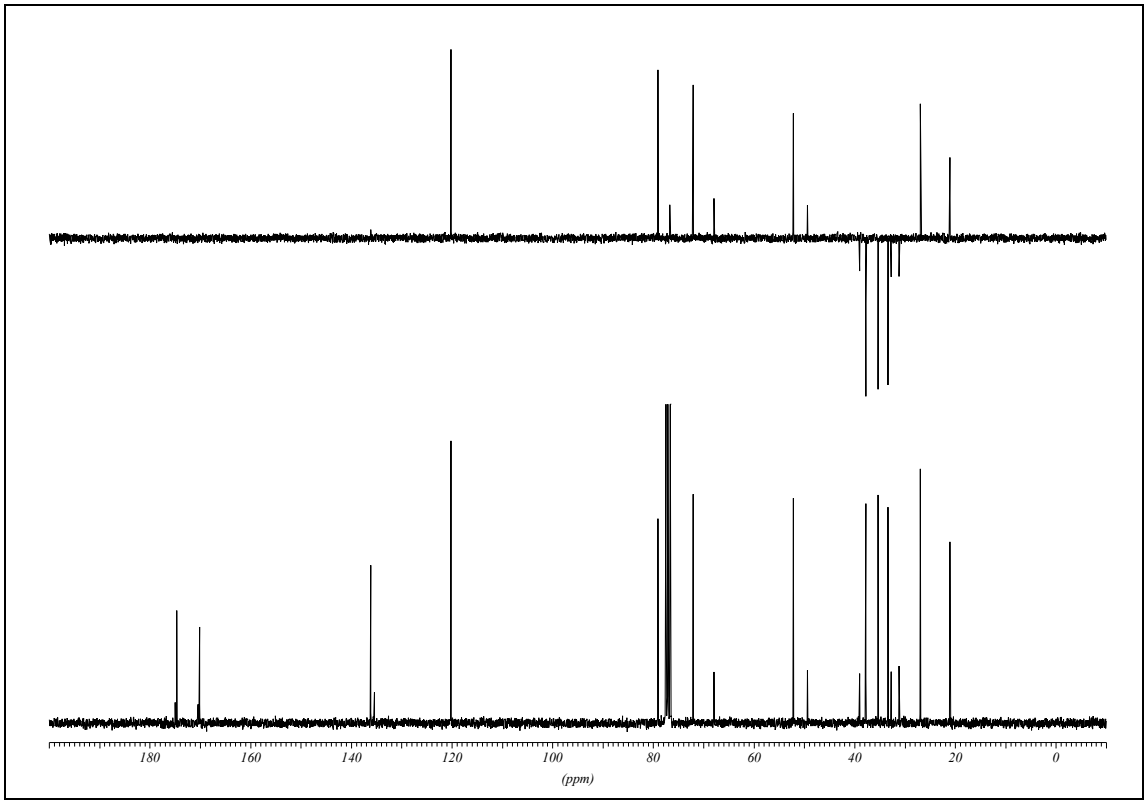
(3a*R*,9a*S*,*Z*)-2-oxo-2,3,3a,4,4a,5,6,7,9,9a-decahydroazuleno[6,5-b]furan-4-yl-acetate (209c), *dr* = 84:16



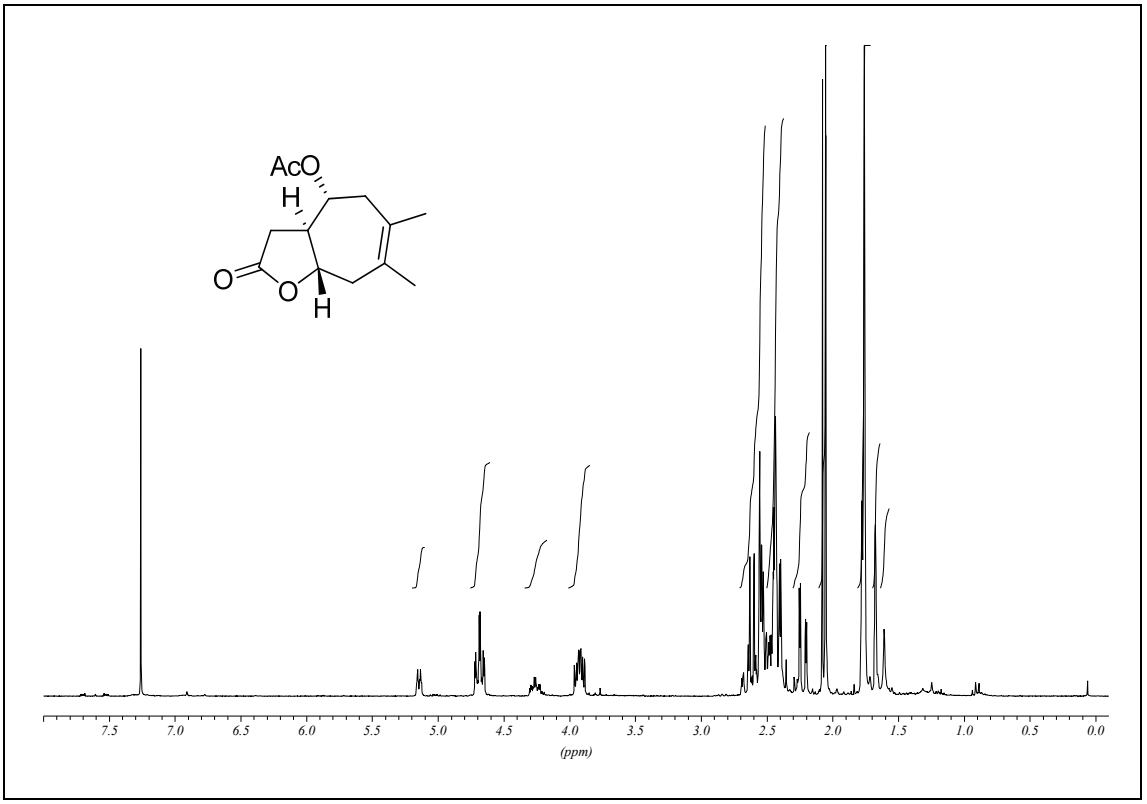


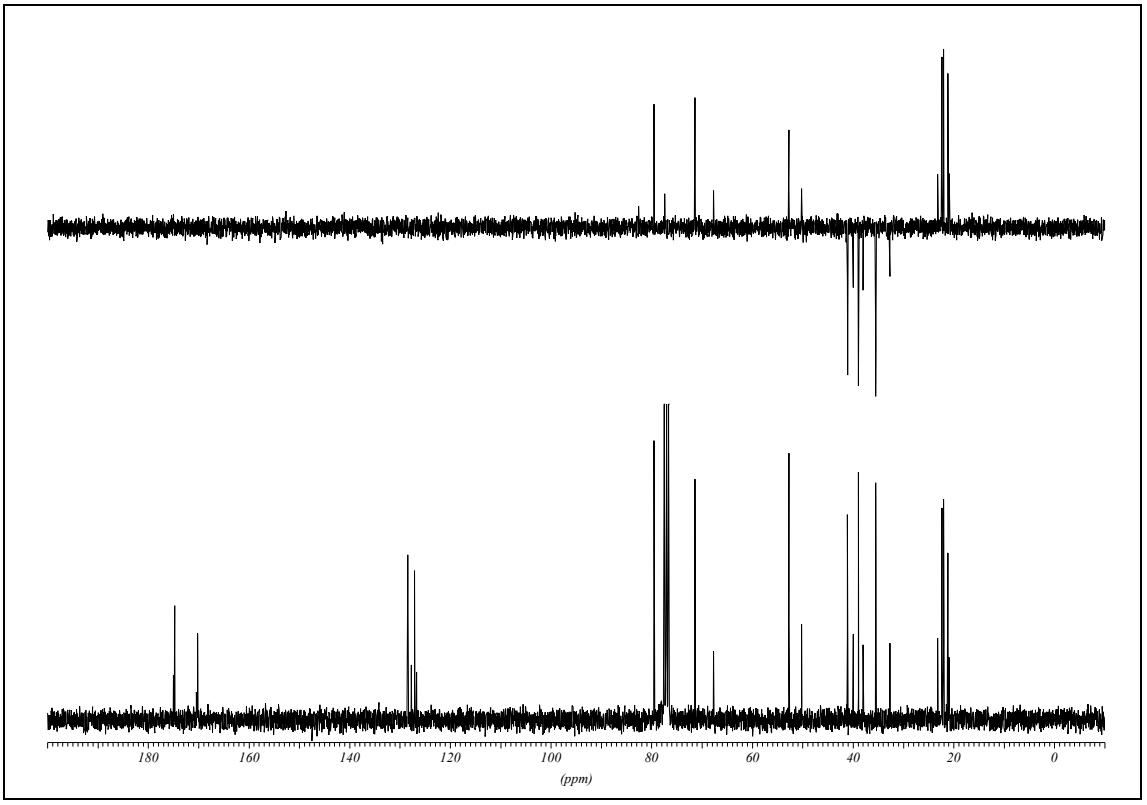
(3a*S*,8a*S*,*Z*)-7-methyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209d), *dr* = 80:20



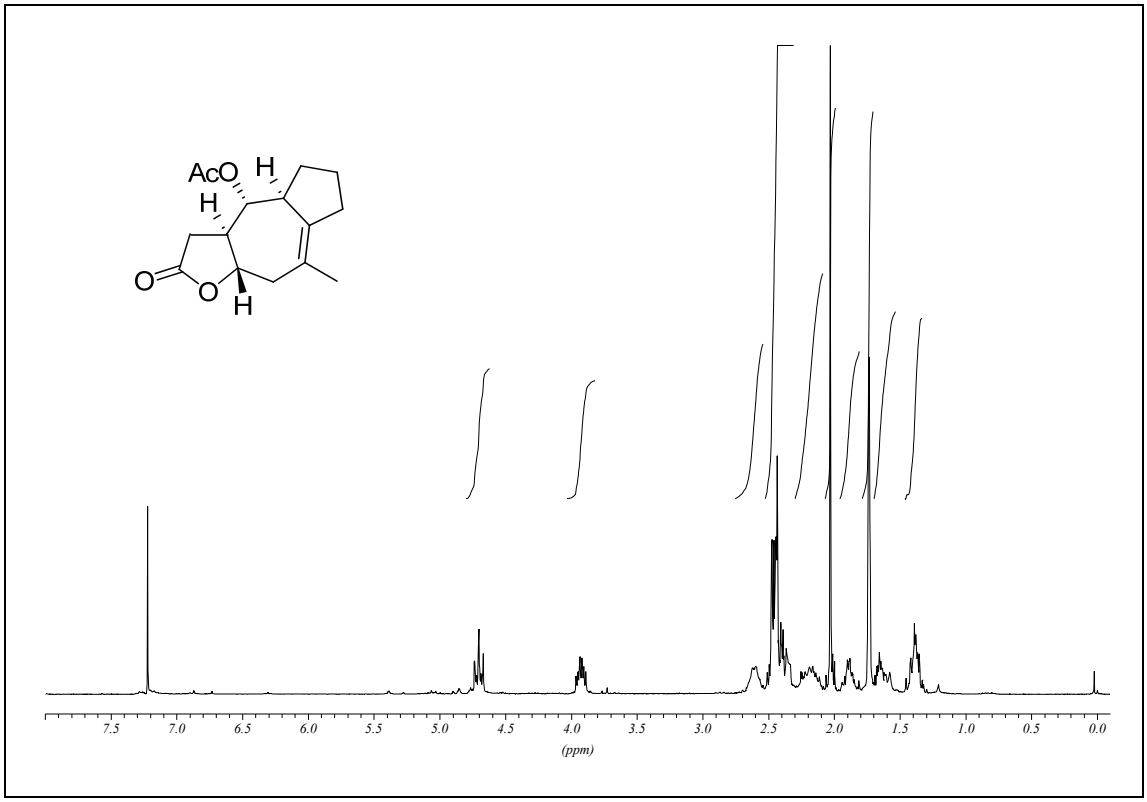


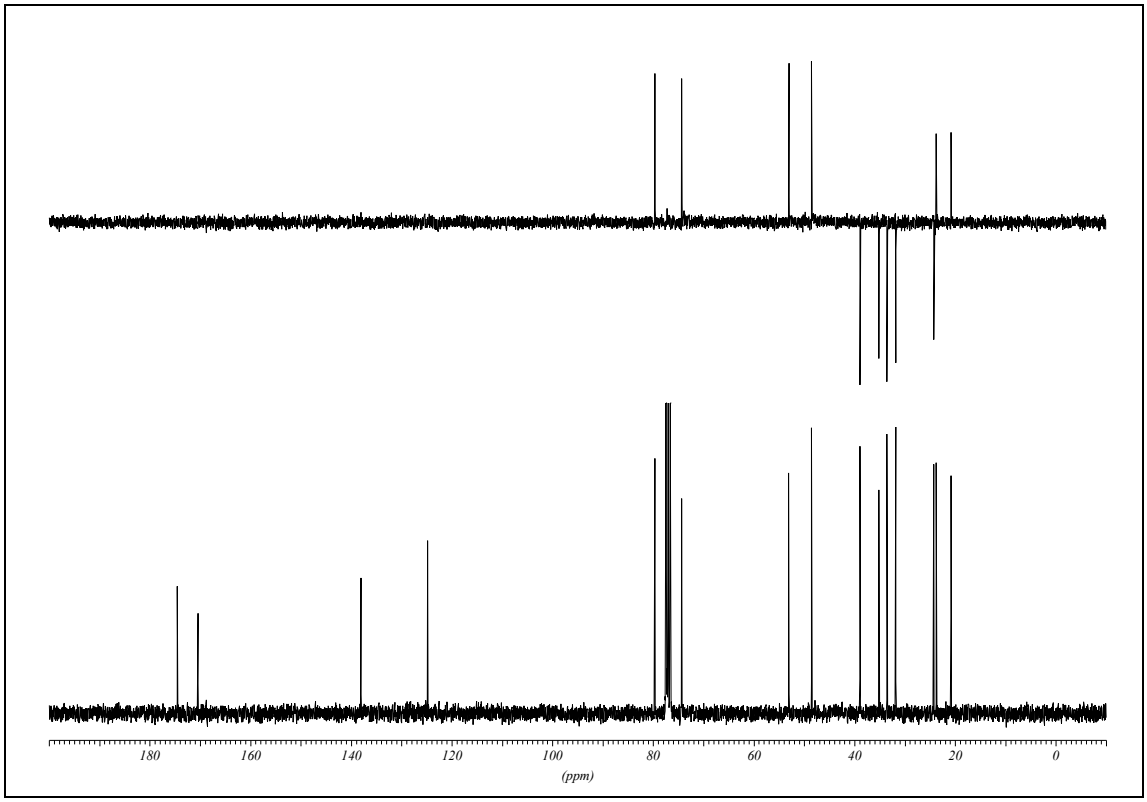
(3a*S*,8a*S*,*Z*)-6,7-dimethyl-2-oxo-3,3a,4,5,8,8a-hexahydro-2H-cyclohepta[b]furan-4-yl acetate (209e), *dr* = 75:25



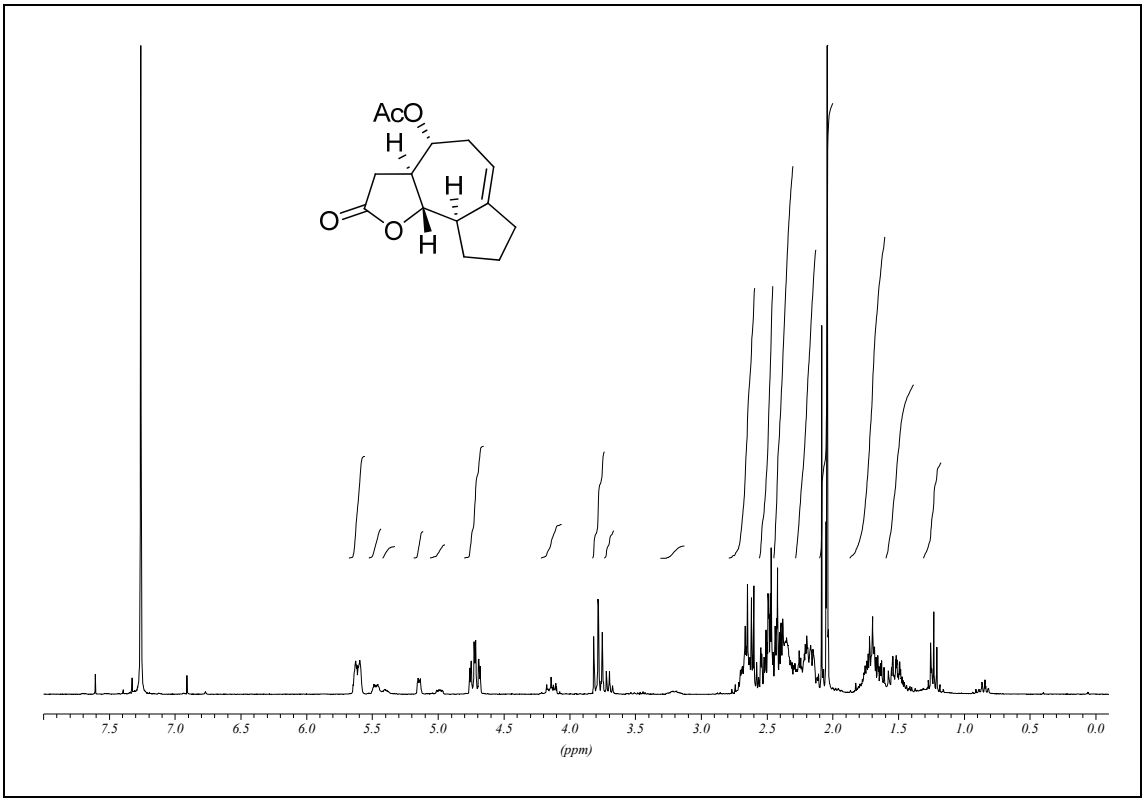


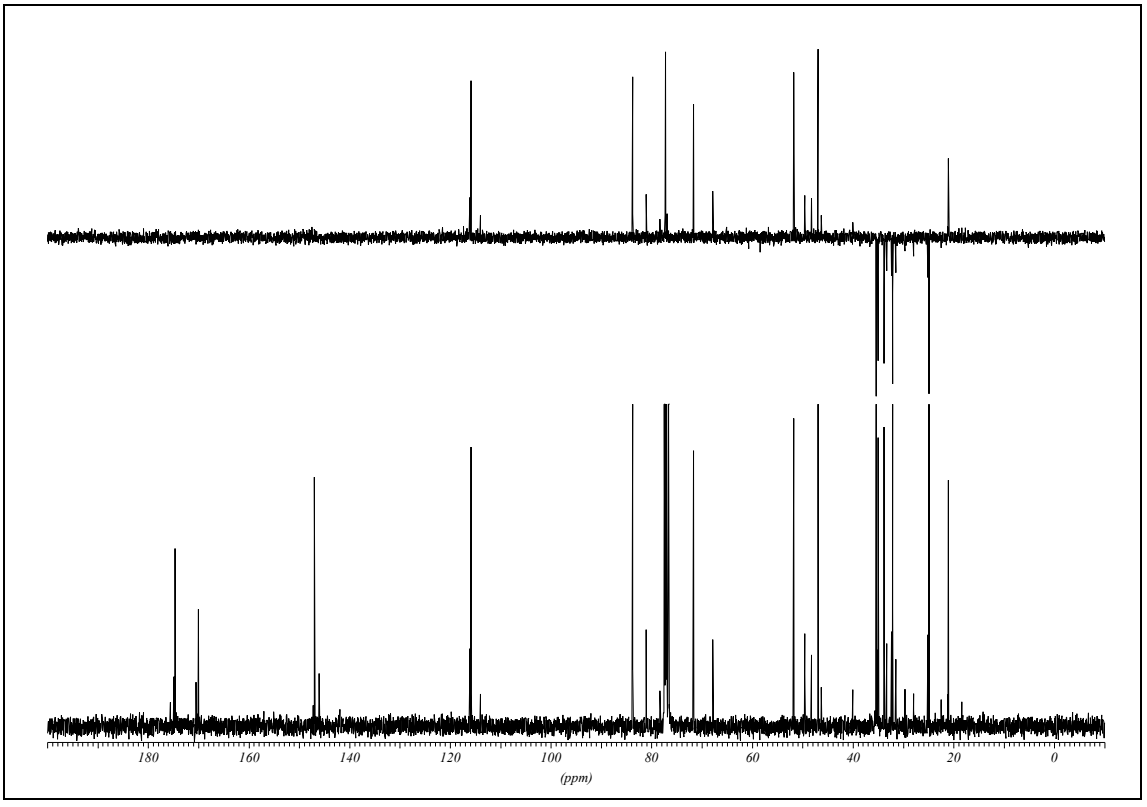
(3a*R*,9a*S*,*Z*)-8-methyl-2-oxo-2,3,3a,4,4a,5,6,7,9,9a-decahydroazuleno[6,5-b]furan-4-yl acetate (209f), *dr* = >99:1



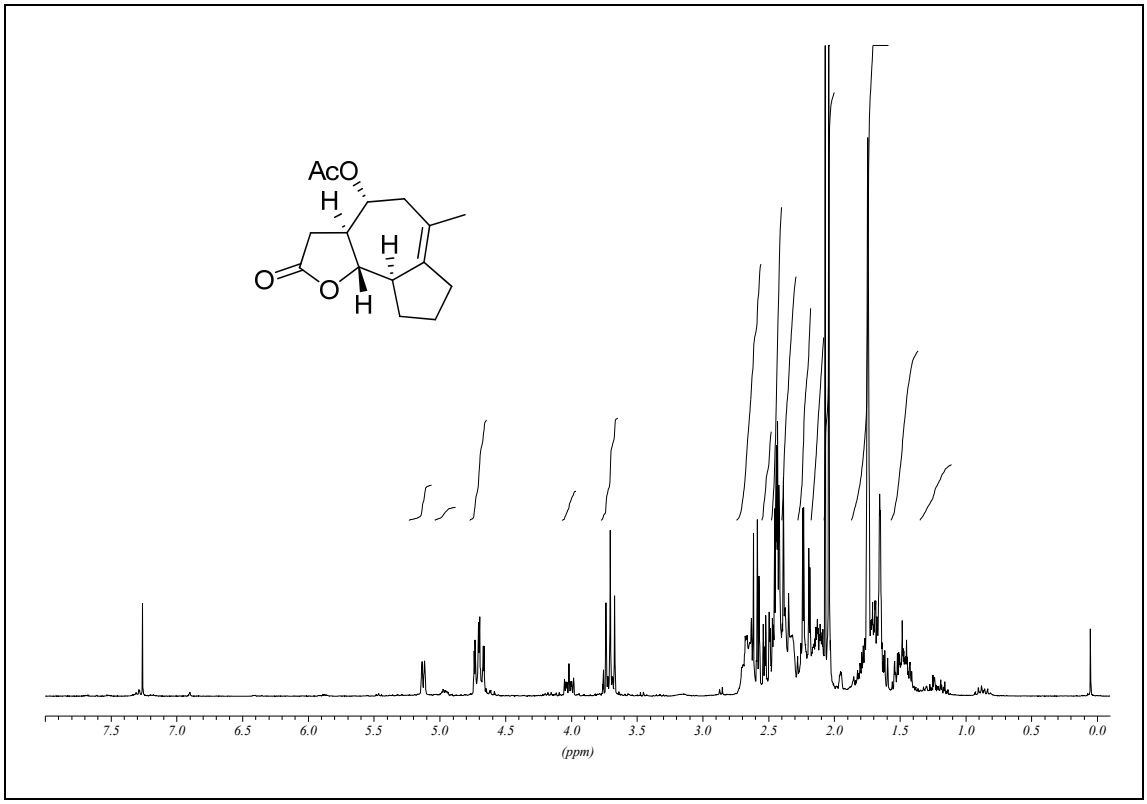


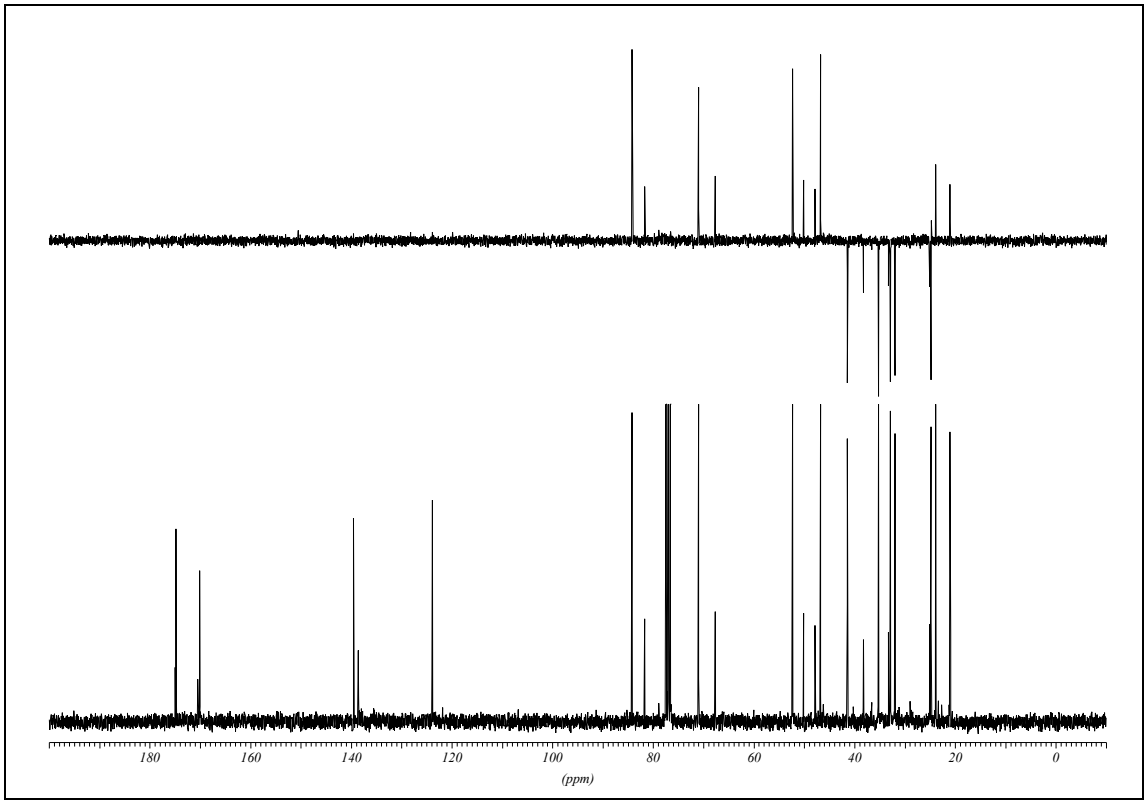
(3a*S*,9a*R*,9b*S*,*Z*)-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (209g), *dr* = 79:21



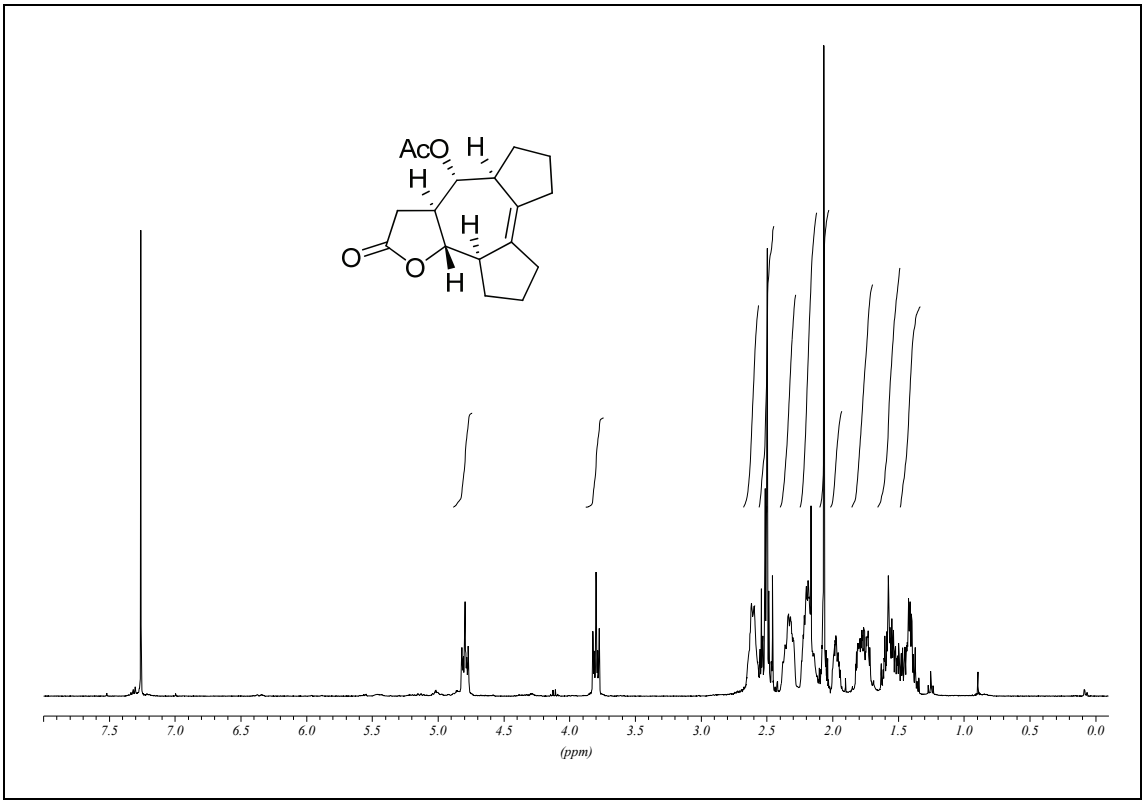


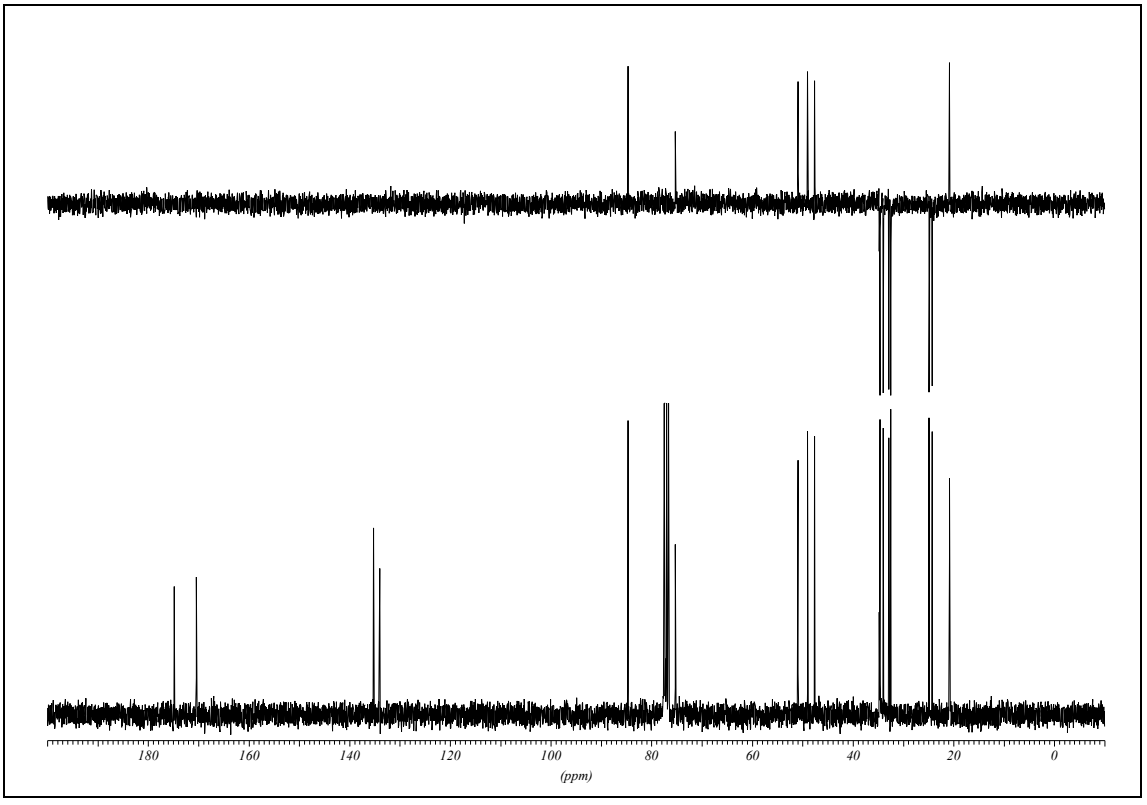
(3a*S*,9a*R*,9b*S*,*Z*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (209h), *dr* = 72:28



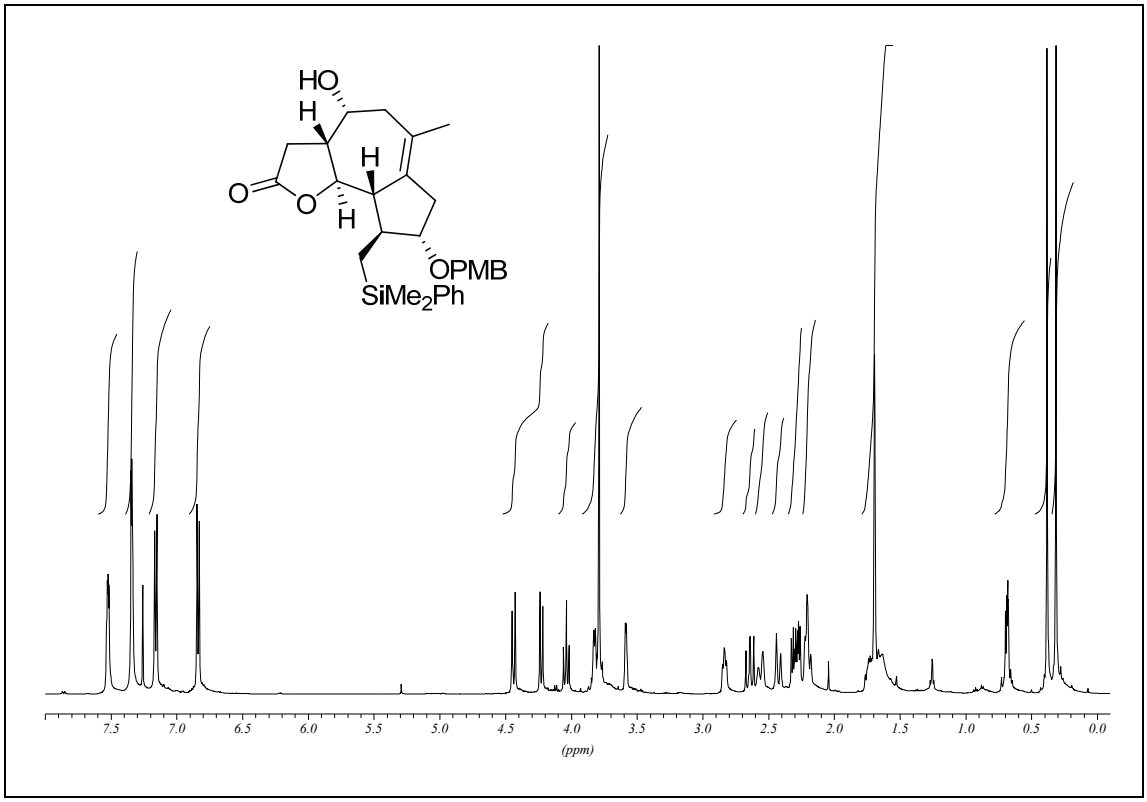


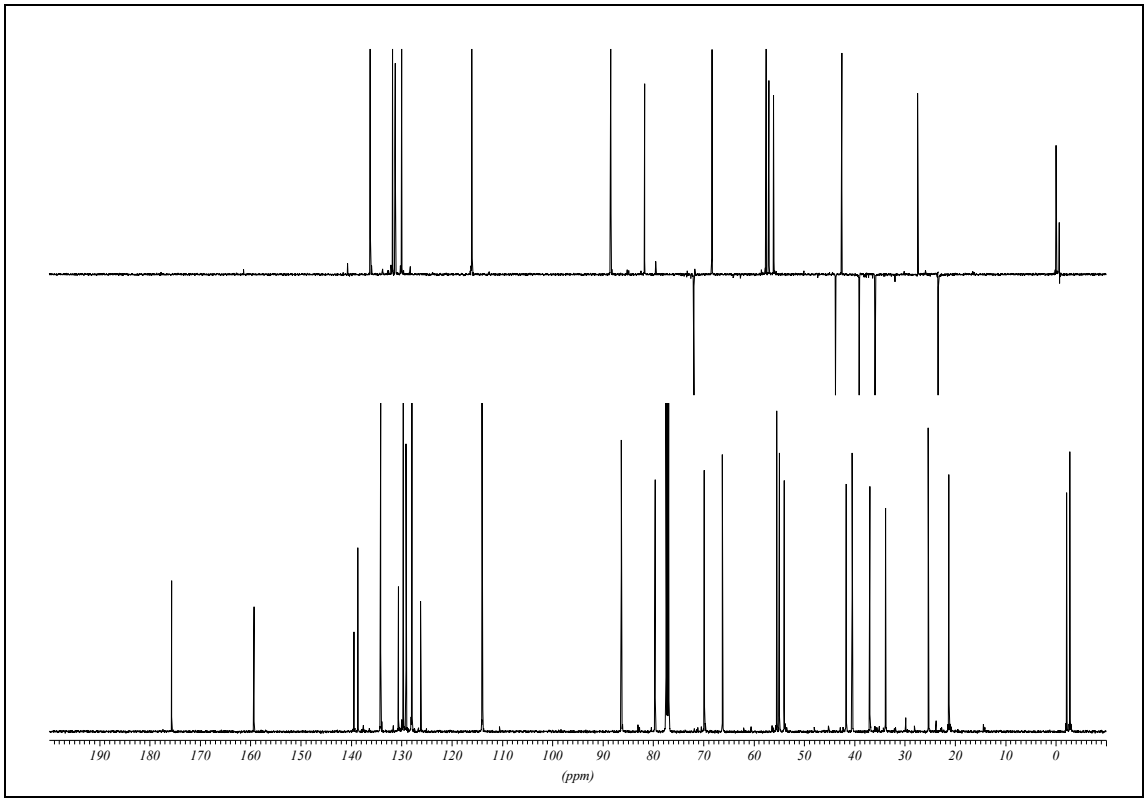
(3a*S*,4*R*,5*S*,9a*R*,9b*S*)-6,5-cyclopentanyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno [4,5-b]furan-4-yl acetate (209i), *dr* = >99:1



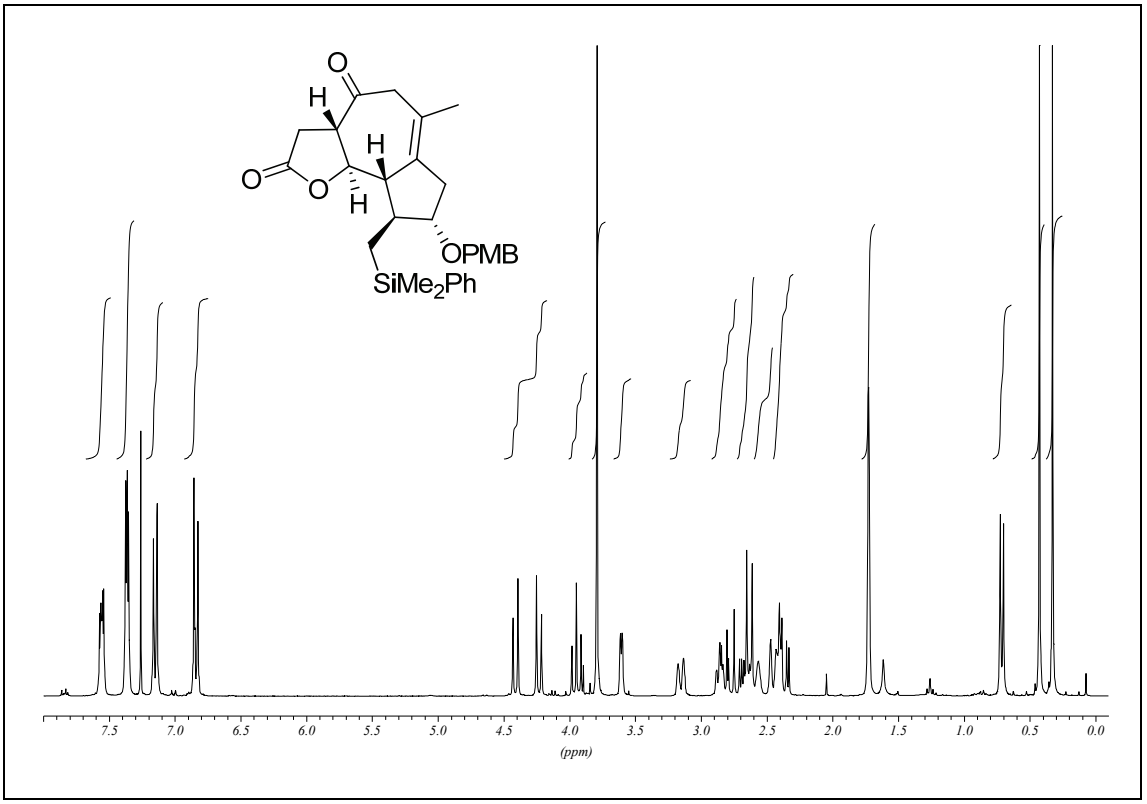


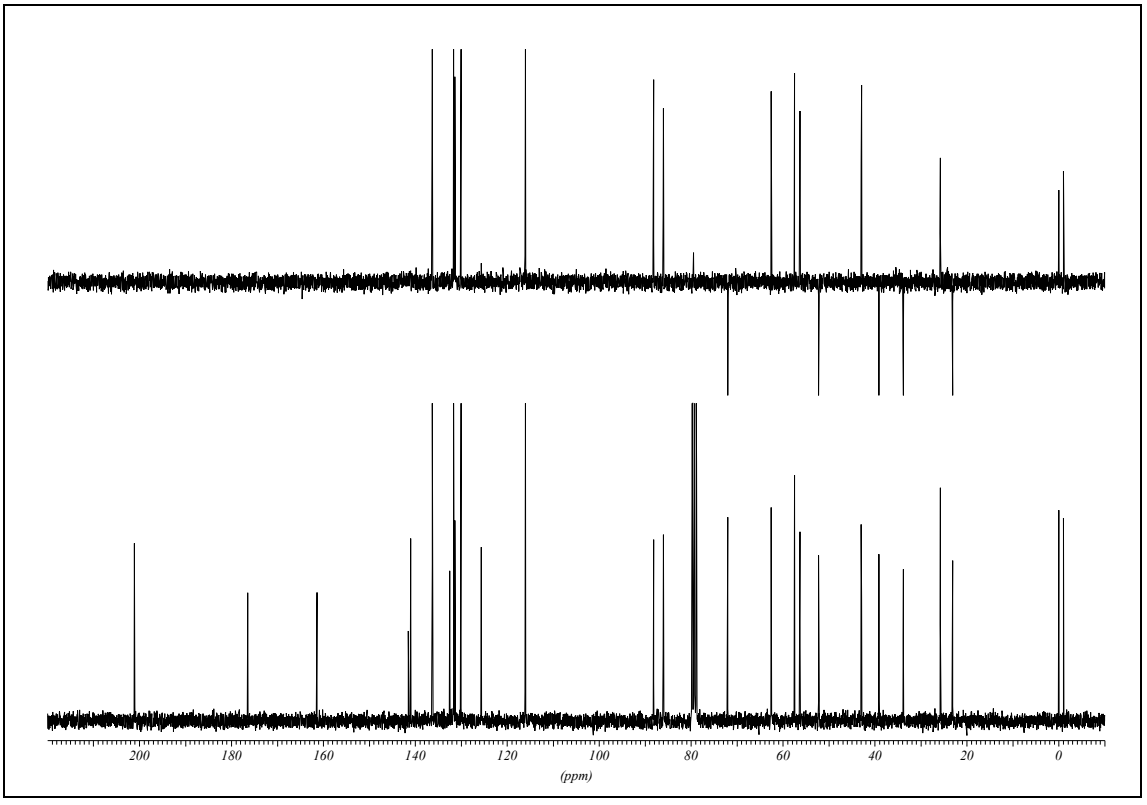
(3a*R*,4*R*,8*S*,9*S*,9a*S*,9b*R*)-9-((dimethyl(phenyl)silyl)methyl)-4-hydroxy-8-(*p*-methoxybenzyloxy)-6-methyl-3,3a,4,5,7,8,9,9a-octahydroazuleno[4,5-b]furan-2(9bH)-one (4*R*-**216)**



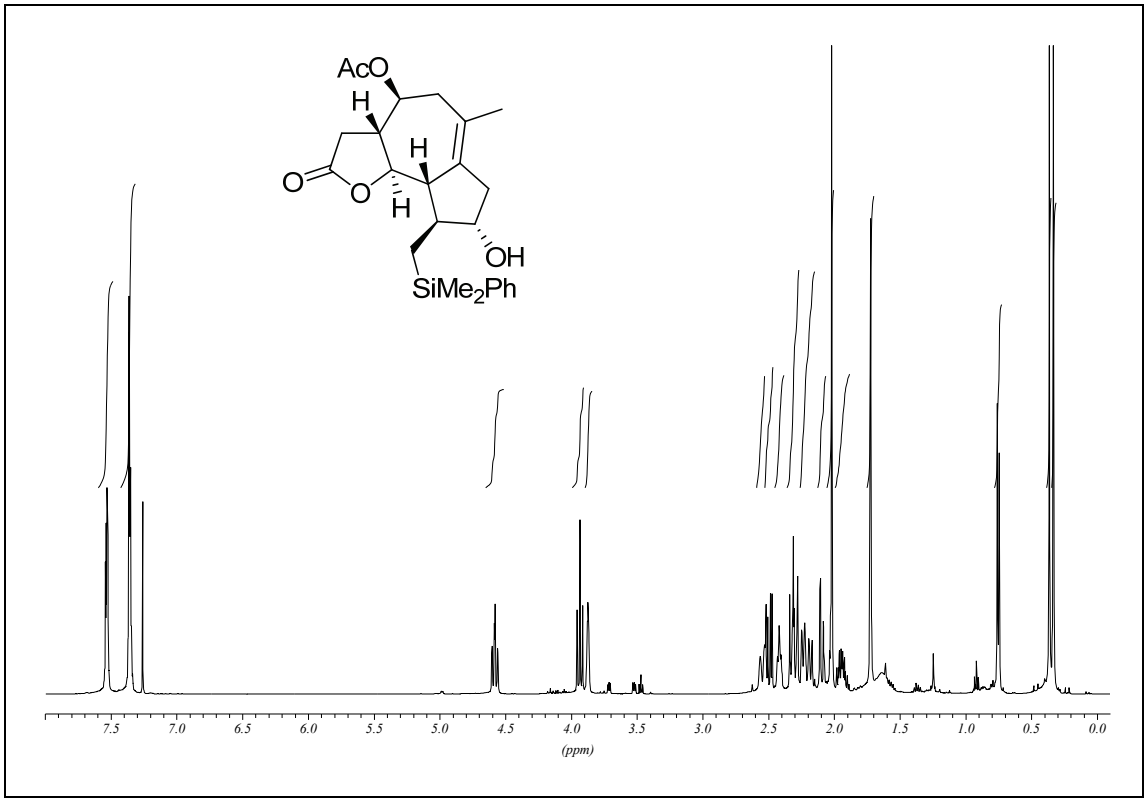


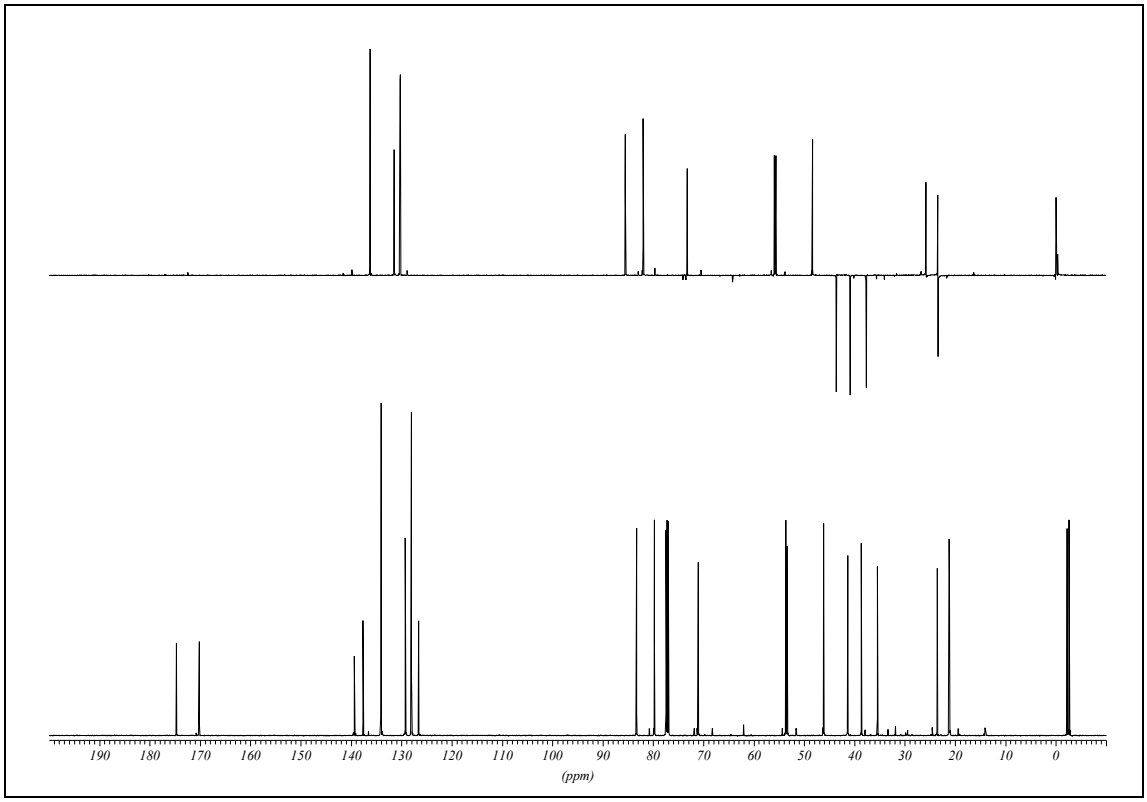
(3a*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-(*p*-methoxybenzyloxy)-6-methyl-3,3a,7,8,9,9a-hexahydroazuleno[4,5-b]furan-2,4(5H,9bH)-dione (217)



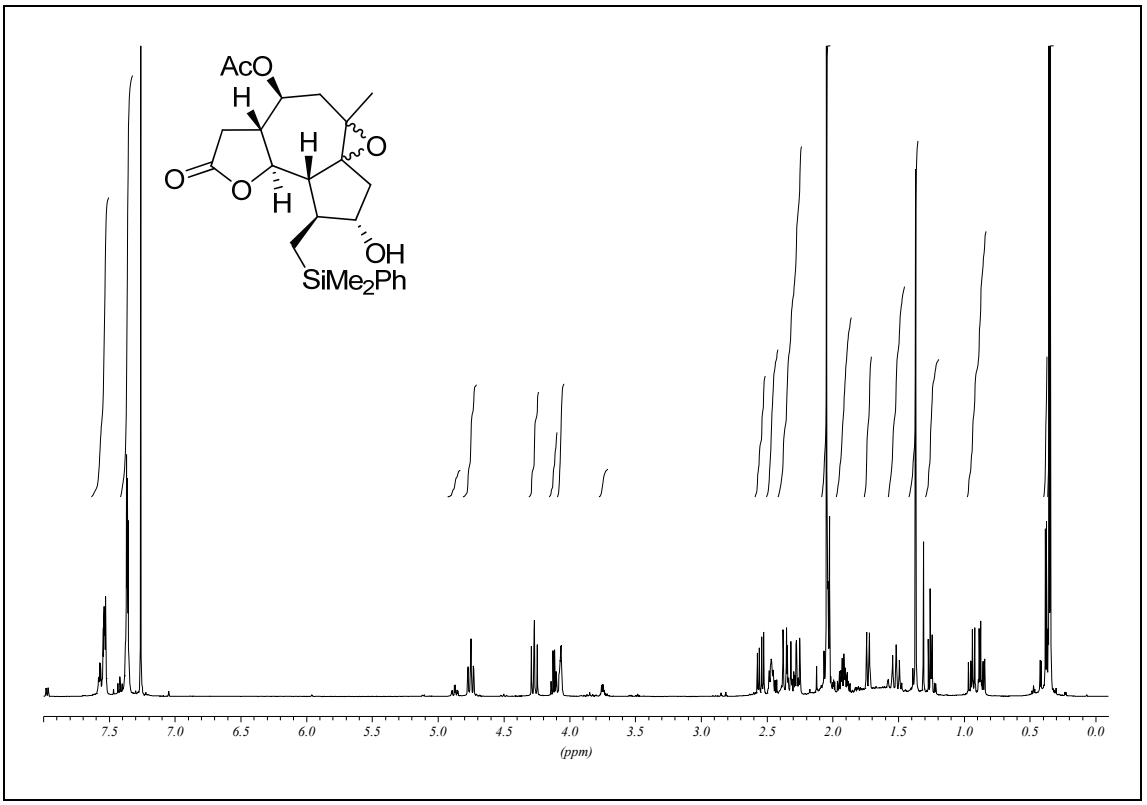


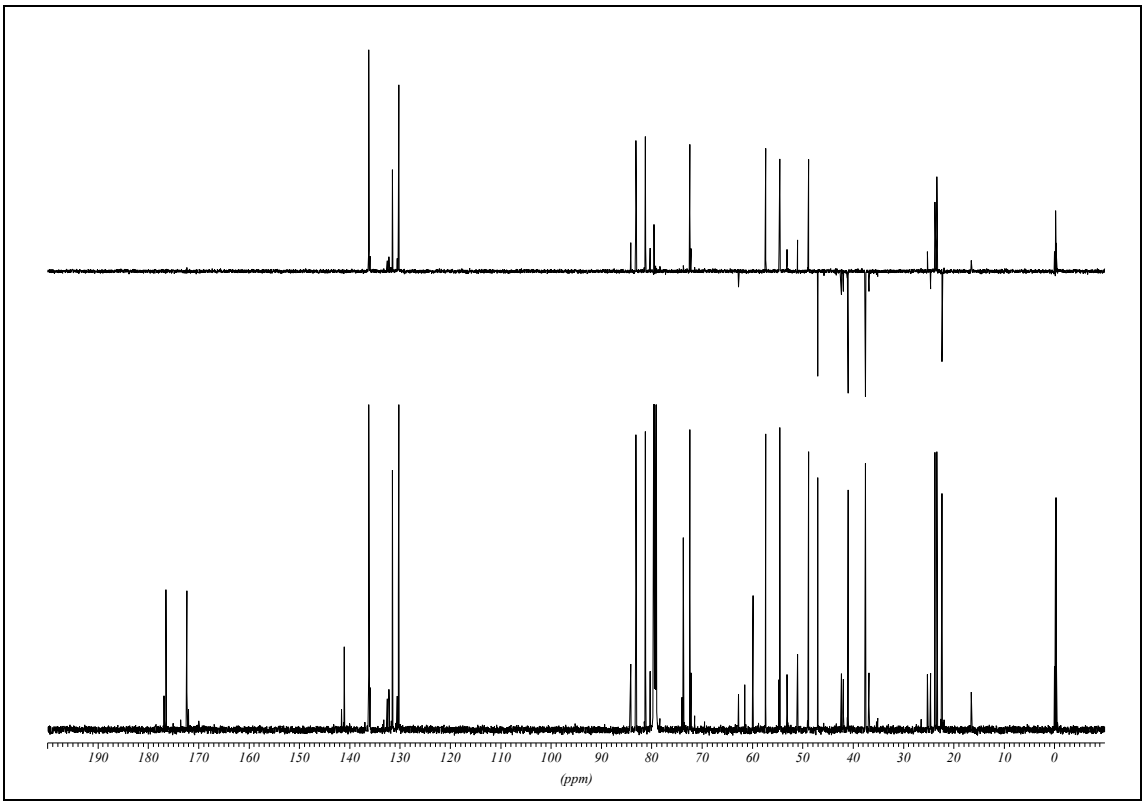
(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (218)



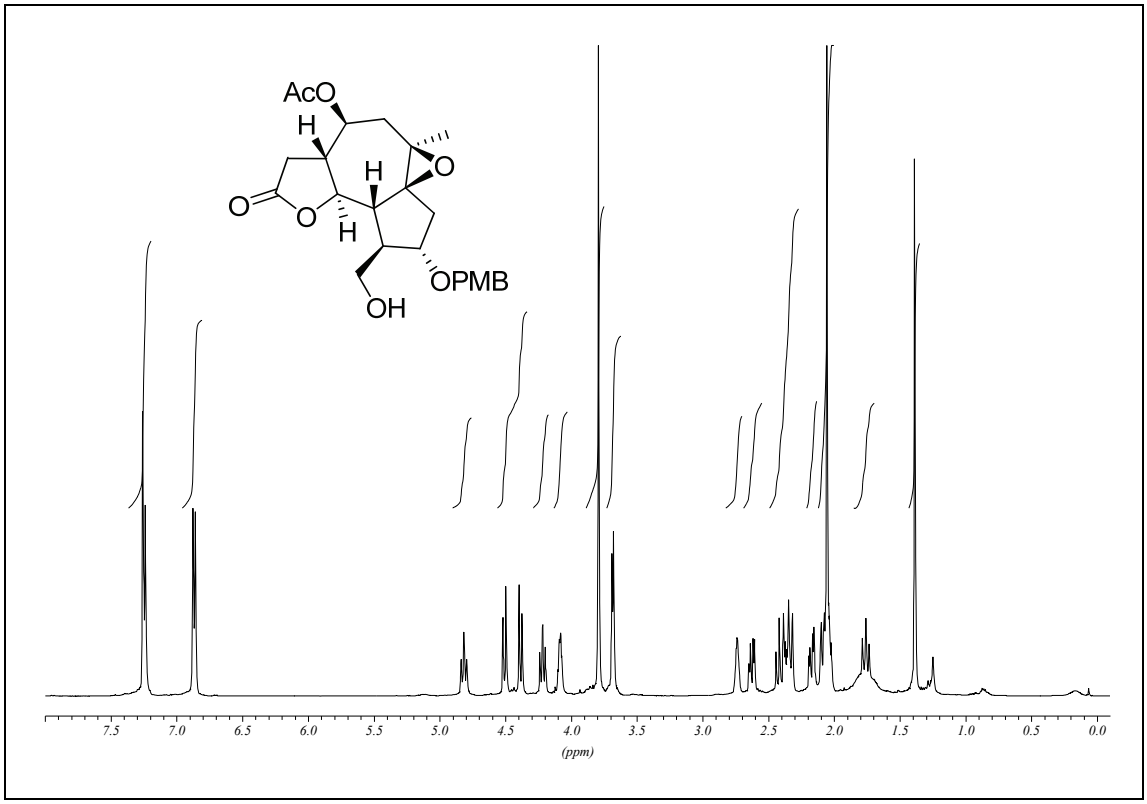


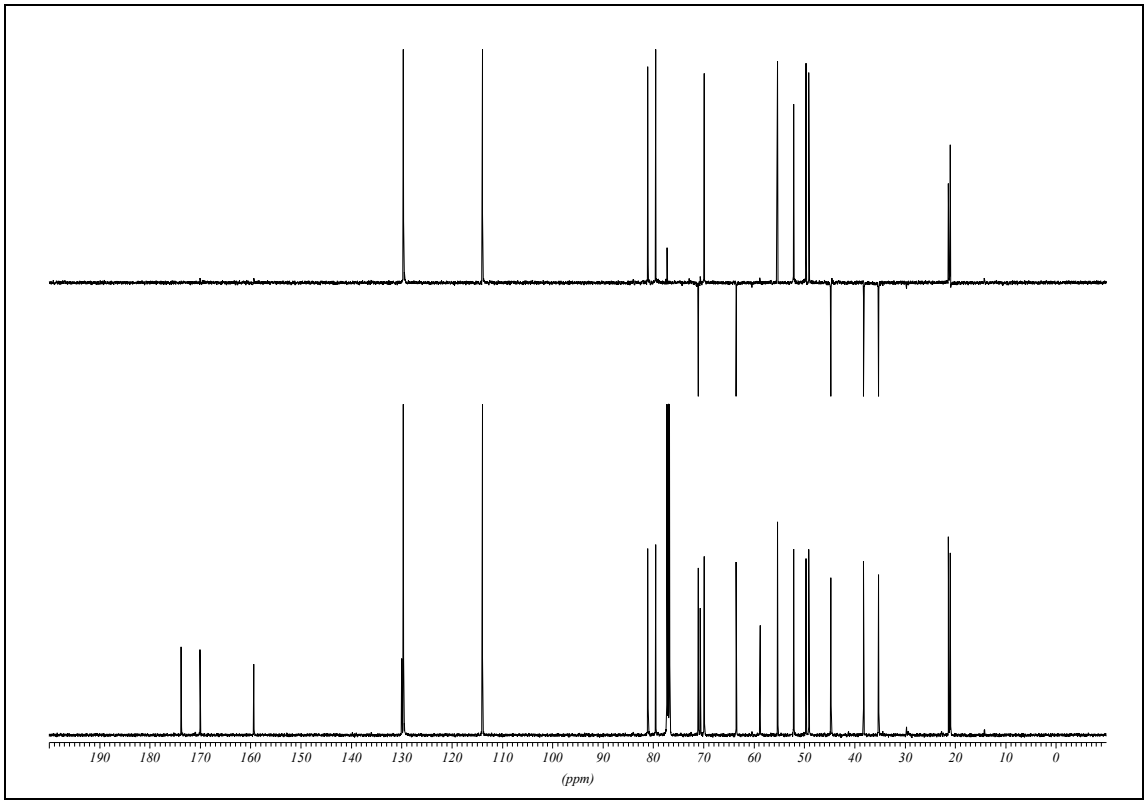
(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*,*Z*)-9-((dimethyl(phenyl)silyl)methyl)-8-hydroxy-6,6a-epoxy-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (219)
α:β = 20:80



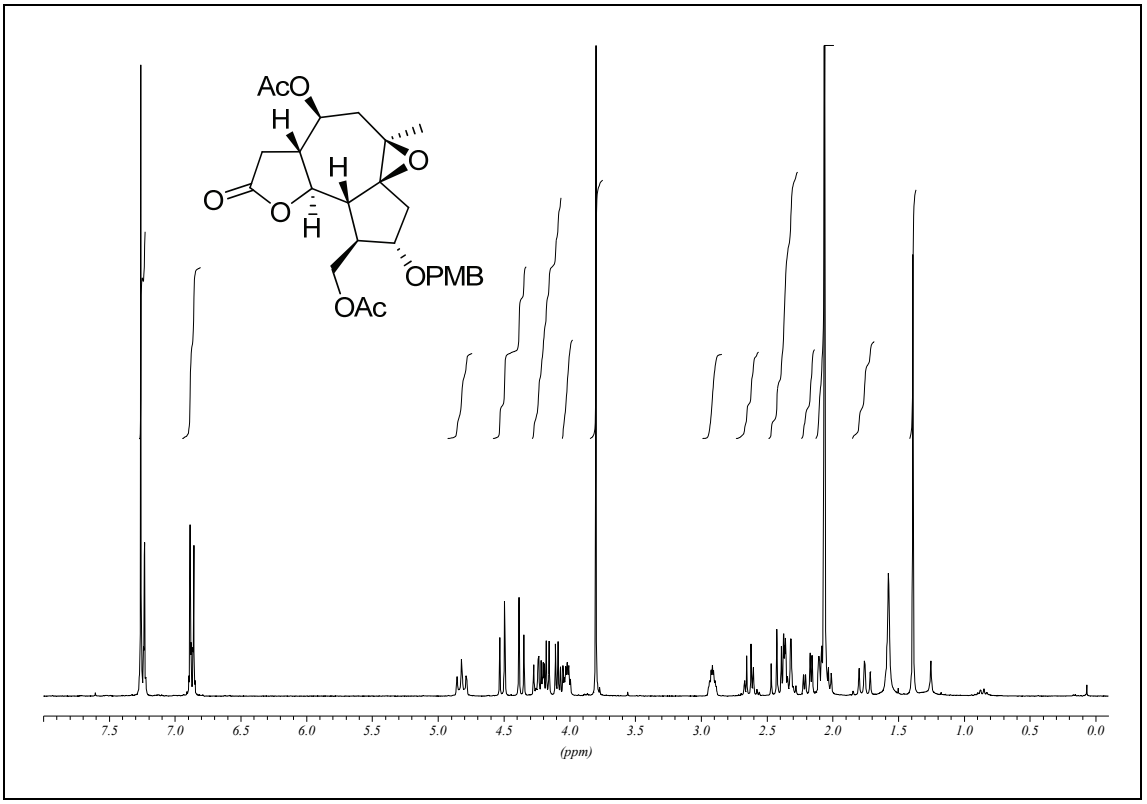


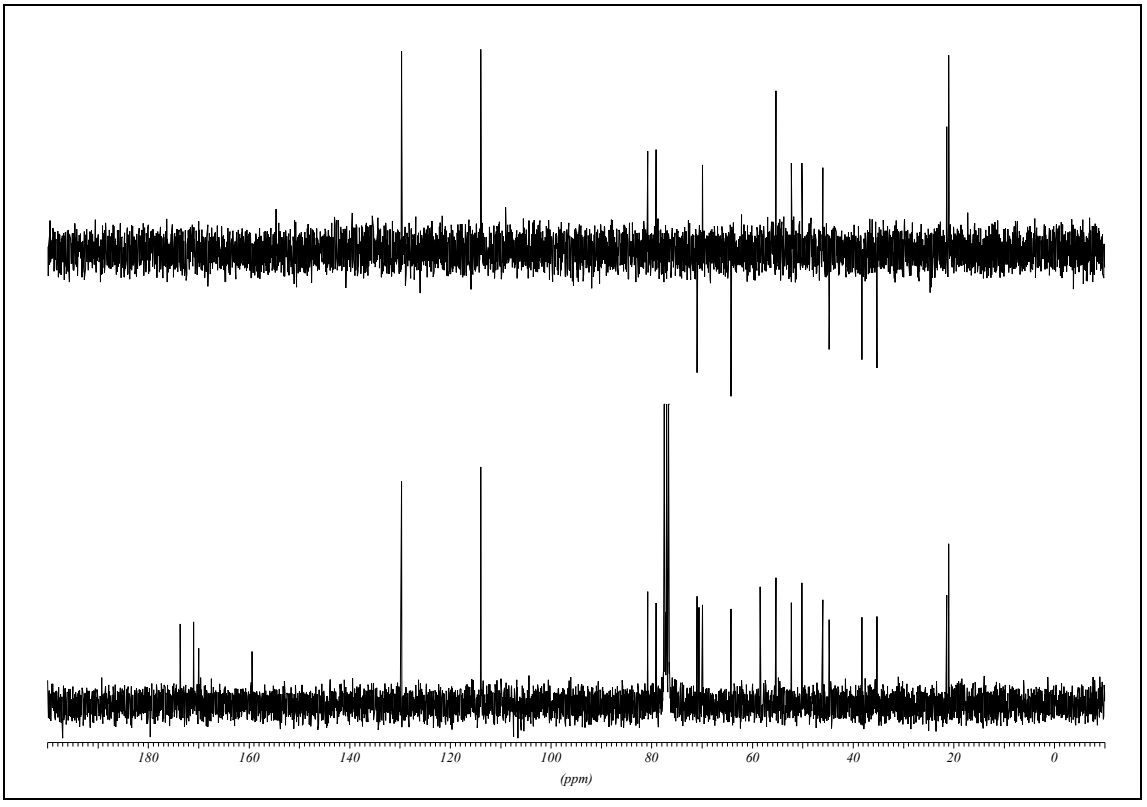
(3a*R*,4*S*,6S,6aS,8*S*,9*R*,9a*S*,9b*R*)-9-(hydroxymethyl)-8-(p-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (225)



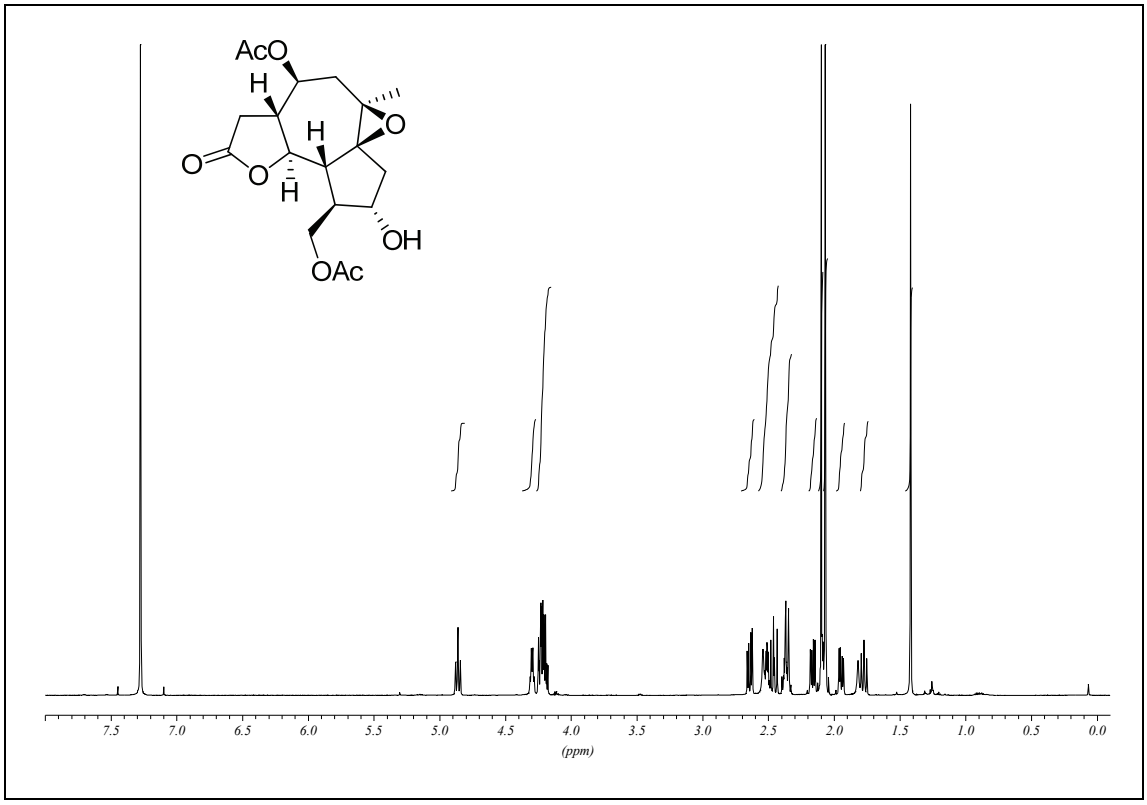


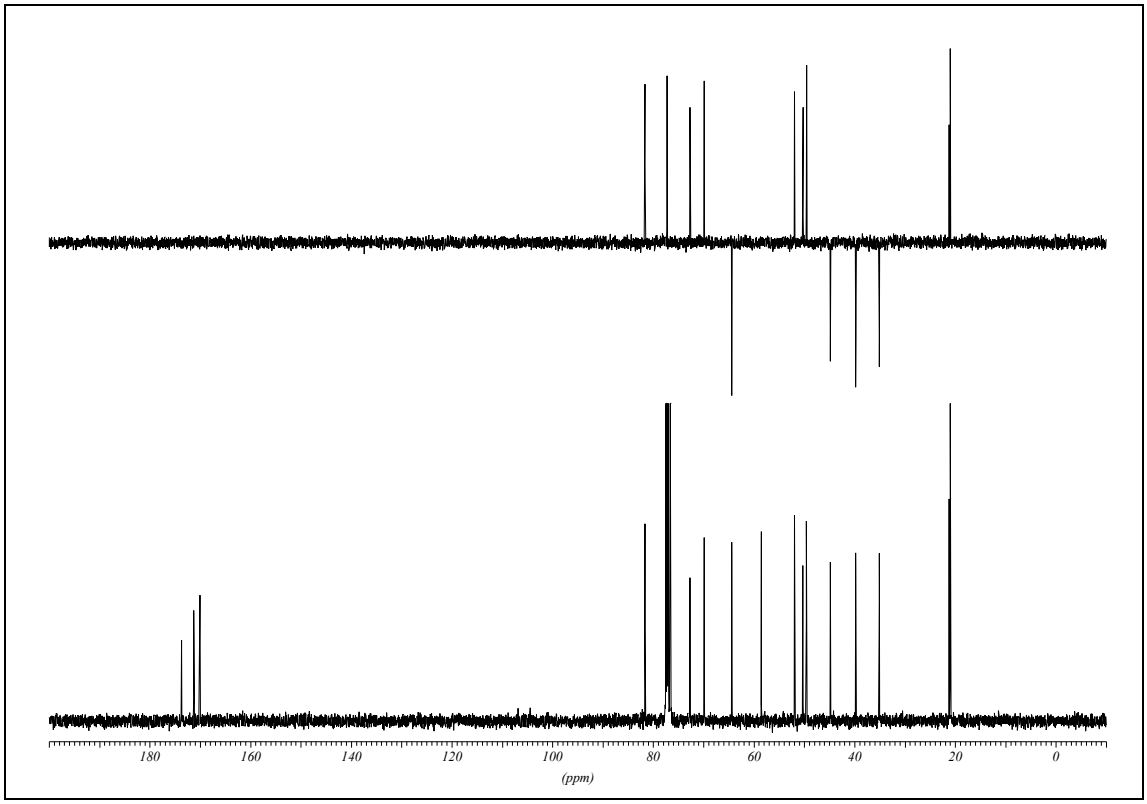
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(acetoxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (226)



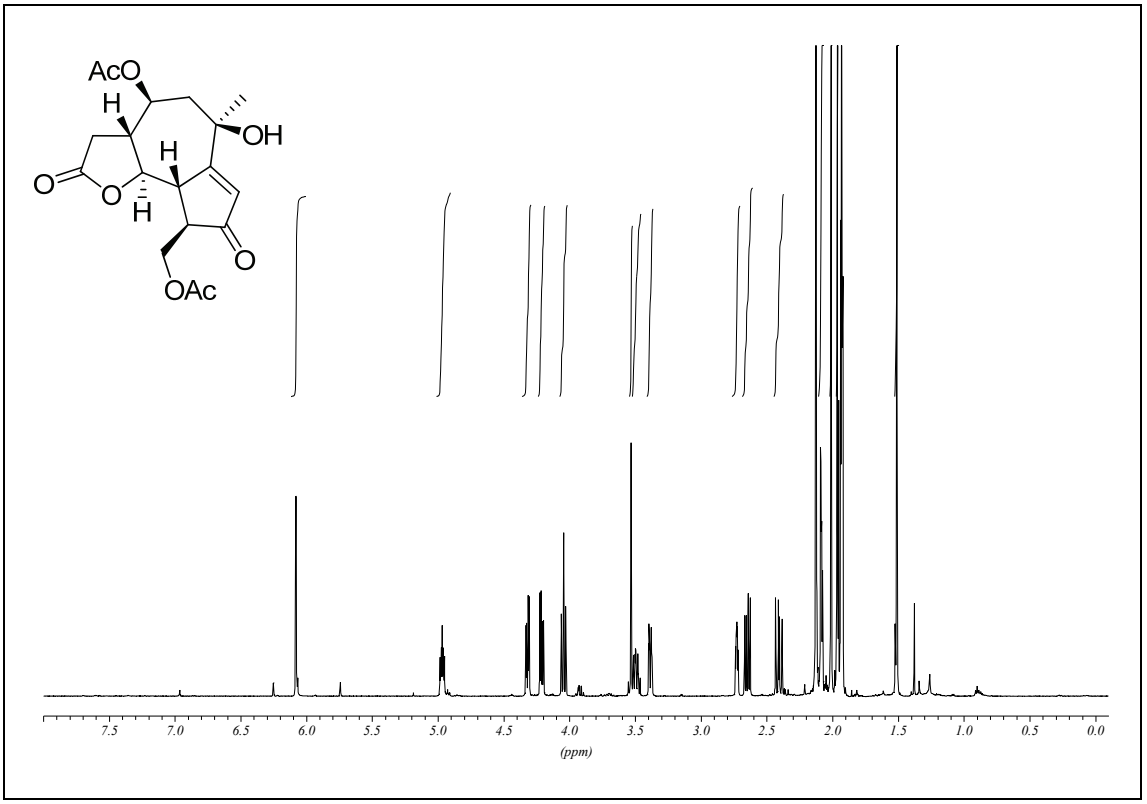


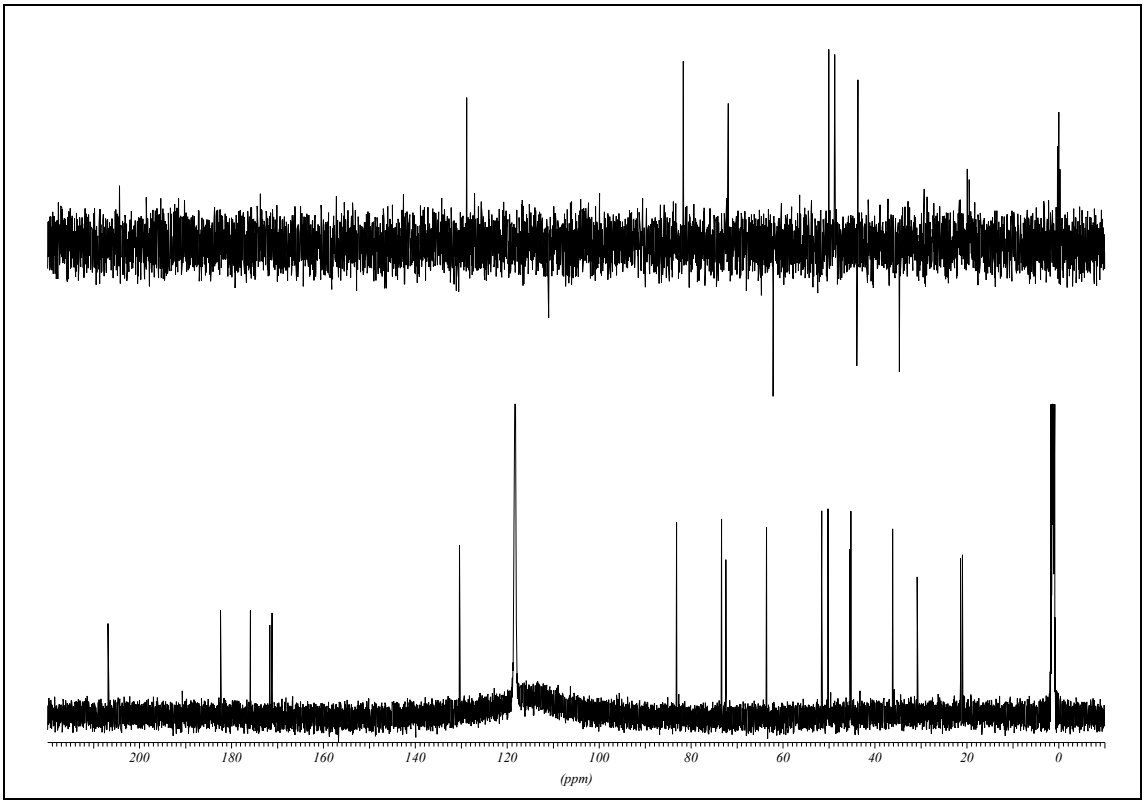
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(acetoxymethyl)-8-hydroxy-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (227)



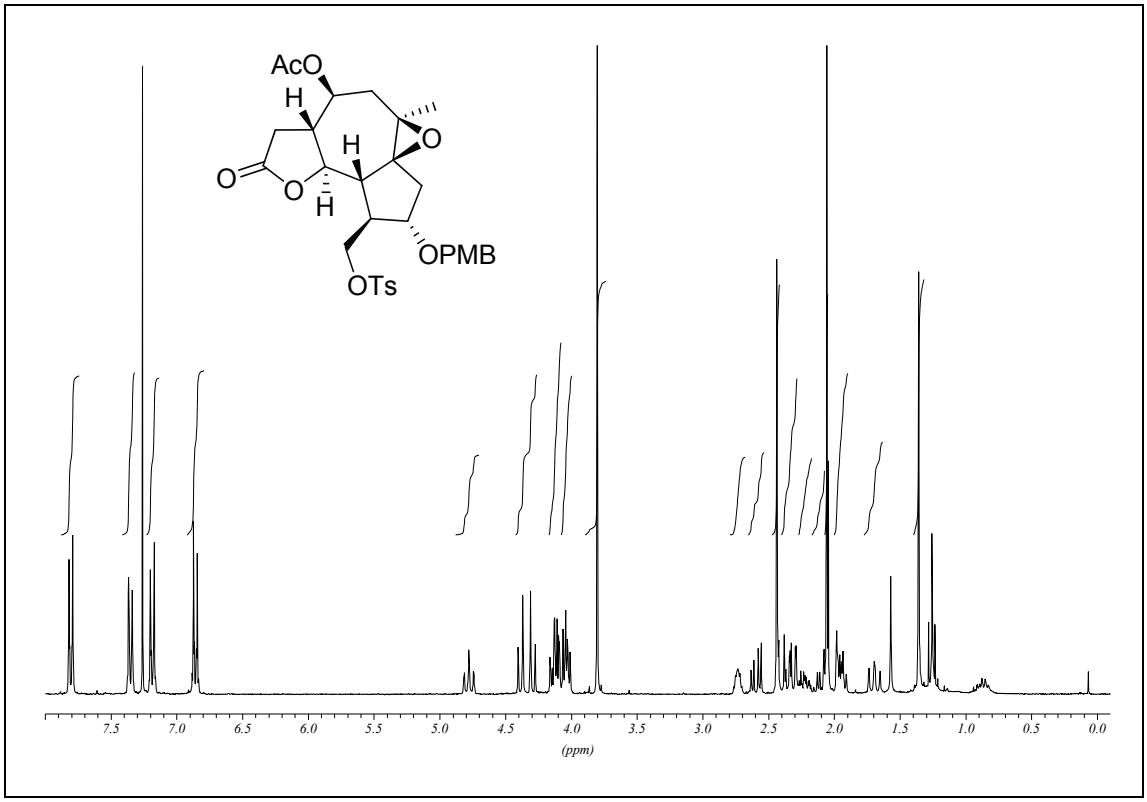


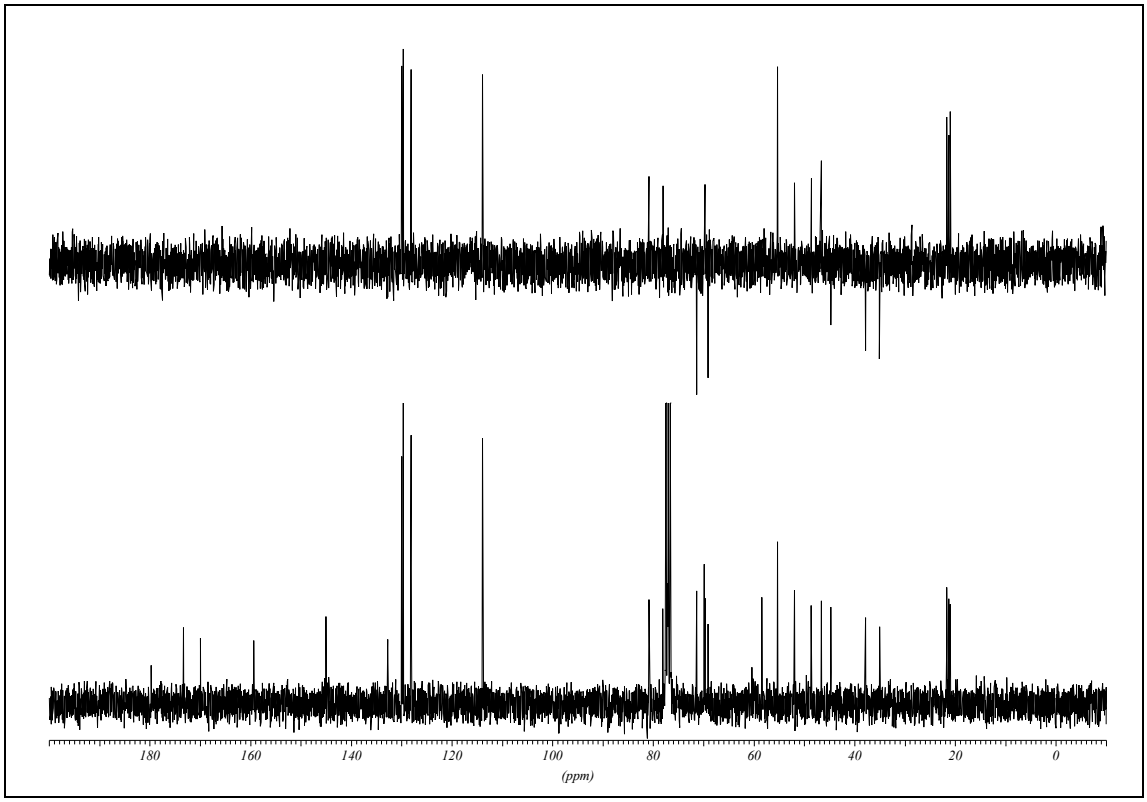
(3a*R*,4*S*,6*R*,9*R*,9a*S*,9b*R*)-6-hydroxy-9-(acetoxymethyl)-6-methyl-2,8-dioxo-2,3,3a,4,5,6,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (231)



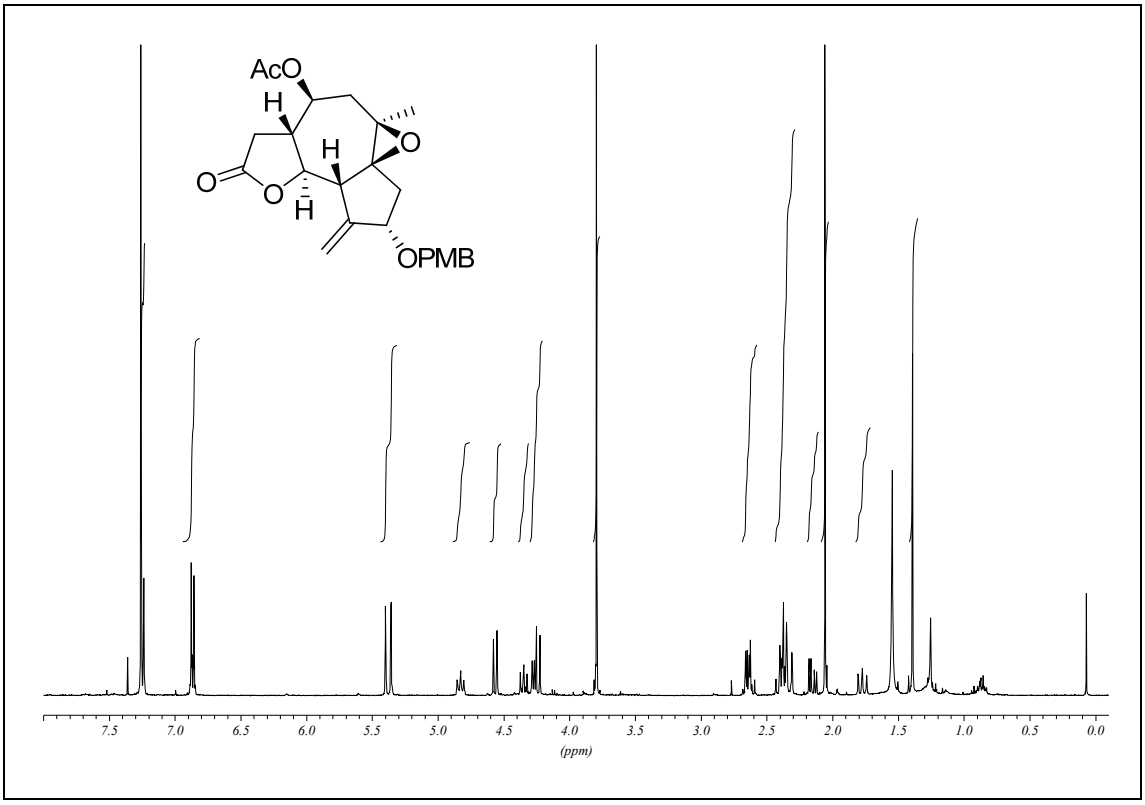


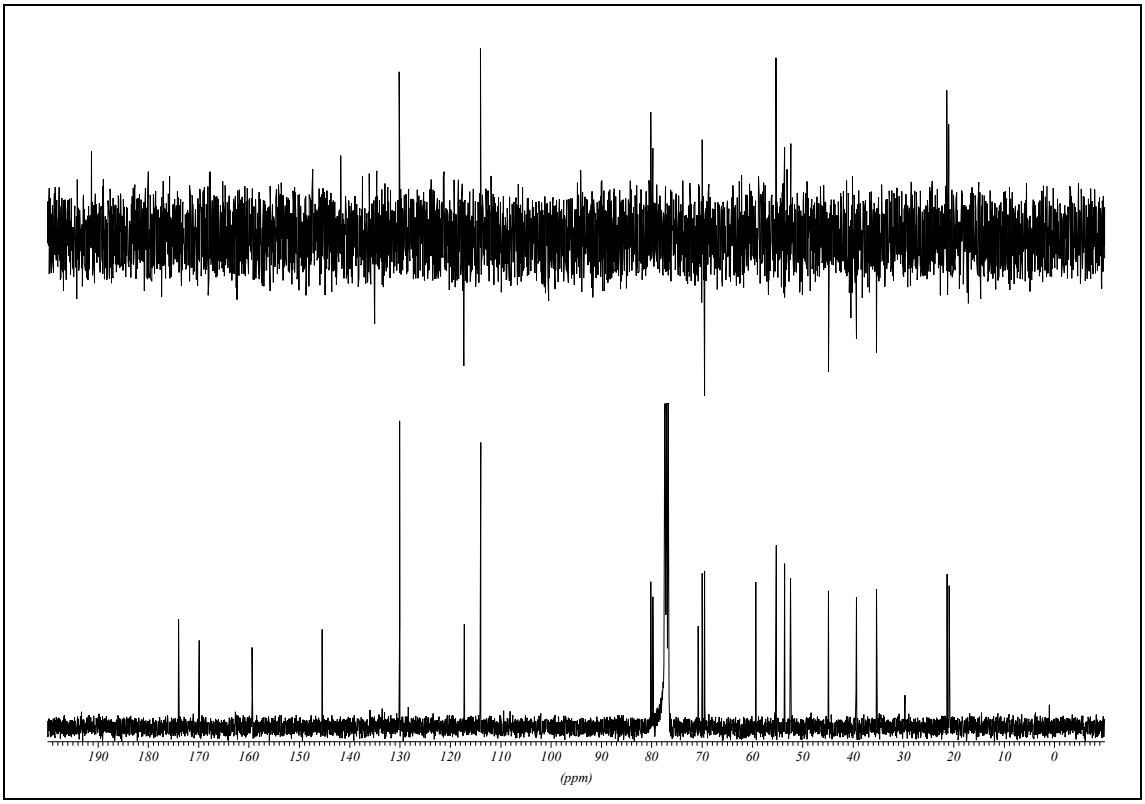
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(tosyloxymethyl)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (234)



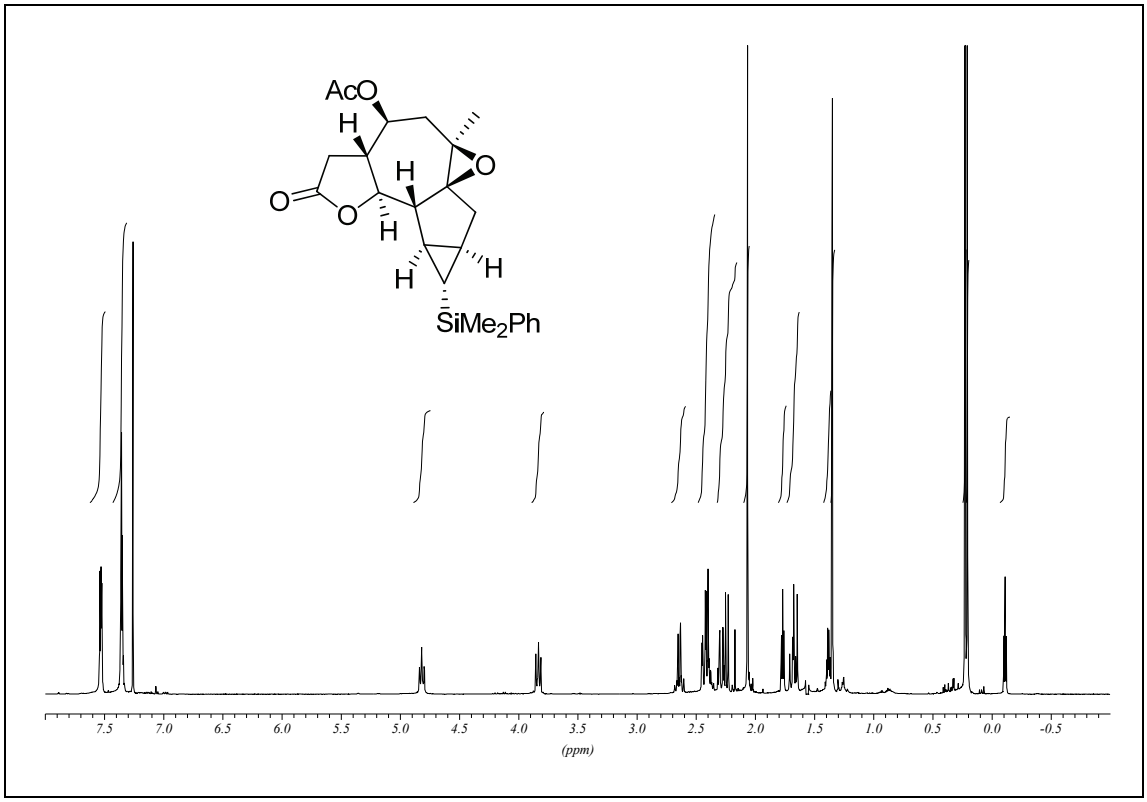


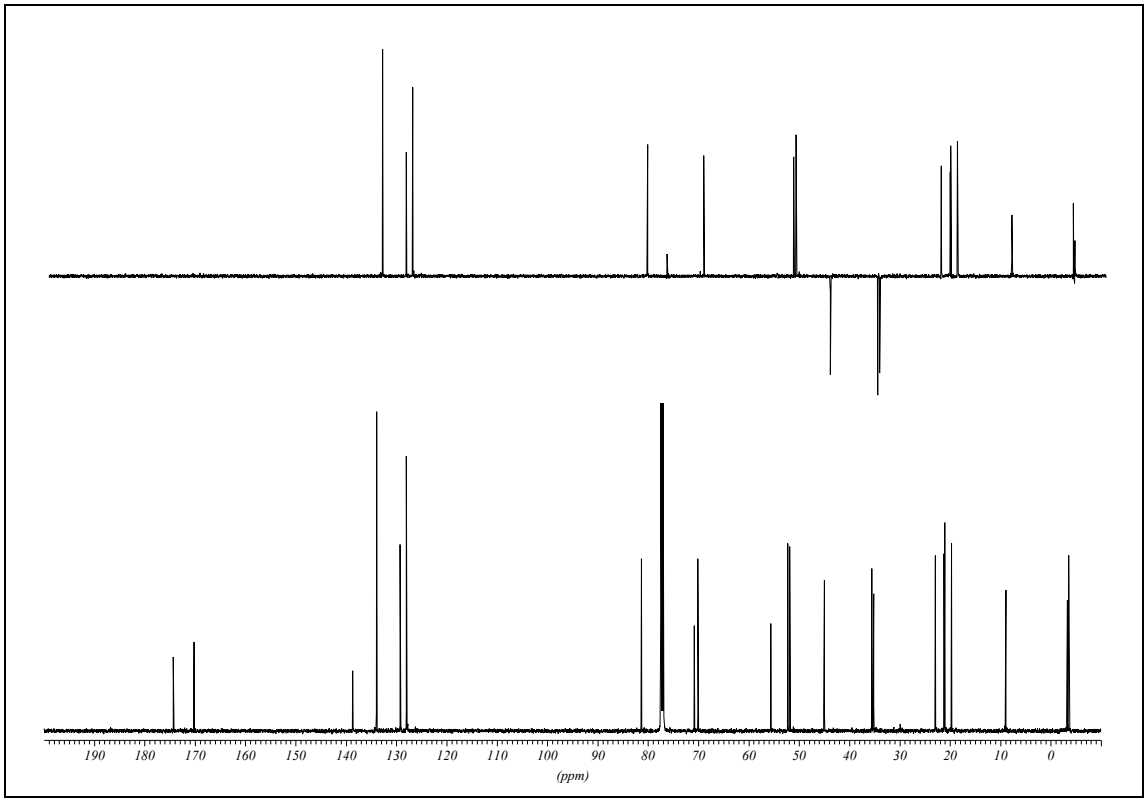
(3a*R*,4*S*,6S,6aS,8*S*,9a*S*,9b*R*)-9-(methylen)-8-(*p*-methoxybenzyloxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (235)



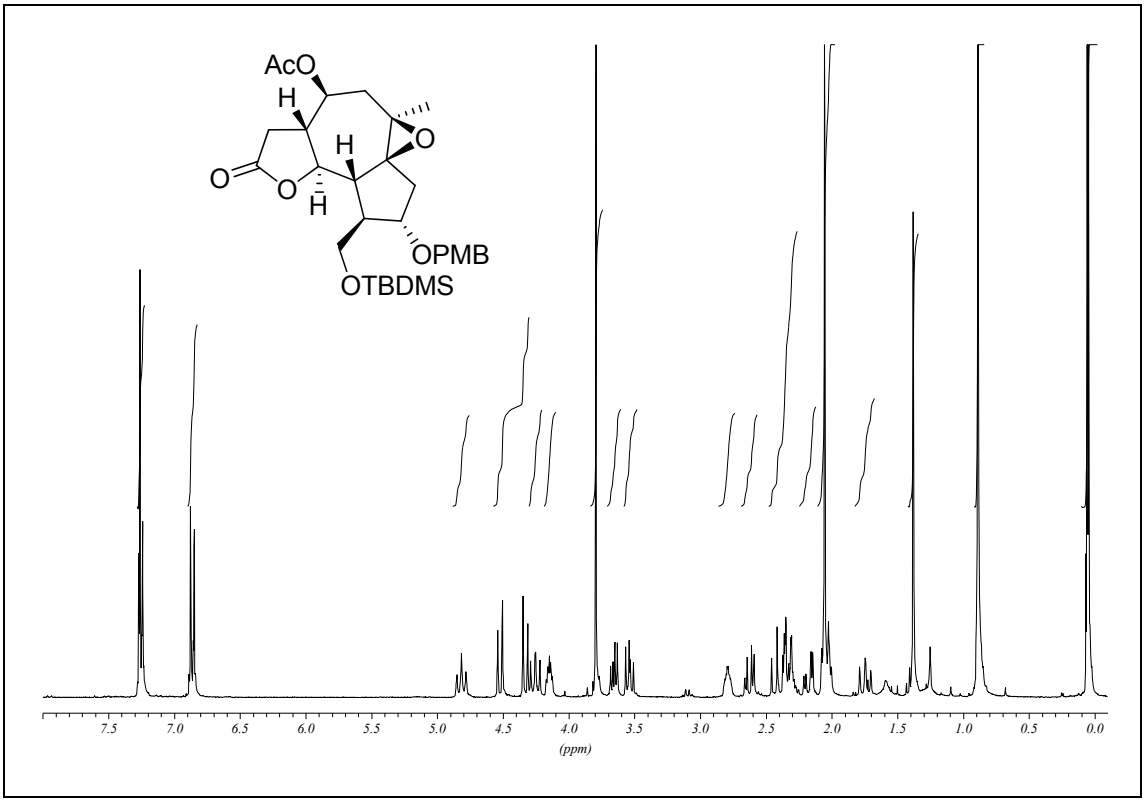


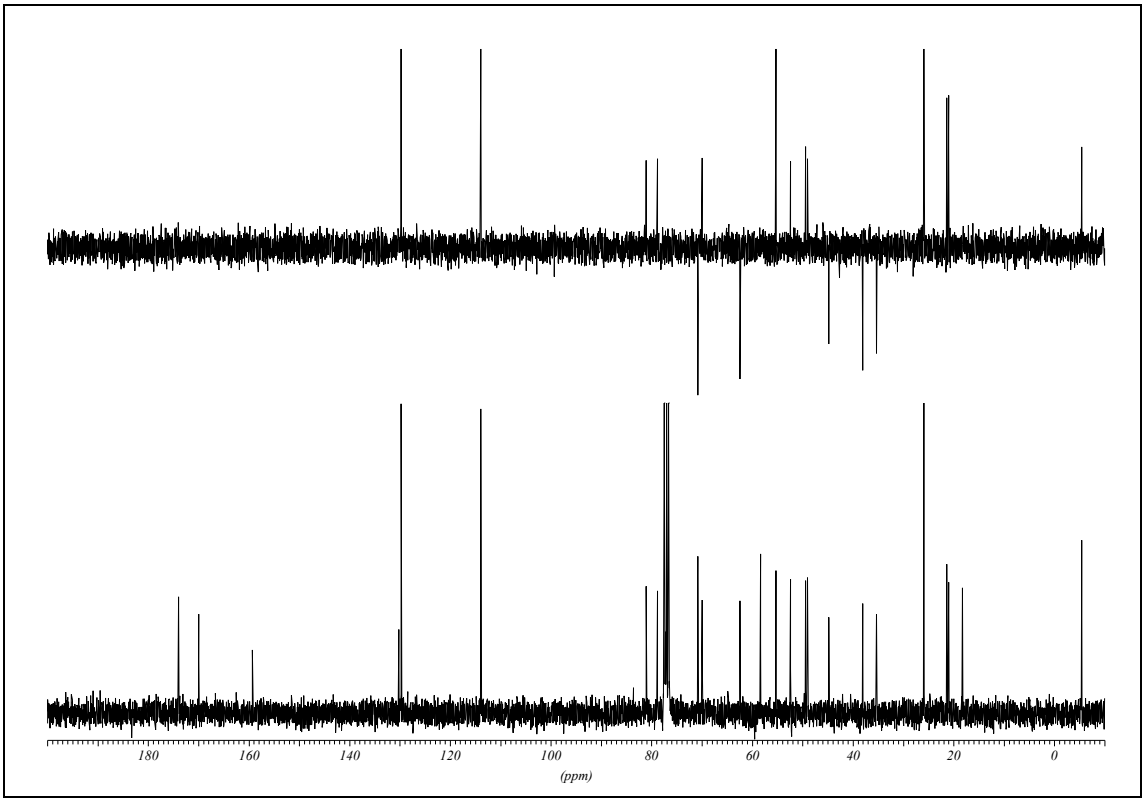
(3a*R*,4*S*,6*S*,6a*S*,9*R*,9a*S*,9b*R*)-6-methyl-2-oxo-1´(dimehtyl(phenyl)silyl)-2,3,3a,4,5,7,8,9,9a, 9b-decahydro-1*H*-cyclopropa[*a*]azulen [4,5-b]furan-4-yl acetate (243)



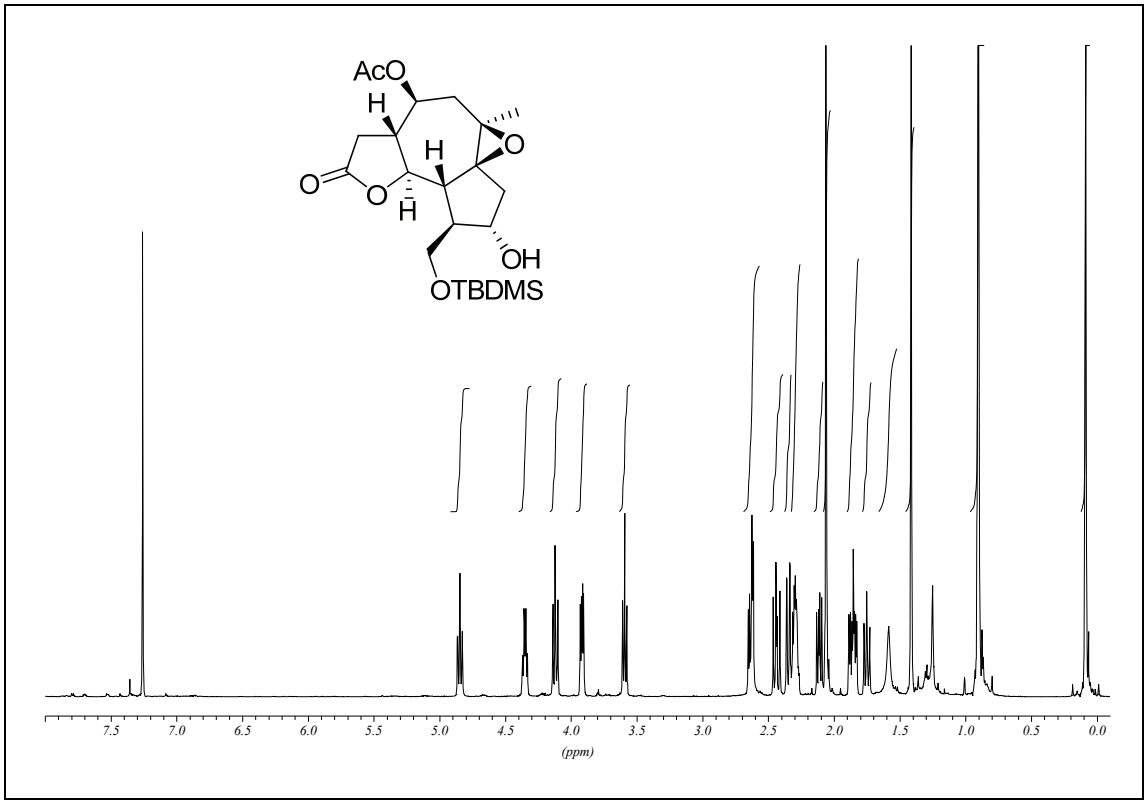


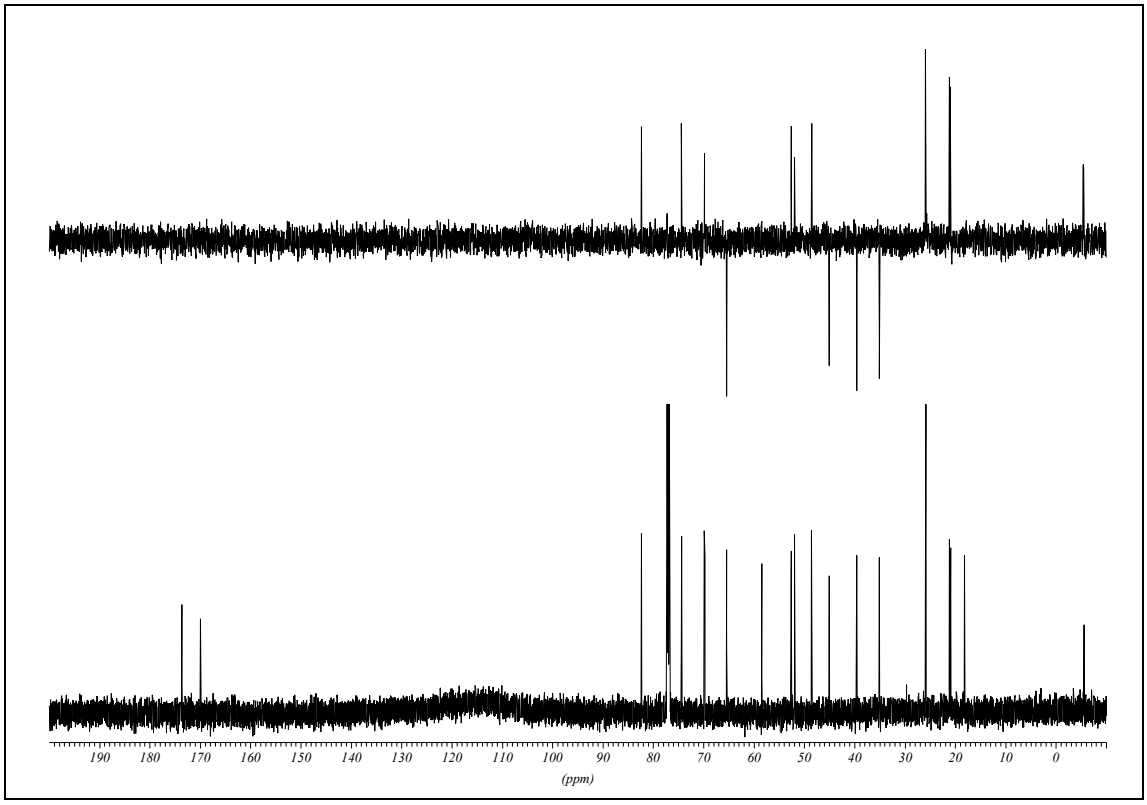
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(*tert*-butyldimethylsiloxymethyl)-8-(-(*p*-methoxybenzyl oxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (246)



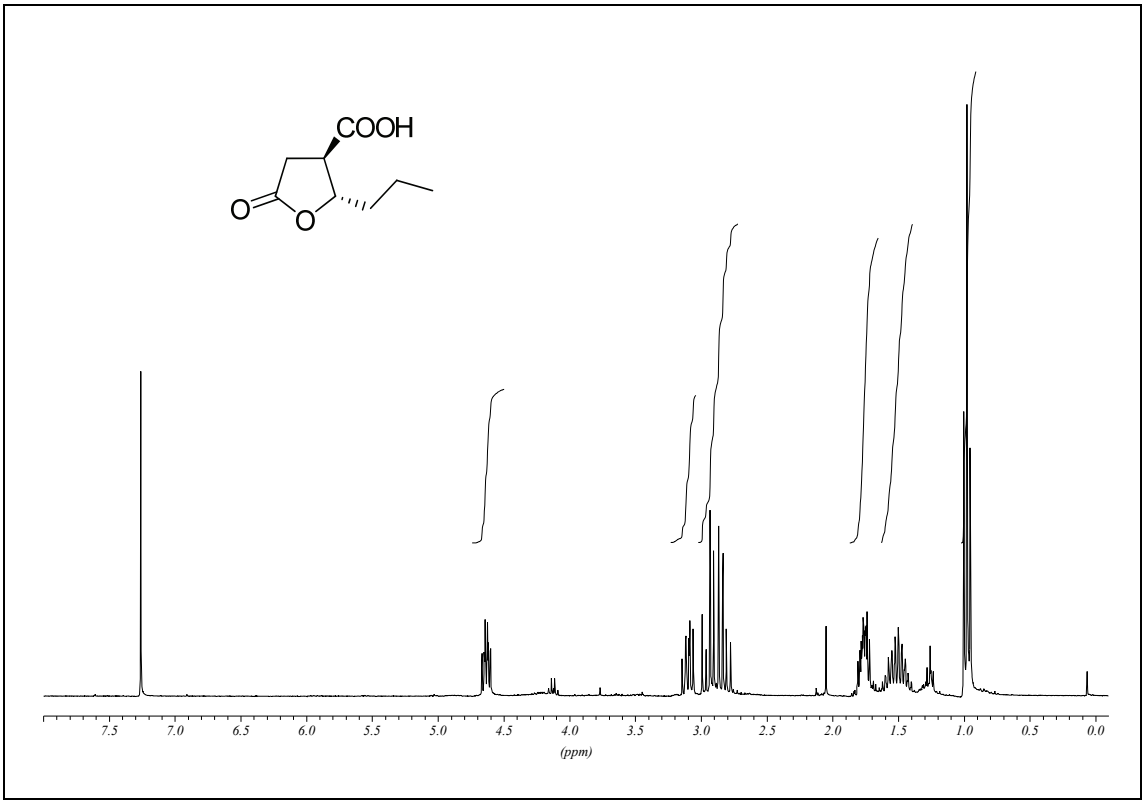


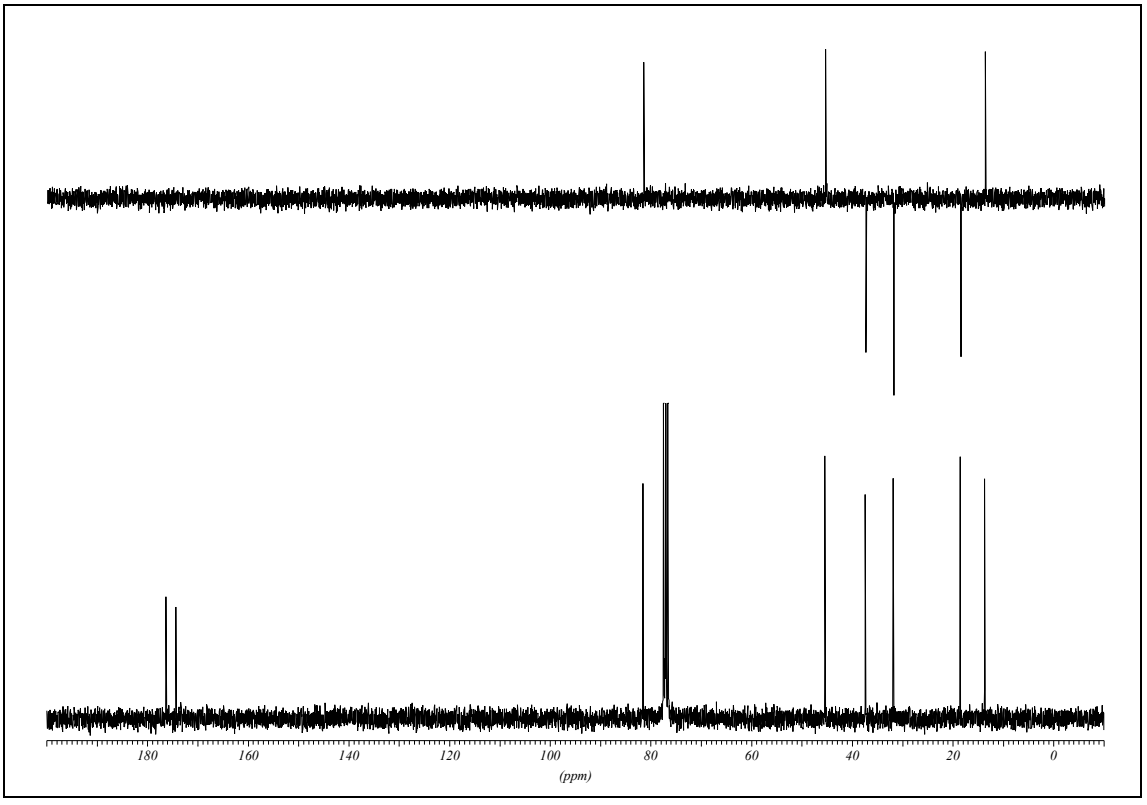
(3a*R*,4*S*,6*S*,6a*S*,8*S*,9*R*,9a*S*,9b*R*)-9-(*tert*-butyldimethylsiloxymethyl)-8-(hydroxy)-6-methyl-6,6a-epoxy-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl acetate (247)



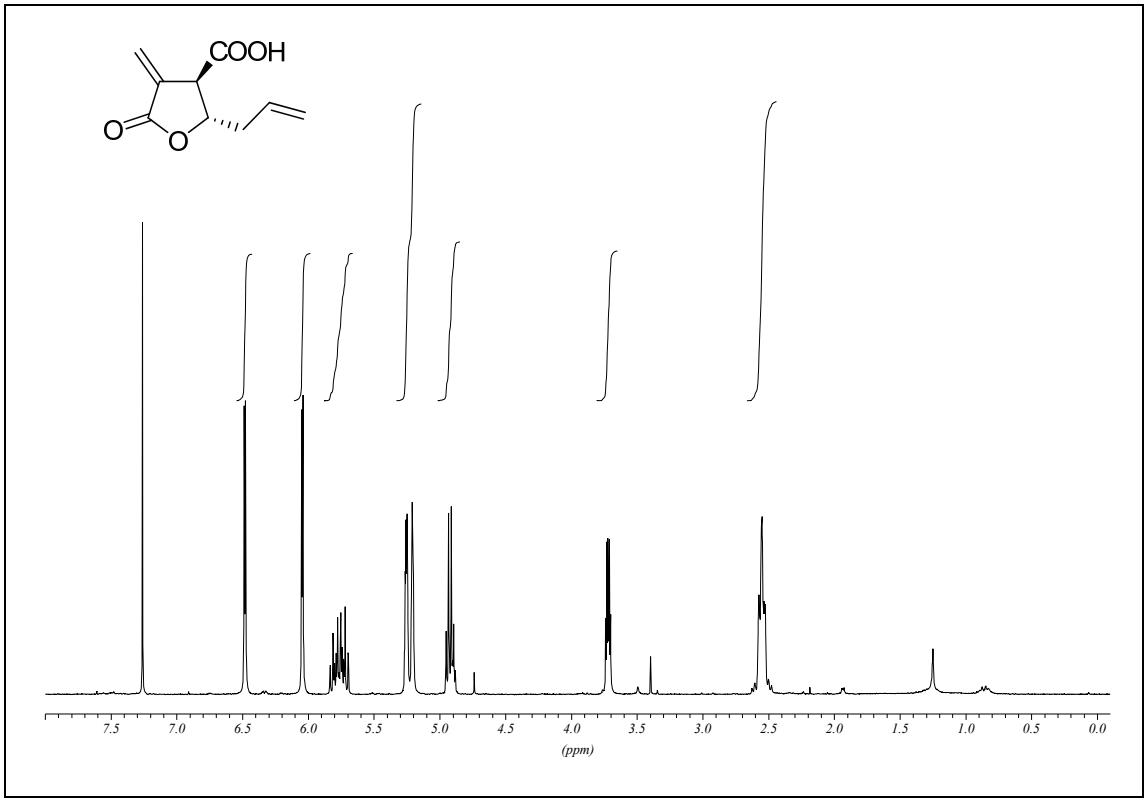


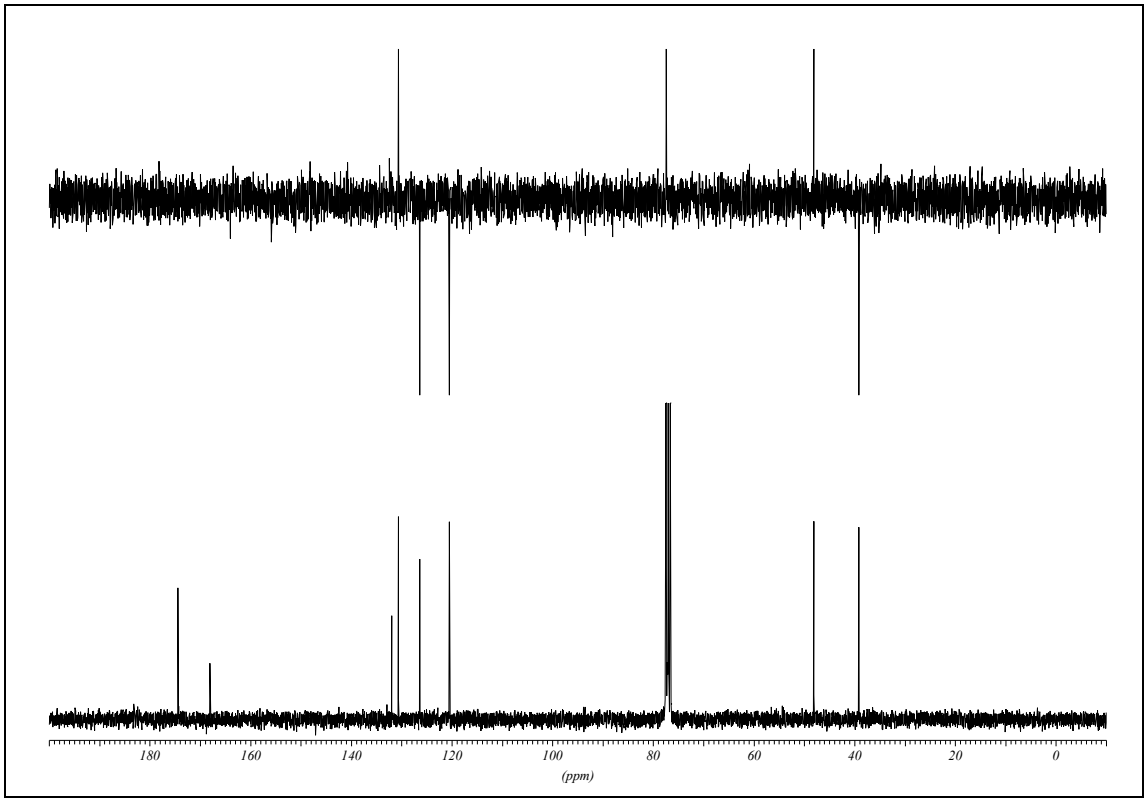
(-)-(2*S*,3*R*)-tetrahydro-5-oxo-2-propylfuran-3-carboxylic acid ((-)-262):



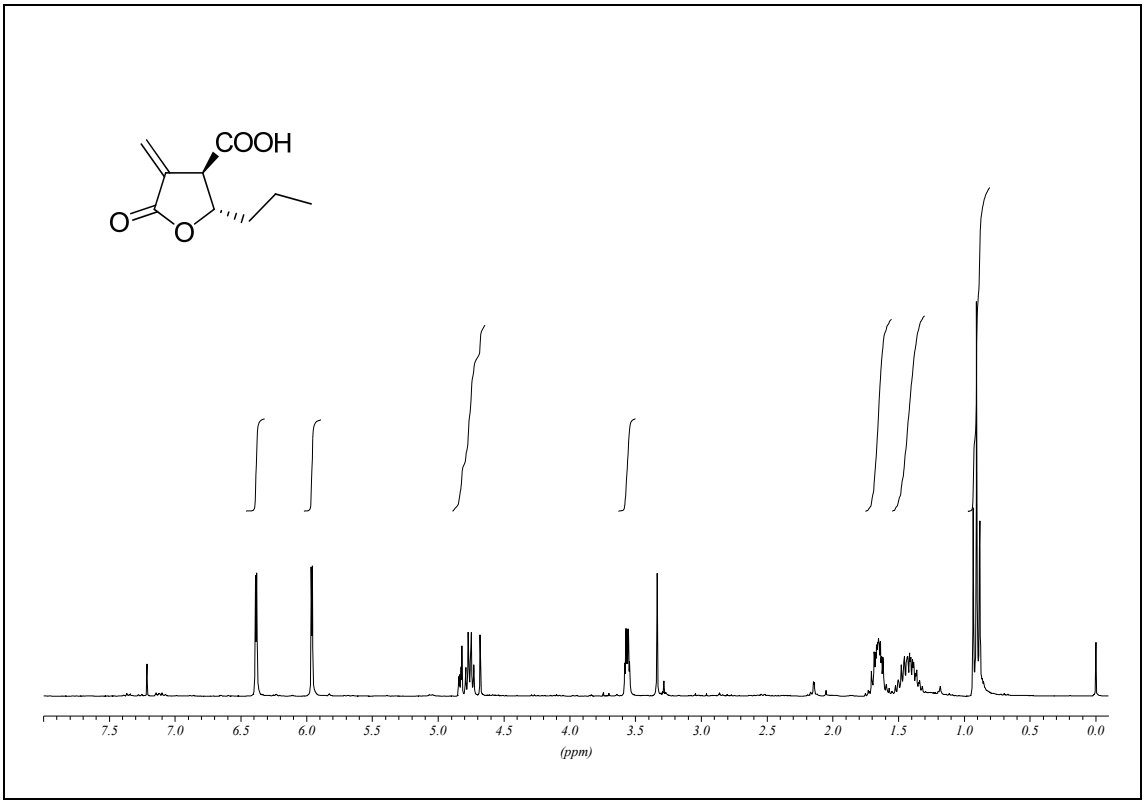


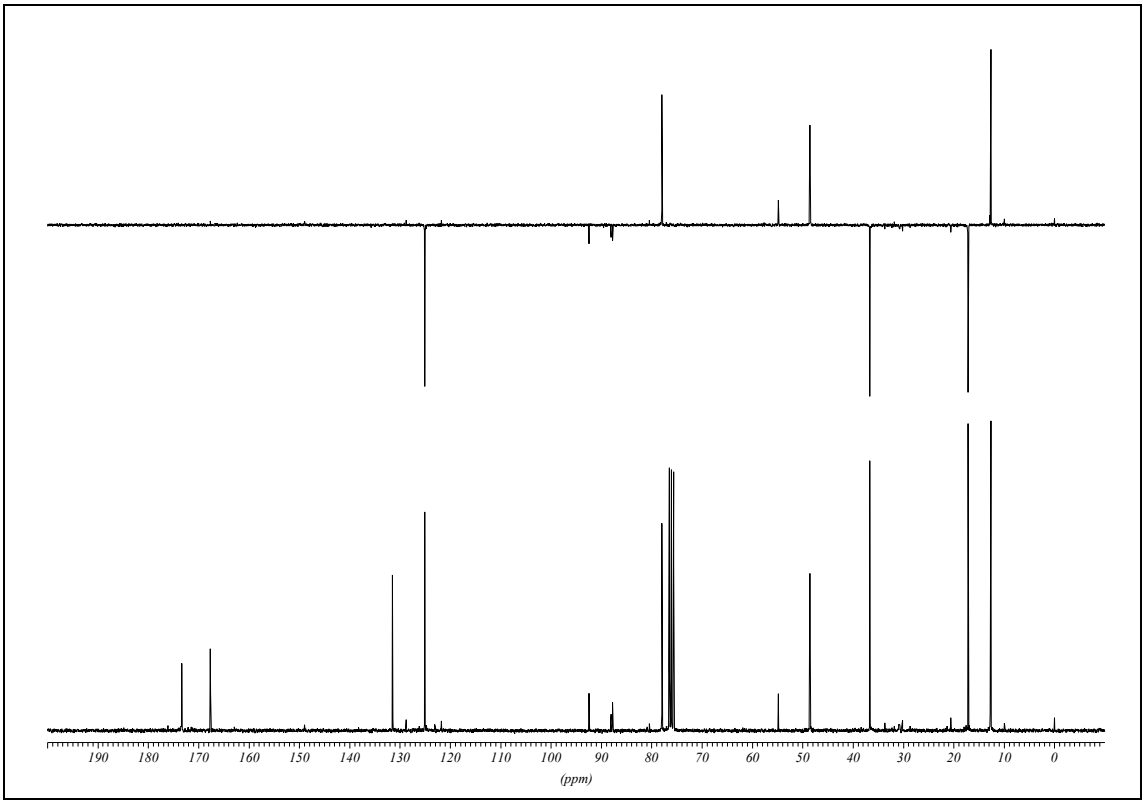
(-)-(2*S*,3*R*)-2-allyl-tetrahydro-4-methylene-5-oxofuran-3-carboxylic acid ((-)-263):



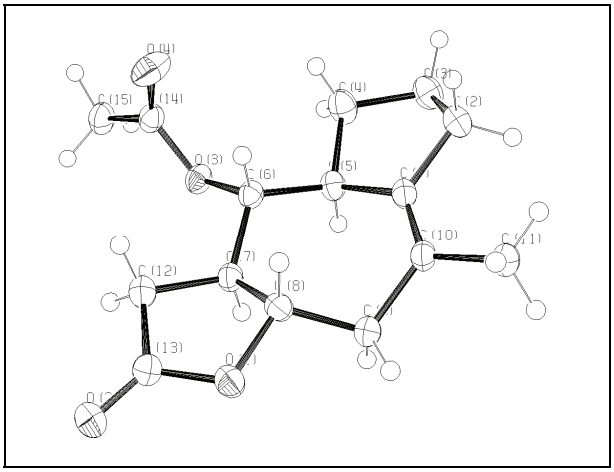


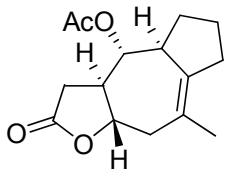
(-)-(2*S*,3*R*)-tetrahydro-4-methylene-5-oxo-2-propylfuran-3-carboxylic acid ((-)-256c):





12.2 X-ray data





209f

Table 11. Crystal data and structure refinement for **209f**

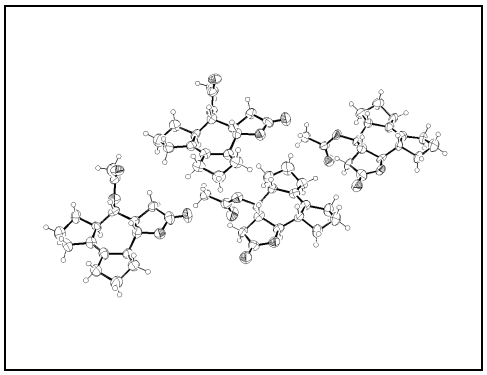
Crystal Data	
Empirical formula	C15 H20 O4
Formula weight	264.31
Crystal size	0.42 x 0.38 x 0.26 mm
Crystal description	prism
Crystal colour	colorless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.2724(4) A alpha = 90 deg.
	b = 14.4760(10) A beta = 90 deg.
	c = 18.2953(17) A gamma = 90 deg.
Volume	1396.36(19) A^3
Z, Calculated density	4, 1.257 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	568
Data Collection	
Measurement device type	STOE-IPDS diffractometer
Measurement method	rotation
Temperature	123(1) K
Wavelength	0.71073 A
Monochromator	graphite
Theta range for data collection	2.63 to 26.82 deg.
Index ranges	-6<=h<=6, -18<=k<=18, -23<=l<=23
Reflections collected / unique	16401 / 2981 [R(int) = 0.0328]
Reflections greater I>2\s(I)	2850
Absorption correction	None

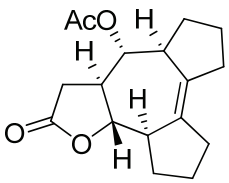
Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	2981 / 0 / 174
Goodness-of-fit on F^2	1.072
Final R indices [I>2sigma(I)]	R1 = 0.0325, wR2 = 0.0859
R indices (all data)	R1 = 0.0338, wR2 = 0.0867
Absolute structure parameter	-0.4(7)
Largest diff. peak and hole	0.227 and -0.130 e.A^{-3}

Table 12. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2x10^3)

Atom	x	y	z	U(eq)
O(1)	-259(2)	1645(1)	6706(1)	30(1)
O(2)	-247(2)	1426(1)	5491(1)	39(1)
O(3)	5441(2)	4129(1)	6636(1)	25(1)
O(4)	3133(2)	5383(1)	6322(1)	41(1)
C(1)	2455(2)	3536(1)	8499(1)	22(1)
C(2)	2504(2)	4297(1)	9078(1)	29(1)
C(3)	4991(2)	4817(1)	8943(1)	32(1)
C(4)	5265(3)	4787(1)	8111(1)	33(1)
C(5)	4378(2)	3804(1)	7897(1)	24(1)
C(6)	3405(2)	3781(1)	7108(1)	22(1)
C(7)	2798(2)	2824(1)	6821(1)	23(1)
C(8)	547(2)	2382(1)	7210(1)	23(1)
C(9)	1086(3)	1995(1)	7967(1)	28(1)
C(10)	1081(2)	2757(1)	8547(1)	24(1)
C(11)	-667(2)	2562(1)	9189(1)	29(1)
C(12)	1940(3)	2765(1)	6022(1)	32(1)
C(13)	390(3)	1884(1)	6009(1)	28(1)
C(14)	5014(2)	4916(1)	6255(1)	25(1)
C(15)	7157(3)	5116(1)	5741(1)	31(1)
H(2A)	2475	4034	9566	34

H(2B)	1060	4706	9023	34
H(3A)	4885	5449	9118	38
H(3B)	6404	4511	9181	38
H(4A)	7014	4888	7966	39
H(4B)	4208	5253	7881	39
H(5)	5837	3387	7933	28
H(6)	1909	4178	7062	26
H(7)	4289	2428	6887	27
H(8)	-817	2839	7248	28
H(9A)	2725	1691	7965	34
H(9B)	-190	1538	8089	34
H(11A)	-526	3052	9540	35
H(11B)	-194	1988	9413	35
H(11C)	-2387	2524	9019	35
H(12A)	916	3295	5888	38
H(12B)	3382	2724	5694	38
H(15A)	7172	4664	5357	37
H(15B)	8734	5093	6002	37
H(15C)	6938	5720	5533	37





209i

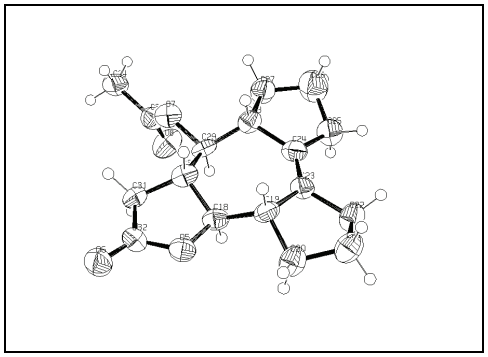


Table 13: Crystal data and structure refinement for **209i.**

Crystal Data	
Empirical formula	C17 H22 O4
Formula weight	290.35
Crystal size	0.470 x 0.170 x 0.020 mm
Crystal description	flat rod
Crystal colour	colorless
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 9.7398(8) A alpha = 90 deg.
	b = 17.5928(17) A beta = 95.326(8) deg.
	c = 17.7549(14) A gamma = 90 deg.
Volume	3029.2(5) A^3
Z, Calculated density	8, 1.273 Mg/m^3
Absorption coefficient	0.729 mm^{-1}
F(000)	1248
Data Collection	
Measurement device type	Oxford Diffraction Gemini Ultra
Measurement method	omega-scan
Temperature	150 K
Wavelength	1.54184 A
Monochromator	graphite
Theta range for data collection	2.50 to 51.25 deg.
Index ranges	-9<=h<=8, -17<=k<=17, -17<=l<=17
Reflections collected / unique	15242 / 6267 [R(int) = 0.0476]
Reflections greater I>2\s(I)	5063

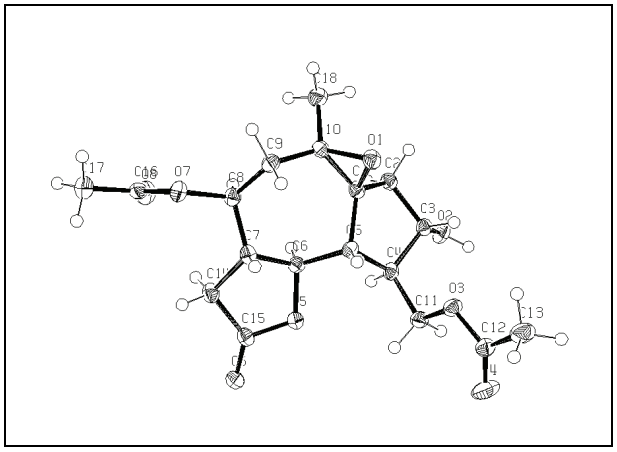
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.13329 and 0.81999
Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	6267 / 1 / 761
Goodness-of-fit on F^2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0649, wR2 = 0.1846
R indices (all data)	R1 = 0.0784, wR2 = 0.1905
Absolute structure parameter	0.2(3)
Largest diff. peak and hole	0.323 and -0.243 e.A^{-3}

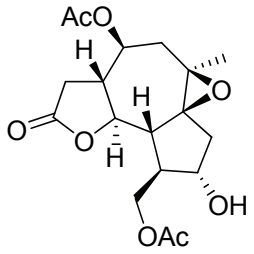
Table 14: Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2x10^3)

Atom	X	Y	Z	U(eq)
O(1)	-573(5)	7109(3)	558(3)	47(2)
O(2)	-462(6)	6957(3)	1819(3)	66(2)
O(3)	4230(5)	7038(3)	473(3)	53(2)
O(4)	4488(5)	8195(3)	997(3)	63(2)
C(1)	372(7)	7300(4)	3(4)	40(3)
C(2)	-168(7)	7014(4)	-758(4)	40(2)
C(3)	-1636(7)	7312(5)	-1008(5)	53(3)
C(4)	-1737(9)	7327(5)	-1856(5)	71(4)
C(5)	-334(7)	7606(4)	-2022(4)	49(3)
C(6)	660(8)	7312(4)	-1377(4)	48(3)
C(7)	1999(8)	7307(4)	-1383(4)	50(3)
C(8)	2802(7)	7642(5)	-2016(4)	55(3)
C(9)	4204(8)	7229(5)	-1937(5)	68(4)
C(10)	4510(8)	7203(5)	-1090(5)	62(3)
C(11)	3128(6)	6998(4)	-782(4)	40(3)
C(12)	2992(7)	7286(4)	12(4)	47(3)
C(13)	1728(7)	6954(4)	347(4)	46(3)
C(14)	1641(6)	7100(4)	1190(4)	46(3)
C(15)	112(9)	7046(4)	1257(5)	53(3)
C(16)	4922(8)	7552(5)	926(4)	48(3)
C(17)	6235(8)	7245(5)	1284(5)	64(3)
O(5)	-892(5)	5831(3)	6287(3)	52(2)
O(6)	-545(5)	5653(3)	7525(3)	64(2)
O(7)	3773(5)	5719(3)	5923(3)	49(2)
O(8)	4647(6)	6894(3)	6069(3)	72(2)
C(18)	-32(7)	6034(4)	5674(4)	44(3)
C(19)	-780(7)	5761(4)	4919(4)	45(3)
C(20)	-2240(8)	6057(5)	4772(4)	54(3)
C(21)	-2445(8)	6078(5)	3920(4)	59(3)
C(22)	-1135(7)	6392(5)	3659(4)	52(3)
C(23)	-17(7)	6058(4)	4255(4)	40(3)
C(24)	1317(8)	6040(4)	4169(4)	48(3)
C(25)	1960(8)	6338(5)	3486(4)	53(3)
C(26)	3328(10)	5980(6)	3510(5)	82(4)
C(27)	3755(8)	5922(5)	4321(4)	57(3)
C(28)	2445(6)	5715(4)	4713(4)	42(3)
C(29)	2522(7)	5998(4)	5519(4)	41(3)

C(30)	1340(7)	5688(4)	5944(4)	44(3)
C(31)	1425(7)	5835(4)	6778(4)	46(3)
C(32)	-95(8)	5763(4)	6933(5)	52(3)
C(33)	4746(8)	6228(5)	6185(4)	50(3)
C(34)	5940(7)	5840(4)	6625(4)	52(3)
O(9)	3642(5)	3596(3)	4294(3)	52(2)
O(10)	3515(5)	3768(3)	3051(3)	67(3)
O(11)	8467(5)	3879(3)	4614(3)	48(2)
O(12)	8801(6)	2779(3)	4022(3)	59(2)
C(35)	4749(7)	3453(4)	4914(4)	41(3)
C(36)	4314(7)	3752(4)	5645(4)	42(3)
C(37)	2884(8)	3436(5)	5835(5)	61(3)
C(38)	2962(7)	3501(5)	6686(4)	59(3)
C(39)	4423(8)	3290(4)	6952(4)	55(3)
C(40)	5285(8)	3533(4)	6318(4)	46(3)
C(41)	6640(8)	3555(4)	6405(4)	47(3)
C(42)	7493(8)	3368(4)	7125(4)	55(3)
C(43)	8987(9)	3624(6)	7041(5)	70(4)
C(44)	9041(8)	3563(5)	6187(4)	57(3)
C(45)	7646(6)	3827(4)	5820(4)	45(3)
C(46)	7375(7)	3546(4)	5024(4)	44(3)
C(47)	5995(7)	3844(4)	4624(4)	39(3)
C(48)	5754(7)	3700(5)	3781(4)	48(3)
C(49)	4181(9)	3698(4)	3643(5)	51(3)
C(50)	9100(8)	3422(5)	4148(5)	52(3)
C(51)	10256(7)	3849(5)	3828(4)	55(3)
O(13)	4634(5)	4984(3)	9272(3)	51(2)
O(14)	4420(6)	5058(3)	8013(3)	67(2)
O(15)	9506(5)	4969(3)	9491(3)	49(2)
O(16)	9486(6)	3794(3)	8962(3)	64(2)
C(52)	5743(7)	4845(4)	9869(4)	45(3)
C(53)	5390(7)	5196(4)	10584(4)	45(3)
C(54)	3977(8)	4968(6)	10808(4)	66(3)
C(55)	4065(8)	5149(5)	11643(4)	67(4)
C(56)	5557(8)	4889(5)	11930(4)	61(3)
C(57)	6381(9)	5001(4)	11265(4)	50(3)
C(58)	7759(8)	4950(4)	11313(4)	44(3)
C(59)	8610(8)	4767(5)	12050(4)	58(3)
C(60)	10097(8)	4923(5)	11899(4)	60(3)
C(61)	10109(8)	4773(5)	11065(4)	56(3)
C(62)	8748(7)	5082(4)	10705(3)	41(3)
C(63)	8356(7)	4778(4)	9914(4)	46(3)
C(64)	7024(7)	5097(4)	9533(4)	43(3)
C(65)	6716(7)	4918(5)	8701(4)	46(3)
C(66)	5119(9)	4984(4)	8585(5)	57(3)
C(67)	10018(8)	4409(5)	9058(4)	51(3)
C(68)	11324(7)	4676(5)	8751(5)	62(3)
H(1)	472	7865	-19	49
H(2)	-165	6445	-761	47
H(3A)	-2343	6970	-827	63
H(3B)	-1767	7828	-803	63
H(4A)	-2471	7679	-2062	86
H(4B)	-1925	6814	-2070	86
H(5A)	-314	8169	-2041	59
H(5B)	-89	7405	-2513	59
H(8A)	2307	7545	-2519	66
H(8B)	2929	8197	-1949	66
H(9A)	4131	6712	-2158	81
H(9B)	4915	7520	-2179	81
H(10A)	4846	7702	-893	74
H(10B)	5217	6813	-943	74
H(11)	3050	6432	-774	49
H(12)	2940	7854	10	57
H(13)	1704	6393	256	55
H(14A)	2155	6710	1504	56
H(14B)	2001	7609	1340	56
H(17A)	6719	7642	1593	76
H(17B)	6812	7079	892	76

H(17C)	6046	6812	1606	76
H(18)	69	6599	5658	52
H(19)	-792	5193	4909	54
H(20A)	-2908	5710	4982	65
H(20B)	-2331	6570	4991	65
H(21A)	-2624	5561	3715	71
H(21B)	-3237	6407	3749	71
H(22A)	-1132	6955	3669	62
H(22B)	-996	6216	3142	62
H(25A)	1392	6199	3015	64
H(25B)	2048	6898	3510	64
H(26A)	3270	5471	3270	98
H(26B)	3978	6299	3251	98
H(27A)	4140	6412	4516	68
H(27B)	4467	5524	4417	68
H(28)	2348	5149	4716	51
H(29)	2513	6566	5526	49
H(30)	1279	5126	5860	53
H(31A)	1790	6349	6904	56
H(31B)	2006	5451	7064	56
H(34A)	6154	6102	7109	62
H(34B)	6747	5854	6334	62
H(34C)	5696	5310	6720	62
H(35)	4926	2894	4960	50
H(36)	4260	4319	5616	51
H(37A)	2117	3745	5592	73
H(37B)	2760	2901	5671	73
H(38A)	2754	4026	6841	71
H(38B)	2303	3148	6896	71
H(39A)	4504	2735	7041	65
H(39B)	4730	3559	7428	65
H(42A)	7466	2815	7223	65
H(42B)	7129	3636	7555	65
H(43A)	9150	4152	7221	84
H(43B)	9666	3282	7318	84
H(44A)	9788	3888	6023	68
H(44B)	9219	3031	6043	68
H(45)	7642	4396	5811	53
H(46)	7412	2979	5007	53
H(47)	5929	4402	4718	47
H(48A)	6146	3206	3644	58
H(48B)	6161	4109	3490	58
H(51A)	10301	3704	3298	66
H(51B)	11131	3723	4119	66
H(51C)	10088	4397	3860	66
H(52)	5811	4283	9951	54
H(53)	5397	5760	10518	54
H(54A)	3238	5267	10524	79
H(54B)	3801	4420	10716	79
H(55A)	3365	4862	11897	80
H(55B)	3938	5699	11730	80
H(56A)	5931	5201	12365	74
H(56B)	5565	4348	12086	74
H(59A)	8490	4228	12191	70
H(59B)	8335	5094	12464	70
H(60A)	10356	5455	12022	72
H(60B)	10739	4578	12198	72
H(61A)	10183	4221	10967	67
H(61B)	10894	5036	10862	67
H(62)	8861	5645	10657	49
H(63)	8275	4212	9940	55
H(64)	7076	5663	9582	51
H(65A)	7026	4400	8583	55
H(65B)	7162	5289	8383	55
H(68A)	11453	4402	8282	75
H(68B)	12110	4578	9124	75
H(68C)	11260	5223	8646	75





227

Table 15. Crystal data and structure refinement for **227**.

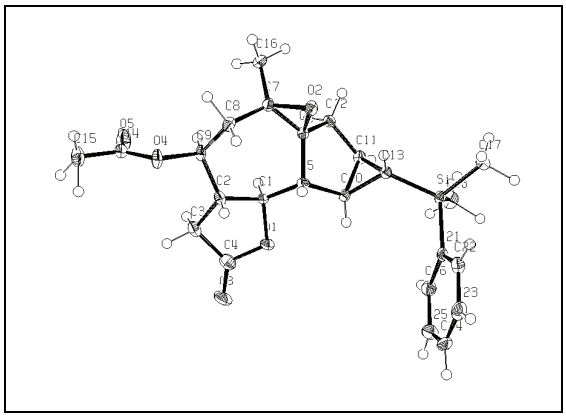
Crystal Data		
	Empirical formula	C18 H24 O8
	Formula weight	368.37
	Crystal size	0.32 x 0.18 x 0.04 mm
	Crystal description	platelike
	Crystal colour	colorless
	Crystal system	Monoclinic
	Space group	P 21
	Unit cell dimensions	a = 10.8348(14) A alpha = 90 deg.
		b = 7.8686(6) A beta = 111.640(14) deg.
		c = 11.4418(15) A gamma = 90 deg.
	Volume	906.7(2) A^3
	Z, Calculated density	2, 1.349 Mg/m^3
	Absorption coefficient	0.106 mm^{-1}
	F(000)	392
Data Collection		
	Measurement device type	STOE-IPDS diffractometer
	Measurement method	rotation
	Temperature	123(1) K
	Wavelength	0.71073 A
	Monochromator	graphite
	Theta range for data collection	2.02 to 26.87 deg.
	Index ranges	-13<=h<=13, -9<=k<=9, -14<=l<=14

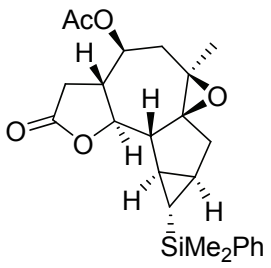
Reflections collected / unique	10211 / 3875 [R(int) = 0.0489]
Reflections greater I>2\s(I)	3115
Absorption correction	None
Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	3875 / 1 / 241
Goodness-of-fit on F^2	0.919
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0630
R indices (all data)	R1 = 0.0478, wR2 = 0.0658
Absolute structure parameter	-0.2(7)
Largest diff. peak and hole	0.211 and -0.144 $e.A^{-3}$

Table 16. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2x10^3)

Atom	X	Y	Z	U(eq)
O(1)	-511(1)	9104(2)	4524(1)	24(1)
O(2)	1737(1)	12982(2)	2957(1)	25(1)
O(3)	3614(1)	9278(2)	5129(1)	23(1)
O(4)	5752(1)	8944(2)	5417(1)	43(1)
O(5)	1480(1)	6922(2)	1624(1)	22(1)
O(6)	1798(1)	4970(2)	343(1)	28(1)
O(7)	-2666(1)	4719(2)	1409(1)	23(1)
O(8)	-3503(1)	5513(2)	-644(1)	32(1)
C(1)	-260(2)	9456(2)	3384(2)	20(1)
C(2)	-86(2)	11320(2)	3114(2)	20(1)
C(3)	1418(2)	11532(2)	3535(2)	20(1)
C(4)	1876(2)	9862(2)	3130(2)	20(1)
C(5)	880(2)	8462(2)	3190(2)	18(1)
C(6)	355(2)	7507(2)	1949(2)	19(1)
C(7)	-475(2)	5901(2)	1836(2)	20(1)
C(8)	-1880(2)	6286(2)	1756(2)	20(1)
C(9)	-1870(2)	6844(2)	3040(2)	22(1)
C(10)	-1554(2)	8730(2)	3310(2)	20(1)

C(11)	3337(2)	9446(3)	3785(2)	22(1)
C(12)	4889(2)	9034(3)	5849(2)	27(1)
C(13)	5113(2)	8887(3)	7220(2)	37(1)
C(14)	-315(2)	5082(3)	686(2)	24(1)
C(15)	1084(2)	5567(3)	831(2)	22(1)
C(16)	-3415(2)	4488(3)	167(2)	23(1)
C(17)	-4102(2)	2798(3)	-43(2)	32(1)
C(18)	-2767(2)	9854(3)	2979(2)	28(1)
H(2A)	-452	12075	3599	25
H(2B)	-530	11574	2207	25
H(2O)	2460(20)	13360(30)	3420(20)	30
H(3)	1819	11649	4471	24
H(4)	1728	10002	2219	24
H(5)	1311	7665	3906	22
H(6)	-179	8320	1283	23
H(7)	-29	5165	2587	24
H(8)	-2286	7191	1115	24
H(9A)	-2749	6603	3081	26
H(9B)	-1202	6164	3702	26
H(11A)	3550	8372	3450	27
H(11B)	3887	10364	3637	27
H(13A)	5436	7743	7517	44
H(13B)	4276	9092	7340	44
H(13C)	5773	9729	7697	44
H(14A)	-418	3832	695	29
H(14B)	-971	5542	-105	29
H(17A)	-4714	2712	-920	38
H(17B)	-4602	2690	514	38
H(17C)	-3441	1887	141	38
H(18A)	-3296	9510	3473	33
H(18B)	-3302	9740	2081	33
H(18C)	-2488	11040	3168	33





243

Table 17. Crystal data and structure refinement for **243**.

Crystal Data	
Empirical formula	C24 H30 O5 Si
Formula weight	426.57
Crystal size	0.32 x 0.18 x 0.04 mm
Crystal description	rectangular
Crystal colour	colorless
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.4369(3) A alpha = 90 deg.
	b = 11.4236(6) A beta = 90 deg.
	c = 29.9411(15) A gamma = 90 deg.
Volume	2201.65(19) A^3
Z, Calculated density	4, 1.287 Mg/m^3
Absorption coefficient	0.139 mm^{-1}
F(000)	912
Data Collection	
Measurement device type	Bruker SMART
Measurement method	rotation
Temperature	100 K
Wavelength	0.71073 A
Monochromator	graphite
Index ranges	-9<=h<=9, -16<=k<=16, -42<=l<=41
Reflections collected / unique	25888 / 6680 [R(int) = 0.0788]
Reflections greater I>2\s(I)	5022

Absorption correction	None
Refinement	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	6680 / 0 / 275
Goodness-of-fit on F^2	0.956
Final R indices [I>2sigma(I)]	R1 =0.0580, wR2 = 0.1033
R indices (all data)	R1 = 0.0805, wR2 = 0.0658
Largest diff. peak and hole	0.396 and -0.301 $e.A^{-3}$

Table 18. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2)

Atom	X	Y	Z	U(eq)
Si	-0.05639(11)	0.45951(6)	0.46741(2)	0.0148(2)
O(1)	0.0096(3)	0.41197(16)	0.28152(6)	0.0211(6)
O(2)	0.4897(3)	0.22341(16)	0.38618(6)	0.0187(6)
O(3)	-0.0658(4)	0.49357(18)	0.21550(6)	0.0331(7)
O(4)	0.6026(3)	0.22018(17)	0.22612(6)	0.0223(6)
O(5)	0.4445(4)	0.07714(19)	0.18752(7)	0.0348(7)
C(1)	0.1445(4)	0.3167(2)	0.29742(8)	0.0144(7)
C(2)	0.3156(4)	0.3140(2)	0.26212(8)	0.0162(7)
C(3)	0.1844(4)	0.3330(3)	0.22026(9)	0.0221(8)
C(4)	0.0289(5)	0.4213(3)	0.23631(9)	0.0250(9)
C(5)	0.2111(4)	0.3385(2)	0.34517(8)	0.0136(7)
C(6)	0.2908(4)	0.2215(2)	0.36402(8)	0.0131(7)
C(7)	0.4668(4)	0.1564(2)	0.34527(8)	0.0167(7)
C(8)	0.5873(4)	0.2038(2)	0.30561(8)	0.0186(8)
C(9)	0.4557(4)	0.2076(2)	0.26324(8)	0.0172(7)
C(10)	0.0318(4)	0.3703(2)	0.37617(8)	0.0143(7)
C(11)	-0.0248(4)	0.2635(2)	0.40325(8)	0.0150(7)
C(12)	0.1127(4)	0.1632(2)	0.38899(9)	0.0154(7)
C(13)	0.0827(4)	0.3670(2)	0.42616(8)	0.0138(7)
C(14)	0.5801(5)	0.1484(2)	0.19072(9)	0.0207(8)
C(15)	0.7483(5)	0.1696(3)	0.15715(10)	0.0280(9)
C(16)	0.4805(5)	0.0262(2)	0.35120(9)	0.0229(8)
C(17)	0.0826(4)	0.4488(2)	0.52208(8)	0.0215(8)
C(18)	-0.3318(4)	0.4112(3)	0.47287(10)	0.0236(8)

C(21)	-0.0564(5)	0.6167(2)	0.44896(8)	0.0166(7)
C(22)	0.0972(5)	0.6961(2)	0.46222(9)	0.0220(8)
C(23)	0.0935(5)	0.8120(3)	0.44753(10)	0.0283(9)
C(24)	-0.0633(6)	0.8506(2)	0.41999(10)	0.0286(9)
C(25)	-0.2167(5)	0.7751(3)	0.40665(10)	0.0301(10)
C(26)	-0.2121(5)	0.6587(3)	0.42092(9)	0.0229(9)
H(1)	0.06540	0.24140	0.29610	0.0170
H(2)	0.40440	0.38490	0.26640	0.0190
H(3A)	0.26900	0.36420	0.19540	0.0270
H(3B)	0.11590	0.25960	0.21060	0.0270
H(5)	0.32240	0.39950	0.34640	0.0160
H(8A)	0.71050	0.15370	0.30030	0.0220
H(8B)	0.63700	0.28370	0.31260	0.0220
H(9)	0.37270	0.13410	0.26000	0.0210
H(10)	-0.08070	0.42330	0.36520	0.0170
H(11)	-0.17450	0.24780	0.40990	0.0180
H(12A)	0.03640	0.10860	0.36930	0.0190
H(12B)	0.16470	0.11950	0.41530	0.0190
H(13)	0.23290	0.35380	0.43310	0.0170
H(15A)	0.87590	0.13030	0.16680	0.0420
H(15B)	0.77370	0.25390	0.15450	0.0420
H(15C)	0.70520	0.13850	0.12810	0.0420
H(16A)	0.62530	0.00390	0.35670	0.0340
H(16B)	0.43040	-0.01280	0.32410	0.0340
H(16C)	0.39480	0.00250	0.37670	0.0340
H(17A)	0.06110	0.37070	0.53480	0.0320
H(17B)	0.02800	0.50800	0.54260	0.0320
H(17C)	0.23140	0.46200	0.51740	0.0320
H(18A)	-0.39600	0.40770	0.44320	0.0350
H(18B)	-0.40800	0.46700	0.49160	0.0350
H(18C)	-0.33630	0.33350	0.48670	0.0350
H(22)	0.20550	0.67070	0.48150	0.0260
H(23)	0.19980	0.86450	0.45660	0.0340
H(24)	-0.06520	0.92980	0.41020	0.0340
H(25)	-0.32560	0.80180	0.38780	0.0360
H(26)	-0.31820	0.60680	0.41120	0.0270

13. References

(1) Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, p 476-541.

(2) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1979; Vol. 38.

(3) Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Letters* **1980**, *21*, 4767-70.

(4) Negishi, E.-I.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707-6738.

(5) Collins, I. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1998**, 1869-1888.

(6) Chhor, R. B.; Nosse, B.; Sorgel, S.; Bohm, C.; Seitz, M.; Reiser, O. *Chemistry--A European Journal* **2003**, *9*, 260-270.

(7) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J. *Synlett* **1996**, 343-345.

(8) Crawforth, J. M.; Rawlings, B. J. *Tetrahedron Letters* **1995**, *36*, 6345-6.

(9) Mulzer, J.; Chucholowski, A. *Angewandte Chemie* **1986**, *98*, 632-4.

(10) Seitz, M.; Reiser, O. *Current Opinion in Chemical Biology* **2005**, *9*, 285-292.

(11) Hoffmann, H. M. R.; Rabe, J. *Angewandte Chemie (International ed. in English)* **1985**, *24*, 94-110.

(12) Hanson, J. R. *The Total Synthesis of Natural Products*; Wiley-Interscience: New York, 1999; Vol. 11.

(13) Grieco, P. A. *Synthesis* **1975**, 67-82.

(14) Zhuzbaev, B. T.; Adekenov, S. M.; Veselovskii, V. V. *Russian Chemical Reviews* **1995**, *64*, 199-200.

(15) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573-80.

(16) Iiono, Y.; A. Tanaka; Yamashita, K. *Agricultural and Biological Chemistry* **1972**, *36*, 2505.

(17) Gross, D. *Phytochemistry* **1975**, *14*, 2105.

(18) Cassady, J. M.; Byrn, S. R.; Stamos, I. K.; Evans, S. M.; McKenzie, A. *Journal of Medicinal Chemistry* **1978**, *21*, 815.

(19) Fujita, E.; Nagao, Y. *Bioorganic Chemistry* **1977**, *6*, 287.

(20) Schlewer, G.; Stampf, J. L.; Benezra, C. *Journal of Medicinal Chemistry* **1980**, *23*, 1031.

(21) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *Journal of Medicinal Chemistry* **1971**, *14*, 1147-52.

(22) Kupchan, S. M.; Giacobbe, T. J.; Krull, I. S.; Thomas, S. M.; Eakin, M. A.; Fessler, D. C. *Journal of Organic Chemistry* **1970**, *35*, 3539-43.

(23) Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science (Washington, DC, United States)* **1970**, *168*, 376-8.

(24) Lee, K.-H.; Hall, I. H.; Mar, E.-C.; Starnes, C. O.; ElGebaly, S. A.; Waddell, T. G.; Hadgraft, R. I.; Ruffner, C. G.; Weidner, I. *Science (Washington, DC, United States)* **1977**, *196*, 533-6.

(25) Arrick, B. A.; Nathan, C. F.; Cohn, Z. A. *Journal of Clinical Investigation* **1983**, *71*, 258-67.

(26) Spring, O.; Kupka, J.; Maier, B.; Hager, A. *Zeitschrift fuer Naturforschung, C: Journal of Biosciences* **1982**, *37C*, 1087-91.

(27) Spurgeon, S. R.; Porter, J. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley and Sons: New York, 1981; Vol. 1, p 1-46.

(28) Qureshi, N.; Porter, J. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; John Wiley and Sons: New York, 1981; Vol. 1, p 47-93.

(29) Bloch, K. *Steroids* **1992**, *57*, 378-383.
(30) Horbach, S.; Sahm, H.; Welle, R. *FEMS Microbiol. Lett.* **1993**, *115*, 135-140.
(31) Rohmer, M.; Seemann, M.; Horbach, S.; Bringer-Meyer, S.; Sahm, H. *Journal of the American Chemical Society* **1996**, *118*, 2564-2566.
(32) Flesch, G.; Rohmer, M. *European Journal of Biochemistry* **1988**, *175*, 405-411.
(33) Bacher, A.; Rieder, C.; Eichinger, D.; Arigoni, D.; Fuchs, G.; Eisenreich, W. *FEMS Microbiology Reviews* **1998**, *22*, 567-598.
(34) Eisenreich, W.; Schwarz, M.; Cartayrade, A.; Arigoni, D.; Zenk, M. H.; Bacher, A. *Chemistry & Biology* **1998**, *5*, R221-R233.
(35) Lichtenthaler, H. K.; Rohmer, M.; Schwender, J. *Physiologia Plantarum* **1997**, *101*, 643-652.
(36) Schwender, J.; Lichtenthaler, H. K.; Disch, A.; Rohmer, M. *Physiology, Biochemistry and Molecular Biology of Plant Lipids, [Proceedings of the International Symposium on Plant Lipids], 12th. Toronto, July 7-12, 1996* **1997**, 180-182.
(37) Eschenmoser, A.; Arigoni, D. *Helvetica Chimica Acta* **2005**, *88*, 3011-3050.
(38) Ruzicka, L. *Rad Jugoslavenske Akademije Znanosti i Umjetnosti* **1989**, *443*, 69-84.
(39) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helvetica Chimica Acta* **1955**, *38*, 1890-1904.
(40) De Kraker, J.-W.; Franssen, M. C. R.; Joerink, M.; De Groot, A.; Bouwmeester, H. J. *Plant Physiology* **2002**, *129*, 257-268.
(41) Bouwmeester, H. J.; Kodde, J.; Verstappen, F. W. A.; Altug, I. G.; De Kraker, J.-W.; Wallaart, T. E. *Plant Physiology* **2002**, *129*, 134-144.
(42) De Kraker, J.-W.; Franssen, M. C. R.; Dalm, M. C. F.; De Groot, A.; Bouwmeester, H. J. *Plant Physiology* **2001**, *125*, 1930-1940.
(43) De Kraker, J.-W.; Franssen, M. C. R.; De Groot, A.; Konig, W. A.; Bouwmeester, H. J. *Plant Physiology* **1998**, *117*, 1381-1392.
(44) Castaneda-Acosta, J.; Fischer, N. H.; Vargas, D. *Journal of natural products* **1993**, *56*, 90-8.
(45) Parodi, F. J.; Fronczek, F. R.; Fischer, N. H. *Journal of Natural Products* **1989**, *52*, 554-66.
(46) Ortega, A.; Maldonado, E. *Heterocycles* **1989**, *29*, 635-8.
(47) Gonzalez, A. G.; Galindo, A.; Mar Afonso, M.; Mansilla, H.; Palenzuela, J. A.; Gomez Rodriguez, M. A.; Martinez-Ripoll, M. *Tetrahedron* **1988**, *44*, 4575-84.
(48) Gonzalez, A. G.; Galindo, A.; Mar Afonso, M.; Mansilla, H.; Lopez, M. *Tetrahedron* **1988**, *44*, 4585-9.
(49) Galindo, A.; Gonzalez, A.; Mansilla, H.; Gutierrez, Z.; Palenzuela, J. A.; Trigos, A. *Revista de la Real Academia de Ciencias Exactas, Fisicas y Naturales de Madrid* **1987**, *81*, 793-5.
(50) Parodi, F. J.; Fischer, N. H. *Journal of the Chemical Society, Chemical Communications* **1986**, 1405.
(51) Gonzalez, A.; Galindo, A.; Palenzuela, J. A.; Mansilla, H. *Tetrahedron Letters* **1986**, *27*, 2771-4.
(52) Gonzalez Gonzalez, A.; Galindo, A.; Mansilla, H. *Tetrahedron* **1980**, *36*, 2015-17.
(53) Nam, N.-H. *Mini-Reviews in Medicinal Chemistry* **2006**, *6*, 945-951.
(54) Yuan, G.; Wahlqvist, M. L.; He, G.; Yang, M.; Li, D. *Asia Pacific Journal of Clinical Nutrition* **2006**, *15*, 143-152.
(55) Bremner, P.; Heinrich, M. *Phytochemistry Reviews* **2005**, *4*, 27-37.
(56) Song, Q.; Gomez-Barrios, M. L.; Hopper, E. L.; Hjortso, M. A.; Fischer, N. H. *Phytochemistry* **1995**, *40*, 1659-65.
(57) Ma, J.-Y.; Wang, Z.-T.; Xu, L.-S.; Xu, G.-J. *Phytochemistry* **1998**, *50*, 113-115.

(58) Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *Journal of the American Chemical Society* **1980**, *102*, 7498-505.
(59) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *Journal of the American Chemical Society* **1984**, *106*, 5585-94.
(60) Jacobi, P. A.; Selnick, H. G. *Journal of the American Chemical Society* **1984**, *106*, 3041-3.
(61) Monde, K.; Takasugi, M.; Katsui, N.; Masamune, T. *Chemistry Letters* **1990**, 1283-6.
(62) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3049-54.
(63) Devreese, A. A.; Demuynck, M.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3039-48.
(64) Demuynck, M.; Devreese, A. A.; De Clercq, P. J.; Vandewalle, M. *Tetrahedron Letters* **1982**, *23*, 2501-4.
(65) Termont, D.; De Clercq, P.; De Keukeleire, D.; Vandewalle, M. *Synthesis* **1977**, 46-8.
(66) Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochemistry* **1978**, *17*, 957-961.
(67) Sanchez-Viesca, F.; Romo, J. *Tetrahedron* **1963**, *19*, 1285-91.
(68) Rigby, J. H.; Senanayake, C. *Journal of the American Chemical Society* **1987**, *109*, 3147-9.
(69) Rigby, J. H.; Wilson, J. Z. *Journal of the American Chemical Society* **1984**, *106*, 8217-24.
(70) Yuuya, S.; Hagiwara, H.; Suzuki, T.; Ando, M.; Yamada, A.; Suda, K.; Kataoka, T.; Nagai, K. *Journal of Natural Products* **1999**, *62*, 22-30.
(71) Rybalko, K. S.; Ban'kovskii, A. I.; Kibal'chich, P. N. *Zhurnal Obshchei Khimii* **1964**, *34*, 1358-9.
(72) Lee, E.; Lim, J. W.; Yoon, C. H.; Sung, Y.-s.; Kim, Y. K.; Yun, M.; Kim, S. *Journal of the American Chemical Society* **1997**, *119*, 8391-8392.
(73) Daniewski, W. M.; Danikiewicz, W.; Gumulka, M.; Pankowska, E.; Krajewski, J.; Grabarczyk, H.; Wichlacz, M. *Phytochemistry* **1993**, *34*, 1639-41.
(74) Jezek, E.; Schall, A.; Kreitmeier, P.; Reiser, O. *Synlett* **2005**, 915-918.
(75) Oliver, S. F.; Hoegenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angewandte Chemie, International Edition* **2003**, *42*, 5996-6000.
(76) Ley, S. V.; Oliver, S. F.; Hogenauer, K.; Simic, O. *Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003* **2003**, ORGN-419.
(77) Ley, S. V.; Antonello, A.; Balskus, E. P.; Booth, D. T.; Christensen, S. B.; Cleator, E.; Gold, H.; Hoegenauer, K.; Huenger, U.; Myers, R. M.; Oliver, S. F.; Simic, O.; Smith, M. D.; Sohoel, H.; Woolford, A. J. A. *Proceedings of the National Academy of Sciences of the United States of America* **2004**, *101*, 12073-12078.
(78) Rasmussen, U.; Broegger Christensen, S.; Sandberg, F. *Acta Pharmaceutica Suecica* **1978**, *15*, 133-40.
(79) Christensen, S. B.; Rasmussen, U.; Christophersen, C. *Tetrahedron Letters* **1980**, *21*, 3829-30.
(80) Patkar, S. A.; Rasmussen, U.; Diamant, B. *Agents and Actions* **1979**, *9*, 53-7.
(81) Lytton, J.; Westlin, M.; Hanley, M. R. *Journal of Biological Chemistry* **1991**, *266*, 17067-71.
(82) Caspersen, C.; Treiman, M. *FEBS Letters* **1995**, *377*, 31-6.
(83) Poulsen, J.-C. J.; Caspersen, C.; Mathiasen, D.; East, J. M.; Tunwell, R. E. A.; Lai, F. A.; Maeda, N.; Mikoshiba, K.; Treiman, M. *Biochemical Journal* **1995**, *307*, 749-58.
(84) Kahler, M. *Archiv der Pharmazie (Weinheim, Germany)* **1830**, *34*, 318.
(85) Birladeanu, L. *Angewandte Chemie (International ed. in English)* **2003**, *42*, 1202-8.

(86) Huffman, J. W.; Pennington, W. T.; Bearden, D. W. *Journal of Natural Products* **1992**, *55*, 1087-92.
(87) Clemo, G. R.; Haworth, R. D. *Journal of the Chemical Society* **1930**, 2579-82.
(88) Clemo, G. R.; Haworth, R. D.; Walton, E. *Journal of the Chemical Society* **1930**, 1110-5.
(89) Barton, D. H. R.; Miki, T.; Pinhey, J. T.; Wells, R. J. *Proceedings of the Chemical Society* **1962**, 112.
(90) Nakazaki, M.; Arakawa, H. *Proceedings of the Chemical Society* **1962**, 151.
(91) 50 g /145.50 Euro, www.sigmaaldrich.com
(92) Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Journal of the American Chemical Society* **1956**, *78*, 1422-6.
(93) Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Proceedings of the Japan Academy* **1954**, *30*, 119-21.
(94) Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Proceedings of the Japan Academy* **1954**, *30*, 116-18.
(95) Marshall, J. A.; Wuts, P. G. M. *Journal of Organic Chemistry* **1978**, *43*, 1086-9.
(96) Roth, H. D. *Angewandte Chemie* **1989**, *101*, 1220-1234.
(97) Barton, D. H. R. *Helvetica Chimica Acta* **1959**, *279*, 2604-2616.
(98) Chapman, O. L.; Englert, L. F. *Journal of the American Chemical Society* **1963**, *85*, 3028-2029.
(99) Fisch, M. H.; Richards, J. H. *Journal of the American Chemical Society* **1963**, *85*, 3029-3030.
(100) Meisel, A.; Weizmann, A. *Journal of the American Chemical Society* **1953**, *75*, 3865.
(101) Suchy, M.; Herout, V.; Sorm, F. *Collection of Czechoslovak Chemical Communications* **1964**, *29*, 1829.
(102) Turdybekov, K. M.; Adekenov, S. M.; Gatilov, Y. V. *Journal of Structural Chemistry* **1989**, *29*, 811-813.
(103) Ando, M.; Akahane, A.; Takase, K. *Chemistry Letters* **1978**, 727-30.
(104) Ando, M.; Kusaka, H.; Ohara, H.; Takase, K.; Yamaoka, H.; Yanagi, Y. *Journal of Organic Chemistry* **1989**, *54*, 1952-60.
(105) Ando, M.; Yamaoka, H.; Takase, K. *Chemistry Letters* **1982**, 501-4.
(106) Romo de Vivar, A.; Cabrera, A.; Ortega, A.; Romo, J. *Tetrahedron* **1967**, *23*, 3903-7.
(107) Romo, J.; Romo de Vivar, A.; Joseph-Nathan, P. *Tetrahedron* **1967**, *23*, 29-35.
(108) Jolad, S. D.; Wiedhopf, R. M.; Cole, J. R. *Journal of Pharmaceutical Sciences* **1974**, *63*, 1321-2.
(109) Ukita, T. *Yakugaku Zasshi* **1939**, *59*, 80.
(110) Semmler, F. W.; Feldstein, J. *Ber.* **1914**, *47*, 2433.
(111) Vichnewski, W.; Gilbert, B. *Phytochemistry (Elsevier)* **1972**, *11*, 2563-6.
(112) Garcia, M.; Da Silva, A. J. R.; Baker, P. M.; Gilbert, B.; Rabi, J. A. *Phytochemistry (Elsevier)* **1976**, *15*, 331-2.
(113) Corbella, A.; Gariboldi, P.; Jommi, G.; Orsini, F.; Ferrari, G. *Phytochemistry (Elsevier)* **1974**, *13*, 459-65.
(114) Ando, M.; Ibayashi, K.; Minami, N.; Nakamura, T.; Isogai, K.; Yoshimura, H. *Journal of Natural Products* **1994**, *57*, 433-45.
(115) Bargues, V.; Blay, G.; Cardona, L.; Garcia, B.; Pedro, J. R. *Journal of Natural Products* **2002**, *65*, 1703-1706.
(116) Herout, V.; Sorm, F. *Collection of Czechoslovak Chemical Communications* **1953**, *18*, 854-69.
(117) Herout, V.; Sorm, F. *Collection of Czechoslovak Chemical Communications* **1954**, *19*, 792-7.

(118) Novotny, L.; Herout, V.; Sorm, F. *Collection of Czechoslovak Chemical Communications* **1960**, *25*, 1492-9.
(119) Beauhaire, J.; Fourrey, J. L.; Lellemand, J. Y.; Vuilhorgne, M. *Tetrahedron Letters* **1981**, *22*, 2269-72.
(120) Beauhaire, J.; Fourrey, J. L.; Vuilhorgne, M.; Lallemand, J. Y. *Tetrahedron Letters* **1980**, *21*, 3191-4.
(121) Karimov, Z. *Kristallografiya* **1985**, *30*, 682-7.
(122) Karimov, Z.; Kasymov, S. Z.; Yagudaev, M. R.; Sidyakin, G. P. *Khimiya Prirodnykh Soedinenii* **1980**, 729-30.
(123) Zhang, W.; Luo, S.; Fang, F.; Chen, Q.; Hu, H.; Jia, X.; Zhai, H. *Journal of the American Chemical Society* **2005**, *127*, 18-19.
(124) Anon. *Deutsche Apotheker Zeitung* **2003**, *143*, 85-86.
(125) Suchy, M.; Herout, V.; Sorm, F. *Collection of Czechoslovak Chemical Communications* **1960**, *25*, 2777-82.
(126) Samek, Z.; Holub, M.; Drozdz, B.; Iommi, G.; Corbella, A.; Gariboldi, P. *Tetrahedron Letters* **1971**, 4775-8.
(127) Schneider, G.; Thiele, K. *Planta Medica* **1974**, *26*, 174-83.
(128) Schneider, G.; Thiele, K. *Planta Medica* **1974**, *25*, 149-57.
(129) Fritsche, J.; Beindorff, C. M.; Dachtler, M.; Zhang, H.; Lammers, J. G. *European Food Research and Technology* **2002**, *215*, 149-157.
(130) Bombardelli, E.; Fontana, G.; Giori, A.; Morazzoni, P.; Ronchi, M.; Arpini, S.; (Indena S.p.A., Italy). Application: WO, WO, 2007, p 11pp.
(131) Rodgers, S.; Glen, R. C.; Bender, A. *Journal of Chemical Information and Modeling* **2006**, *46*, 569-576.
(132) Cravotto, G.; Nano, G. M.; Binello, A.; Spagliardi, P.; Seu, G. *Journal of the Science of Food and Agriculture* **2005**, *85*, 1757-1764.
(133) Choi, S. Z.; Choi, S. U.; Lee, K. R. *Archives of Pharmacal Research* **2005**, *28*, 1142-1146.
(134) Cho, J. Y.; Kim, A. R.; Jung, J. H.; Chun, T.; Rhee, M. H.; Yoo, E. S. *European Journal of Pharmacology* **2004**, *492*, 85-94.
(135) Cho, J. Y.; Kim, A. R.; Joo, H.-G.; Kim, B.-h.; Rhee, M. H.; Yoo, E. S.; Katz, D. R.; Chain, B. M.; Jung, J. H. *Biochemical and Biophysical Research Communications* **2004**, *313*, 954-961.
(136) Cho, J. Y.; Baik, K. U.; Jung, J. H.; Park, M. H. *European Journal of Pharmacology* **2000**, *398*, 399-407.
(137) Cho, J. Y.; Park, J.; Yoo, E. S.; Baik, K. U.; Jung, J. H.; Lee, J.; Park, M. H. *Planta Medica* **1998**, *64*, 594-597.
(138) Bachelier, A.; Mayer, R.; Klein, C. D. *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 5605-5609.
(139) Barbosa, M. D. F. S.; Yang, G.; Fang, J.; Kurilla, M. G.; Pompliano, D. L. *Antimicrobial Agents and Chemotherapy* **2002**, *46*, 943-946.
(140) Eschenburg, S.; Priestman Melanie, A.; Abdul-Latif Farid, A.; Delachaume, C.; Fassy, F.; Schonbrunn, E. *The Journal of biological chemistry* **2005**, *280*, 14070-5.
(141) Dai, H. J.; Parker, C. N.; Bao, J. J. *Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences* **2002**, *766*, 123-132.
(142) Asada, H.; Miyase, T.; Fukushima, S. *Chemical & Pharmaceutical Bulletin* **1984**, *32*, 3403-9.
(143) Asada, H.; Miyase, T.; Fukushima, S. *Chemical & Pharmaceutical Bulletin* **1984**, *32*, 3036-42.
(144) Asada, H.; Miyase, T.; Fukushima, S. *Chemical & Pharmaceutical Bulletin* **1984**, *32*, 1724-8.

(145) Nishimura, K.; Miyase, T.; Ueno, A.; Noro, T.; Kuroyanagi, M.; Fukushima, S. *Chemical & Pharmaceutical Bulletin* **1985**, *33*, 3361-8.
(146) Seto, M.; Miyase, T.; Fukushima, S. *Chemical & Pharmaceutical Bulletin* **1986**, *34*, 4170-6.
(147) Seto, M.; Miyase, T.; Umehara, K.; Ueno, A.; Hirano, Y.; Otani, N. *Chemical & Pharmaceutical Bulletin* **1988**, *36*, 2423-9.
(148) Okunade, A. L.; Wiemer, D. F. *Phytochemistry (Elsevier)* **1985**, *24*, 1199-201.
(149) Srivastava, R. P.; Proksch, P.; Wray, V. *Phytochemistry* **1990**, *29*, 3445-8.
(150) Ma, J.-Y.; He, A.-M.; Zhang, D.-C.; Wang, Z.-T.; Xu, L.-S.; Xu, G.-J.; Namba, T.; Kadota, S. *Studies in Plant Science* **1999**, *6*, 394-398.
(151) Suh, J.; Jo, Y.; Kim Nam, D.; Bae Song, J.; Jung Jee, H.; Im Kwang, S. *Archives of pharmacal research* **2002**, *25*, 289-92.
(152) Ma, J.-Y.; Wang, Z.-T.; Xu, L.-S.; Xu, G.-J.; Kadota, S.; Namba, T. *Phytochemistry* **1998**, *48*, 201-203.
(153) Na, Z.; Cho, J.-Y.; Lee, H. J.; Chung, J. H.; Park, K. D.; Lee, Y. J.; Shin, S. C.; Rim, Y. S.; Park, K.-H.; Moon, J.-H. *Magnetic Resonance in Chemistry* **2007**, *45*, 275-278.
(154) Fleming, I.; Barbero, A.; Walter, D. *Chemical Reviews (Washington, D. C.)* **1997**, *97*, 2063-2192.
(155) Hosomi, A. *Accounts of Chemical Research* **1988**, *21*, 200-6.
(156) Sakurai, H. *Pure and Applied Chemistry* **1982**, *54*, 1-22.
(157) Hosomi, A.; Sakurai, H. *Journal of the American Chemical Society* **1977**, *99*, 1673-5.
(158) Hosomi, A.; Sakurai, H. *Tetrahedron Letters* **1976**, 1295-8.
(159) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876-7.
(160) Dols, P. P. M. A.; Klunder, J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515-38.
(161) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Haefner, B.; Schwarz, S. *Synthesis* **1988**, 540-1.
(162) Theil, F.; Schick, H.; Weichert, D.; Tannenberger, K.; Klappach, G. *Journal fuer Praktische Chemie (Leipzig)* **1991**, *333*, 497-9.
(163) Deardorff, D. R.; Myles, D. C. *Organic Syntheses* **1989**, *67*, 114-20.
(164) Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. J. *Journal of Organic Chemistry* **1989**, *54*, 2759-62.
(165) Laumen, K.; Schneider, M. *Tetrahedron Letters* **1984**, *25*, 5875-8.
(166) Duhamel, L.; Herman, T. *Tetrahedron Letters* **1985**, *26*, 3099-102.
(167) Nara, M.; Terashima, S.; Yamada, S. *Tetrahedron* **1980**, *36*, 3161-70.
(168) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67-70.
(169) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983-2004.
(170) Curran, T. T.; Hay, D. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2791-2792.
(171) L3126 Lipase from porcine pancreas, Type II, (100-400 units/mg protein (using olive oil (30 min incubation)), 30-90 units/mg protein (using triacetin), purchased from Sigma-Aldrich.
(172) Joeng, W. B., University of Regensburg, 2006.
(173) Rai, A. N.; Basu, A. *Tetrahedron Letters* **2003**, *44*, 2267-2269.
(174) Corey, E. J.; Eckrich, T. M. *Tetrahedron Letters* **1983**, *24*, 3163-4.
(175) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593-1598.
(176) For NMR the solvent has to be filtered over basic aluminia first, to avoid decomposition in the NMR tube, due to traces of acid present
(177) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Letters* **1980**, *21*, 3915-18.
(178) De Santos, C.; El-Khateeb, M.; Rege, P.; Tian, K.; Johnson, F. *Biochemistry* **2004**, *43*, 15349-15357.

(179) Bohm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *European Journal of Organic Chemistry* **2000**, 2955-2965.
(180) Böhm, C.; Reiser, O. *Organic Letters* **2001**, *3*, 1315-8.
(181) Evans, D. A.; Woerpel, K. A.; Nosse, B.; Schall, A.; Shinde, Y.; Jezek, E.; Haque, M. M.; Chhor, R. B.; Reiser, O.; Wipf, P.; Jayasuriya, N. *Organic Syntheses* **2006**, *83*, 97-102.
(182) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helvetica Chimica Acta* **1988**, *71*, 1553-65.
(183) Temme, O.; Taj, S. A.; Andersson, P. G. *Journal of Organic Chemistry* **1998**, *63*, 6007-6015.
(184) Mengel, A.; Reiser, O. *Chemical Reviews (Washington, D. C.)* **1999**, *99*, 1191-1223.
(185) Brückner, R. *Reaktionsmechanismen*; 3 ed.; Elsevier: München, 2004.
(186) Bohlmann, F.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry (Elsevier)* **1981**, *20*, 1613-22.
(187) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Boehm, C.; Reiser, O. *Organic Letters* **2003**, *5*, 941-944.
(188) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chemical Reviews* **2004**, *104*, 3371-3403.
(189) Stork, G.; Baine, N. H. *Journal of the American Chemical Society* **1982**, *104*, 2321-3.
(190) Stork, G.; Baine, N. H. *Tetrahedron Letters* **1985**, *26*, 5927-30.
(191) Jenkins, P. R.; Symons, M. C. R.; Booth, S. E.; Swain, C. J. *Tetrahedron Letters* **1992**, *33*, 3543-6.
(192) Stork, G.; Mook, R., Jr. *Tetrahedron Letters* **1986**, *27*, 4529-32.
(193) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Letters* **1986**, *27*, 4525-8.
(194) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Advanced Synthesis & Catalysis* **2005**, *347*, 1869-1874.
(195) I am very grateful to the Degussa AG for the friendly donation.
(196) Sato, Y.; Oketani, H.; Yamada, T.; Singyouchi, K.-I.; Ohtsubo, T.; Kihara, M.; Shibata, H.; Higuti, T. *Journal of Pharmacy and Pharmacology* **1997**, *49*, 1042-1044.
(197) Rybalko, K. S.; Sheichenko, V. I.; Maslova, G. A.; Kiseleva, E. Y.; Gubanov, I. A. *Khimiya Prirodnykh Soedinenii* **1968**, *4*, 251-2.
(198) Mukhametzhanov, M. N.; Abdrakhmanov, O. A.; Adekenov, S. M. *Teoreticheskie Osnovy Pererabotki Mineral'nogo i Organicheskogo Syr'ya* **1976**, *3*, 104-7.
(199) Luche, J.-L. *Journal of the American Chemical Society* **1978**, *100*, 2226-2227.
(200) Nosse, B., University of Regensburg, 2005.
(201) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chemical Reviews (Washington, DC, United States)* **1993**, *93*, 1307-70.
(202) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *Journal of the American Chemical Society* **1981**, *103*, 7690-2.
(203) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694-6.
(204) Tamao, K.; Ishida, N. *Journal of Organometallic Chemistry* **1984**, *269*, C37-C39.
(205) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1995**, 317-37.
(206) Fleming, I. *Chemtracts: Organic Chemistry* **1996**, *9*, 1-64.
(207) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Organic Syntheses* **1990**, *69*, 96-105.
(208) Fleming, I.; Henning, R.; Plaut, H. *Journal of the Chemical Society, Chemical Communications* **1984**, 29-31.
(209) Fleming, I. *International Congress Series* **1979**, *457*, 86-92.
(210) Fleming, I.; Ghosh, S. K. *Studies in Natural Products Chemistry* **1996**, *18*, 229-268.

(211) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *Journal of Organic Chemistry* **1999**, *64*, 6005-6018.
(212) Archibald, S. C.; Barden, D. J.; Bazin, J. F. Y.; Fleming, I.; Foster, C. F.; Mandal, A. K.; Mandal, A. K.; Parker, D.; Takaki, K.; Ware, A. C.; Williams, A. R. B.; Zwicky, A. B. *Organic & Biomolecular Chemistry* **2004**, *2*, 1051-1064.
(213) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Letters* **1987**, *28*, 4229-32.
(214) Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Letters* **1972**, 5369-72.
(215) Whitmore, F. C.; Woodward, G. E. *Organic Syntheses* **1941**, *1*, 159.
(216) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.
(217) Henry, P. M. *Journal of Organic Chemistry* **1971**, *36*, 1886.
(218) Zhang, S.; Zhao, M.; Bai, L.; Hasegawa, T.; Wang, J.; Wang, L.; Xue, H.; Deng, Q.; Xing, F.; Bai, Y.; Sakai, J.-i.; Bai, J.; Koyanagi, R.; Tsukumo, Y.; Kataoka, T.; Nagai, K.; Hirose, K.; Ando, M. *Journal of Natural Products* **2006**, *69*, 1425-1428.
(219) Dai, J.; Yang, L.; Sakai, J.-i.; Ando, M. *Journal of Molecular Catalysis B: Enzymatic* **2005**, *33*, 87-91.
(220) Zhang, S.; Wang, J.; Xue, H.; Deng, Q.; Xing, F.; Ando, M. *Journal of Natural Products* **2002**, *65*, 1927-1929.
(221) I thank Prof. Dr. G. Cravotto, Dipartimento di Scienza and Tecnologia del Farmaco, Università di Torino, for a sample of Cynaropicrin, isolated from its natural source.
(222) Ishihara, M.; Masatsuga, Y.; Uneyama, K. *Tetrahedron* **1992**, *48*, 10265-76.
(223) Ishihara, M.; Tsuneya, T.; Shiga, M.; Uneyama, K. *Phytochemistry* **1991**, *30*, 563-6.
(224) Barton, D. H. R.; McCombie, S. W. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* **1975**, 1574-85.
(225) Barton, D. H. R.; Crich, D. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* **1986**, 1603-11.
(226) Dolan, S. C.; MacMillan, J. *Journal of the Chemical Society, Chemical Communications* **1985**, 1588-9.
(227) Barton, D. H. R.; Crich, D. *Tetrahedron Letters* **1985**, *26*, 757-60.
(228) Barton, D. H. R.; Crich, D. *Journal of the Chemical Society, Chemical Communications* **1984**, 774-5.
(229) Barton, D. H. R.; Hartwig, W.; Motherwell, R. S. H.; Motherwell, W. B.; Stange, A. *Tetrahedron Letters* **1982**, *23*, 2019-22.
(230) Nowak, A.; Schaumann, E. *Synthesis* **1998**, 899-904.
(231) Nace, H. R. *Org. Reactions (Arthur C. Cope, editor, John Wiley, Inc.)* **1962**, *12*, 57-100.
(232) Zard, S. Z. *Angewandte Chemie, International Edition in English* **1997**, *36*, 673-685.
(233) Khapli, S.; Dey, S.; Mal, D. *Journal of the Indian Institute of Science* **2001**, *81*, 461-476.
(234) Strahl, B. D.; Allis, C. D. *Nature* **2000**, *403*, 41-45.
(235) Jenuwein, T.; Allis, C. D. *Science* **2001**, *293*, 1074-1080.
(236) Cosgrove, M. S.; Wolberger, C. *Biochemistry and Cell Biology* **2005**, *83*, 468-476.
(237) Sun, K.; Xu, K. *Shengming Kexue Yanjiu* **2004**, *8*, 102-105.
(238) Kortenhorst Madeleine, S. Q.; Carducci Michael, A.; Shabbeer, S. *Cellular oncology* **2006**, *28*, 191-222.
(239) Schaefer, S.; Jung, M. *Archiv der Pharmazie (Weinheim, Germany)* **2005**, *338*, 347-357.
(240) Santos-Rosa, H.; Caldas, C. *European Journal of Cancer* **2005**, *41*, 2381-2402.
(241) Gray, S. G.; De Meyts, P. *Diabetes/Metabolism Research and Reviews* **2005**, *21*, 416-433.

(242) Biel, M.; Kretsovali, A.; Karatzali, E.; Papamatheakis, J.; Giannis, A. *Angewandte Chemie, International Edition* **2004**, *43*, 3974-3976.
(243) Rojas, J. R.; Trievel, R. C.; Zhou, J.; Mo, Y.; Li, X.; Berger, S. L.; Allis, C. D.; Marmorstein, R. *Nature (London)* **1999**, *401*, 93-98.
(244) Trievel, R. C.; Rojas, J. R.; Sterner, D. E.; Venkataramani, R. N.; Wang, L.; Zhou, J.; Allis, C. D.; Berger, S. L.; Marmorstein, R. *Proceedings of the National Academy of Sciences of the United States of America* **1999**, *96*, 8931-8936.
(245) Tanner, K. G.; Trievel, R. C.; Kuo, M.-H.; Howard, R. M.; Berger, S. L.; Allis, C. D.; Marmorstein, R.; Denu, J. M. *Journal of Biological Chemistry* **1999**, *274*, 18157-18160.
(246) He, G.; Matsuura, H.; Yoshihara, T. *Phytochemistry (Elsevier)* **2004**, *65*, 2803-2807.
(247) Thiele, C. M.; Marx, A.; Berger, R.; Fischer, J.; Biel, M.; Giannis, A. *Angewandte Chemie, International Edition* **2006**, *45*, 4455-4460.
(248) De Azevedo, M. B. M.; Murta, M. M.; Greene, A. E. *Journal of Organic Chemistry* **1992**, *57*, 4567-9.
(249) Li, K.; Ran, L.; Yu, Y.-H.; Tang, Y. *Journal of Organic Chemistry* **2004**, *69*, 3986-3989.
(250) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *Journal of Organic Chemistry* **1989**, *54*, 3738-40.
(251) L3126 Lipase from porcine pancreas, Type II, (100-400 units/mg protein (using olive oil (30 min incubation)), 30-90 units/mg protein (using triacetin), purchased from Sigma-Aldrich.
(252) CP Chiralsil-Dex CB, 25mx0.25mmx0.25μm; 5min 50°C, 3K/min, T(i) = 250°C, T(d)= 250°C RT 29.9 min, 30.0 min
(253) Love, B. E.; Jones, E. G. *Journal of Organic Chemistry* **1999**, *64*, 3755-3756.
(254) 2-bromo-trimethylallylsilane was purchased from Aldrich

CURRICULUM VITAE

Andreas Schall

Personal Data

* October 8th, 1977, Roding, Germany

Institute of Organic Chemistry
University of Regensburg
Universitätsstr. 31
D-93053 Regensburg, Germany
Phone: +49-941-2902205 Fax: +49-941-943-4121
e-Mail: andreas.schall@yahoo.de

Education

03/2006 - 05/2006	**Research Exchange** (with Prof. Dr. P. R. Hanson), Department of Chemistry, University of Kansas, USA
since 10/2003	**PhD Thesis** in Chemistry (with Prof. Dr. O. Reiser), Institute of Organic Chemistry, University of Regensburg, Germany "*Studies Towards the Total Synthesis of Biological Active γ-Butyrolactones"*
09/2003	**Diploma** in Chemistry (final mark 1.2)*
01/2003 - 09/2003	**Diploma Thesis** (with Prof. Dr. O. Reiser), Institute of Organic Chemistry, University of Regensburg, Germany "*Investigations on the Total Synthesis of Xanthatin*"
04/2001 - 12/2002	**Study of Chemistry**, University of Regensburg, Germany
01/2001 - 03/2001	**Research Project** (with Prof. Dr. C. T. Imrie), Institute of Organic Chemistry, University of Aberdeen, Scotland "*Synthesis and Analysis of Polymer Liquid Crystal Electrolytes"*
08/2000 - 03/2001	**Study of Chemistry**, University of Aberdeen, Scotland
08/2000	**Intermediate Exam** (final mark: 1.3)*
11/1998 - 08/2000	**Student of General Chemistry**, University of Regensburg
09/1988 - 06/1997	**Joseph von Fraunhofer Gymnasium**, Cham, Germany High School Graduation (final mark: 2.2)*

* German system: 1.0 = outstanding, 4.0 = passed

Professional Experience & Awards

11/2001 - 12/2002	**Internships** at the Institutes of Physical, Inorganic and Organic Chemistry, University of Regensburg, Germany
08/2001 - 10/2001	**Summer Research Intern** (with Dr. S. Weigand), Bayer AG, Pharma Research, Wuppertal, Germany
02/1997	**Regional Competition** "Jugend Forscht", 3rd prize, Neumarkt, Germany

Scholarships

07/2004 - 09/2006	"*Fonds der Chemischen Industrie*" PhD-Scholarship
06/2006 - 08/2006	Tutor in the DAAD-RISE program
03/2006 - 05/2006	DAAD-Exchange Scholarship
08/2000 - 03/2000	Erasmus/Sokrates-Exchange Scholarship

Languages

German (native) English (fluently)

Additional Activities

Running (marathon) Kyokushinkai Karate (EKO, 6th Kyu)

Scuba Diving (PADI, OWD 2003) Ballroom dancing (Gold level 2006)

German Chemical Society (student membership)

Presentations

1) Schall, A.; Jezek, E.; Nosse, B.; Reiser, O., Radical cyclization and RCM as keysteps for the stereoselective synthesis of bi- and tricyclic sesquiterpene lactones. *Schering Chemistry Workshop*, **2005**, Berlin and *Summerschool Medicinal Chemistry*, **2005**, Shanghai.

2) Schall, A.; Jezek, E.; Reiser, O., Stereoselective radical cyclizations towards the synthesis of Xanthatin. *16. Irseer Naturstofftage*, **2004**, Irsee.

3) Bandichhor, R.; Jezek, E.; Nosse, B.; Schall, A.; Reiser, O., Radical cyclizations on anti 2,3-di-substituted γ-butyrolactone derivatives. *GDCH-Jahrestagung Chemie*, **2003**, Munich.

Publications

1) Kalidindi, S.; Joeng, W. B.; Schall, A.; Chhor, R. B.; Nosse, B.; Reiser, O., First enantioselective total synthesis of arglabin. *Angewandte Chemie*, **2007**, in print.
2) Schall, A.; Reiser, O., 25.6.7 Synthesis by formylation of arylpalladium intermediates. *Science of Synthesis*, Thieme: Stuttgart, **2007**, Vol. 25, 655-665.
3) Schall, A.; Reiser, O., 25.6.6 Synthesis by formylation of arene-hydrogen bonds. *Science of Synthesis*, Thieme: Stuttgart, **2007**, Vol. 25, 605-653.
4) Schall, A.; Reiser, O., 25.6.5 Synthesis by formylation of arylmetal reagents. *Science of Synthesis*, Thieme: Stuttgart, **2007**, Vol. 25, 585-604.
5) Evans, D. A.; Woerpel, K. A.; Nosse, B.; Schall, A.; Shinde, Y.; Jezek, E.; Haque, M. M.; Chhor, R. B.; Reiser, O., Synthesis of (-)-(*S,S*)-bis(4-Isopropxyoxazoline). *Organic Synthesis* **2006**, (83), 97-99.
6) Jezek, E.; Schall, A.; Kreitmeier, P.; Reiser, O., Radical cyclizations as key step for the stereoselective synthesis of bi- and tricyclic sesquiterpene lactones. *Synlett* **2005**, (6), 915-918.
   - Highlighted in *Synfacts* **2005**, (0), 21-21.
7 Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O., Optimization of ring-closing metathesis: Inert gas sparging and microwave irradiation. *Advanced Synthesis & Catalysis* **2005,** 347, (14), 1869-1874.
8) Lin, H.; Schall, A.; Reiser, O., Cyclization reactions of vinyl radicals via 1,6-H-atom transfer: Facile access to 2,3-disubstituted dihydrobenzo-furans. *Synlett* **2005**, (17), 2603-2606.
9) Schall, A.; Reiser, O., Tandem epoxidation/stereoselective intramolecular [4+3] cycloaddition reaction. *Chemtracts* **2004,** 17, (8), 436-441.

Professional References

Prof. Dr. Oliver Reiser
Institute of Organic Chemistry
University of Regensburg
Universitätsstr. 31
D-93053 Regensburg, Germany
oliver.reiser@chemie.uni-regensburg.de

Dr. Stefan Weigand
Senior Research Scientist Chemistry
Roche Diagnostics GmbH
D-82372 Penzberg, Germany
stefan.weigand@roche.com

Prof. Dr. Paul R. Hanson
Department of Chemistry
University of Kansas
1251 Wescoe Hall Dr.
Lawrence, KS 66045-7582
phanson@ku.edu

Acknowledgement

"Science is facts;
just as houses are made of stones,
so is science made of facts;
but a pile of stones is not a house
and a collection of facts
is not necessarily science."

Henri Poincare (1854-1912)

University of Regensburg:

First I would like to express my special thanks to Prof. Dr. Oliver Reiser for offering me the possibility to work on this challenging topic and giving me the chance for a fantastic stay at the University of Kansas. Also for his continuous support in publishing and his discussions on chemical problems I am deeply grateful.

For the helpful and cooperative environment in and outside the institute I have to thank all former and current members of the Reiser group. I do not want to forget all the barbecues and beer/cocktail sessions, Dult- and brewery visits organized by Hans, Florian, Tobias, Alex and Michael. I had a lot of fun and interesting discussions with Gudrun, Valerio, Markus, Dominic and Sinduh and Anu concerning all thinkable topics, thanks for that. Special thanks to my lab colleagues Martin Schanderl, Inga Prediger and Srinivas Kalidindi not only for their colleagueship, but also for the good lab atmosphere and all the discussions on chemistry and far beyond. Kirsten´s doors (office and lab) were always open for discussion or questions on all topics, thank you for that.

Very helpful hands were offered by Georg Adolin, Klaus Döring, Andrea Roithmeier and Robert Tomahogh with supplying, searching and synthesis of compounds, measurements of HPLC, always filled nitrogen cans and a never empty coke-fridge.

I am also very grateful to Dr. Peter Kreitmeier for his patience while dealing with all my problems concerning computers, lab equipment, chemistry and much more.

For outstanding proof reading and her brilliant remarks, I am very grateful to Sabine, who had a hard time dealing with my pages.

The full characterization of all compounds was highly supported by the central analytic department of the University of Regensburg:

Dr. Thomas Burgemeister, Annette Schramm, Fritz Kastner, Georgina Stühler from the NMR-department did a great job on solving even the most difficult NMR-problems and I have to thank them a lot.

The mass spectrometry department of Josef Kiermaier and Wolfgang Söllner sometimes had a hard time measuring all my samples and I am very grateful to each one of them for recording all the desired experiments.
For the method development and measurements of GC and HPLC I have to thank Dr. Rudi Vasold and his team.
The X-Ray analysis was performed by Dr. Manfred Zabel and his colleagues, where I always found open doors for all my questions concerning crystallography.

University of Kansas:
I am very grateful to Prof. Dr. Paul Hanson, for offering me lab space, chemicals and his full support in all questions concering organization, chemistry and much more.
I thank also the whole Hanson group, especially Toby Long, Alan Whitehead and Alan Rolfe for helping me in the labs at KU and beyond, but also for showing me the best bars and restaurants. Shelly and Josh Waetzig not only offered me a ride whenever needed but also became dear friends over time.
Not to forget David Vanderveld and Sarah Neuenswander for their patience with me while using the NMR-services at KU.

For financial support I have to thank the "Fonds der Chemischen Industrie" and the DAAD for offering me scholarships during the time while I was working on these projects.

Writing this thesis was only possible with the full support of my family: Special thanks to my Mum and Dad for their financial and mental contributions during my study and the time working on this thesis: Their steady believe in me always confirmed and encouraged me in all my decisions.

Most of all, I have to thank a very special person: My beloved Caroline for her never ending patience and believe in me. She continuously supported and encouraged me in all my visions and dreams. Only she knows how to make me smile even in hard and bad times. These are only some of the countless reasons, why I love her so much.