Asymmetric methodologies for the construction of 5,7,5- and 6,6,6-tricyclic sesquiterpene lactones towards the synthesis of Arglabin

Dissertation

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To my father, mother, and family.

Index

Abbreviations

abs.	absolute
Ac	Acetyl
AcOH	Acetic acid
AIBN	Azoisobutyronitrile
anhyd.	anhydrous
Ar	Argon
Bn	Benzyl
BnBr	Benzylbromide
BOX	Bisoxazoline
Bu	Butyl
BuLi	Butyllithium
cat.	catalytic amounts
CD	Circular Dichroism
CE	Cotton Effect
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	Diethylazodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
diast.	Diastereomer(s)
DIPA	Diisopropylamine
DMAP	Dimethylaminopyridine
DMDO	Dimethyldioxiranes
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMS	Dimethylsulfide
dr	Diastereomeric ratio
EA	Ethyl Acetate
EDG	Electron Donating Group
EDG	Electron Donating Group
ee	Enantiomeric excess
ent	enantiomer
epi	epimer
eq.	equivalents
Et	Ethyl
EtOH	Ethanol
EWG	Electron Withdrawing Group
GBL	γ-butyrolactone
GL(s)	Guaianolide(s)
h	hour(s)
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass spectroscopy
IR	Infrared Spectroscopy
L.A.	Lewis Acids
LDA	Lithiumdiisopropyl amide
M.S.	Molecular Sieve
M.W.	Microwave irradidation
MAOS	Microwave Assisted Organic Synthesis
*m*CPBA	*meta*-chloroperbenzyoic acids
Me	Methyl
MeI	Methyliodide
MeOH	Methanol
Mes	Mesityl
min	minute(s)
Ms	Methansulfonyl
MS	Mass Spectroscopy
NaHMDS	Sodium-hexamethyldisilazane
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
org.	organic
PCC	Pyridinium Chlorochromate
PE	Petroleum Ether
PG	Protecting Group
PGL(s)	Pseudoguaianolide(s)
Ph	Phenyl

PMB	*para*-methoxybenzyl	TBDMS	*tert*-butyldimethylsilyl
PMBCl	*para*-methoxybenzylchloride	TBDPS	*tert*-butyldiphenylsilyl
PPh_3	Triphenylphosphine	TBME	*tert*-butylmethylether
PPL	Porcine Pancreatine Lipase	^{t}Bu	*tert*-butyl
Prod.	Product(s)	*tert*	tertiary
PTSA	*para*-toluenesulfonicacid	TES	Triethylsilyl
quant.	quantitative	Tf_2O	Trifluoromethanesulfonic
RCM	Ring Closing Metathesis		Anhydride
rt.	room temperature	THP	Tetrahydropyran
S.M.	Starting Material(s)	TMEDA	N,N,N',N'-
sat.	saturated		Tetramethylethylenediamine
sec	secondary	TMS	Trimethylsisly
SLs	Sesquiterpene Lactones	TMSCl	Trimethylsilylchloride
TBAF	Tetrabutylammoniumfluoride		

A. Introduction

1. Anticancer drug discovery

The etymology of cancer is thought to be originated either from *Karcinos* and *Karkinos* in Greek or *Cancrum* in Latin which means crabs. Figure 1 represents the cancer as a crab which permeates and invades the surroundings.[1]

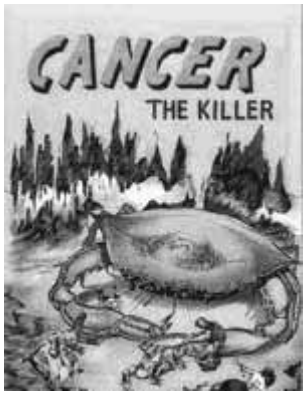

Figure 1. Illustration of cancer as a crab.[1]

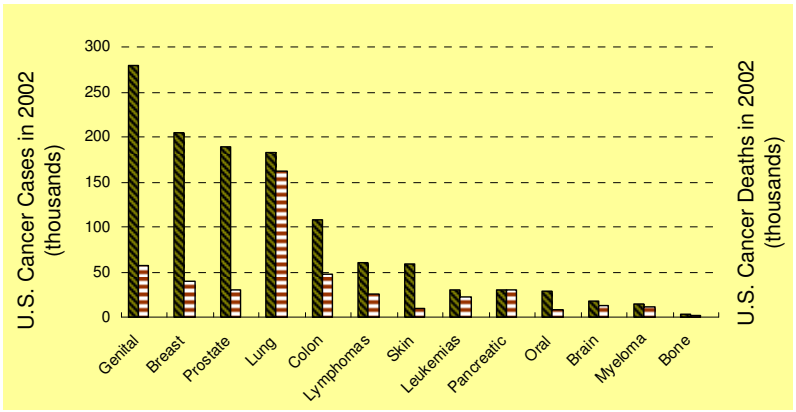

Figure 2. The estimated number of new cancer cases and deaths in the USA in 2002.[2]

Cancer is a genetic disease because it can be traced to alterations within specific genes. Nevertheless, in most cases it is not an inherited disease.[3] Cancer, so-called malignant tumor, tends to metastasize from one organ to others through lymph or blood, whereas a benign one has no ability to metastasize. The causes of cancer are various. There are external factors like tobacco, chemicals, radiations, infectious organisms or internal factors such as inherited mutation, hormones, immune conditions, or mutations that occur from metabolism.[2] Cancer is a major cause of death in the developed countries. According to survey,[2] 1,284,900 of new cancer cases and 555,500 of deaths were estimated in 2002 in the USA. This implies that more than 1,500 people died per day due to cancerous diseases (Figure 2). Since the National Cancer Institute (NCI) began in the 1960's a search for plants with chemotherapeutic effects for cancer, a lot of efforts have been made for the development of new anticancer agents. The research, however, for new drugs is time consuming and expensive. For example, the drug development process typically takes nearly 15 years and costs $500 million. On average, starting from 5,000-10,000 of initial drug candidates, only one will be successfully developed into a drug.[4]

2. The methodological advances of drug development process

The traditional drug development is a sequential process[5] and it consist of discovery and

validation of target, assay development, screening and hits to leads, lead optimization, preclinical tests with animal, clinical trials with human, registration and finally approval. Nowadays several new methodologies allow of getting drug candidates more efficiently leading to cost-reduction and shortening of development time. Genomics, proteomics, and functional genomics enable the identification and validation of targets effectively in an interdisciplinary effort. HTS[6] (High Throughput Screening) helps rapid assay of a large number of compounds on a given target. Computer-aided drug design (CADD) and structure-based drug design (SBDD) give better chances to find lead compounds. QSAR[7] (Quantitative Structure Activity Relationship), which is a tool based on the structural knowledge of a target, helps to predict the activity of new compounds. Combinatorial chemistry has led to large libraries of synthetic compounds for the screening. Upon getting the structural information of a target protein by X-ray crystallography, the computer-aided (*in silico*) virtual screening,[8] such as Docking and Scoring,[9] can help envision the structure of ligand-target complex and the binding affinity. Combining these techniques active compounds can be identified from huge chemical libraries. High bioavailability, metabolic stability (sufficient $t_{1/2}$ allowing only once or twice daily administrations), no significant interaction with existing drugs and low toxicity to the normal cell are needed for drug properties. In recent times *in vitro* ADMET[10] (Absorption, Distribution, Metabolism, Excretion, and Toxicology) is simultaneously considered at the optimization step of lead compounds in order to allow early evaluation of drug-like properties. Nevertheless, although great methodological advances of *de novo* drug development has been accomplished, natural products still play a significant role as lead structures in the drug discovery process[11] not only because they can serve as starting point for diversity oriented synthesis but also because they contain high similarities of gene families with organisms on earth.[12] Among all the available anticancer drugs from the 1940's to 2002, over 60% of them are originated from natural sources.[11] The recent development of anticancer drugs are directed mainly towards target specific properties such as i) signal transduction pathway targets, *e.g.* growth factor receptor tyrosine kinases (RTKs),[13] ii) cell cycle,[14] iii) apoptosis-related,[15] iv) extracellular matrix,[16] v) angiogenesis, vi) metastasis,[17] vii) cell-lifespan (Table 1).

Novel cancer therapies are developed by using these target-specific drugs[18] in different types of cancers. Together with such target-specific drugs, diverse therapeutic methods are also under development. Besides the common cancer therapies such as surgery, radiotherapy, and chemotherapy, new approaches such as biological (immune) therapy,[19] hormone therapy especially for the treatment of prostate, breast and ovarian cancers, and vaccine therapy are used to treat the cancers. Gene therapy[20] is also under development since 1990's through the injection of normal-functioned genes into cancer cell via viral or nonviral vectors as mediators leading the recovery of the genetic defects. Antisense therapy,[21] a kind of gene therapy, is aimed to inhibit the translation of a targeted gene through complementary oligonucleotide binding to target mRNA.

Table 1. Some anticancer agents for novel cancer therapies.[13-15, 18b, 22]

Types of targets	Drugs or candidates	Mode of action
cell signal transduction pathway	Iressa (AstraZeneca)	RTK inhibitor
	Glivec (Novartis)	RTK inhibitor
	Herceptin (Genentech)	RTK inhibitor
	Tarceva (Roche)	EGFR inhibitor
	Erbitux (Merck)	EGFR inhibitor
	R115777(Johnson & Johnson)	FTIs
	SCH66336(Schering-Plough)	FTIs
cell cycle	Cisplatin & Carboplatin	Inhibit the repair of DNA damage
	Efudix (5-FU, Roche)	Preventing cell-division
	Velcade (Jansen)	Proteosome inhibitor
	Camptothecin	Topoisomease inhibitor
	Paclitaxel (Bristol Myers Squibb)	Microtubule inhibitor
apoptosis	Genasense (Genta Inc.)	Bcl-2 antisense oligonucleotide
	Affinitak (Eli Lilly & Co.)	PKC-alpha antisense agent
angiogenesis	Avastin (Genetech)	
	Thalidomide (Celgene)	Inhibition of VEGF
	Batimastat (British Biotech)	Inhibition of VEGF/MMP inhibitor
	Marimastat (British Biotech)	MMP inhibitor
	Endostatin (EntreMed)	Inhibition of VEGF
	Neovastat (Aeterna Lab.)	For treatment of solid tumor

RTK: receptor tyrosine kinase, TKI: tyrosine kinase inhibitor, EGFR: endothelial growth factor receptor, FTI: farnesyl transerase inhibitor, VEGF: vescular endothelial growth factor, MMP: matrix metallo proteinase.

3. FTIs (farnesyl transferase inhibitors) as novel anticancer therapeutic agents

One of the aspects being extensively investigated in anticancer drug development is the intracellular signal transduction pathway. In signal transduction processes, several components such as growth factor, transmembrane receptors, intracellular second messengers and nuclear transcription factors are involved.[13] In cancer cells any of these key components may be altered by oncogenes, leading to dysregulated cell signaling. Ras protein regulated by *ras* oncogene plays an important role in the posttranslational signal transduction cascade. Mediated by the enzyme farnesyltransferase (FTase), Ras is modified *via* farnesylation at its C-terminus to become a pivotal switch during the signal transduction cascade. Therefore the inhibition of FTase may be a target for anticancer drug.

The FTase is a heterodimer comprised of two subunits, 48 kD (α) and 46 kD (β). These α and β subunits look like a helical hairpin and barrel respectively. They form two active binding

sites, one for the COOH-terminal of CaaX peptide (C: cystein, a: aliphatic amino acids, X: methionine or serine) and another for FPP (farnesyl pyrophosphate). A single Zn ion binds to the β-subunit (Figure 3B). The one cleft runs parallel to the rim of the α-α barrel near the subunit interface (Figure 3A). This active site is for the binding of C-terminus of CaaX peptide. Another pocket is considered for the binding site for the FPP which is nearly orthogonal to the peptide binding site. This hydrophobic active site shows 15-16 Å in diameter and 14 Å of depth (Figure 3C). If the C-terminus of the FPP binds at the bottom of the pocket, the length of FPP is so fair that the diphosphate moiety could well interact CaaX moiety.[23]

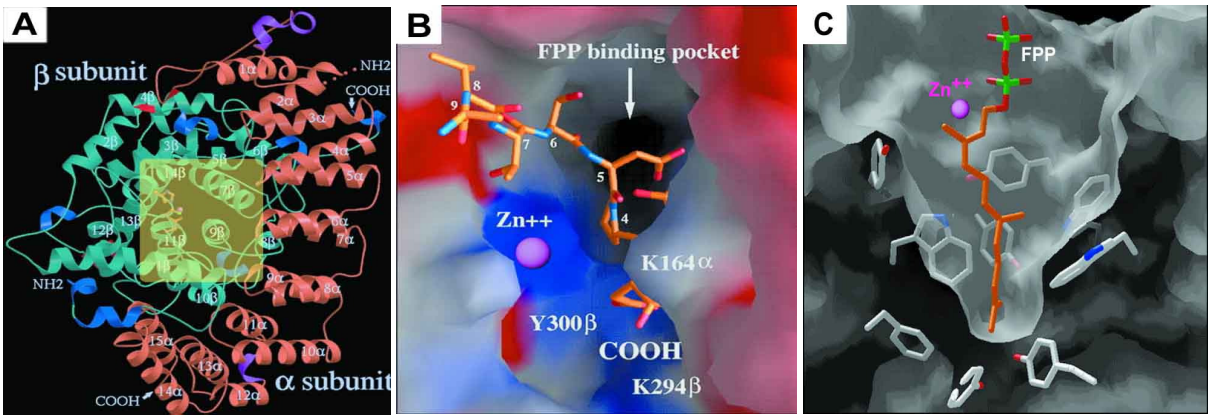

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Figure 3. (A) Crystal structure of the heterodimeric rat FTase, sharing 97% identity with the human enzyme. (B) The expanded diagram at highlighted region in Fig 3A; The COOH-terminus with the six residues of the nonapeptide (Ala^9-Val^8-Thr^7-Ser^6-Asp^5-Pro^4) are visible, which is bound in one cleft being parallel to the rim of the α-α barrel subunit near the subunit interface. (C) The putative FPP binding pocket (hydrophobic due to 10 highly conserved aromatic residues) is nearly orthogonal to the peptide binding site.

Upon binding of the growth factor to the extracellular domain of the corresponding receptor such as receptor tyrosine kinase (RTK), the dimerization of the receptor and the transphosphorylation on the tyrosine residue in the cytoplasmic part occurs subsequently. This phosphorylation leads to the binding of an adapter protein Grb2 (*growth* factor *receptor binding*), and to subsequent translocation of SOS (*son of sevenless*) on Grb2. The farnesylated Ras at the sulfur atom of Cys is transformed subsequently at the C-terminus by the enzymes endoprotease and methyltransferase. It was known that such lipophilic attachment of the C-terminus of the Ras protein not only by farnesylation but also by the palmitoylation and the myristoylation at the N-terminus can contribute to the hydrophobic interaction with the inner cell membrane. As a consequence the farnesylated Ras translocates itself on the inner cell-membrane and interacts effectively with the Grb2-Sos complex

(Figure 4). The GDP-bound inactive Ras is phosphorylated by the action of GEFs (guanine nucleotide exchange factors) into the GTP-bound active state. The GTP-bound Ras interacts with downstream effectors such as Raf and the subsequent downstream MAPK (Mitogen Activated Protein Kinase) signal transduction cascade causes the transcription, replication of DNA, the expression of genes and the proliferation of cells. At the end of signal transduction pathway, the GTP-Ras is hydrolyzed into the inactive GDP-bound Ras by GAP (GTPase activating protein).[24] Caused by point mutation of the corresponding *ras* gene, the unregulated GTPase activates the Ras protein permanently. This continuous stimulation results in the overexpression of mutated genes and overproliferation of the tumor cells.

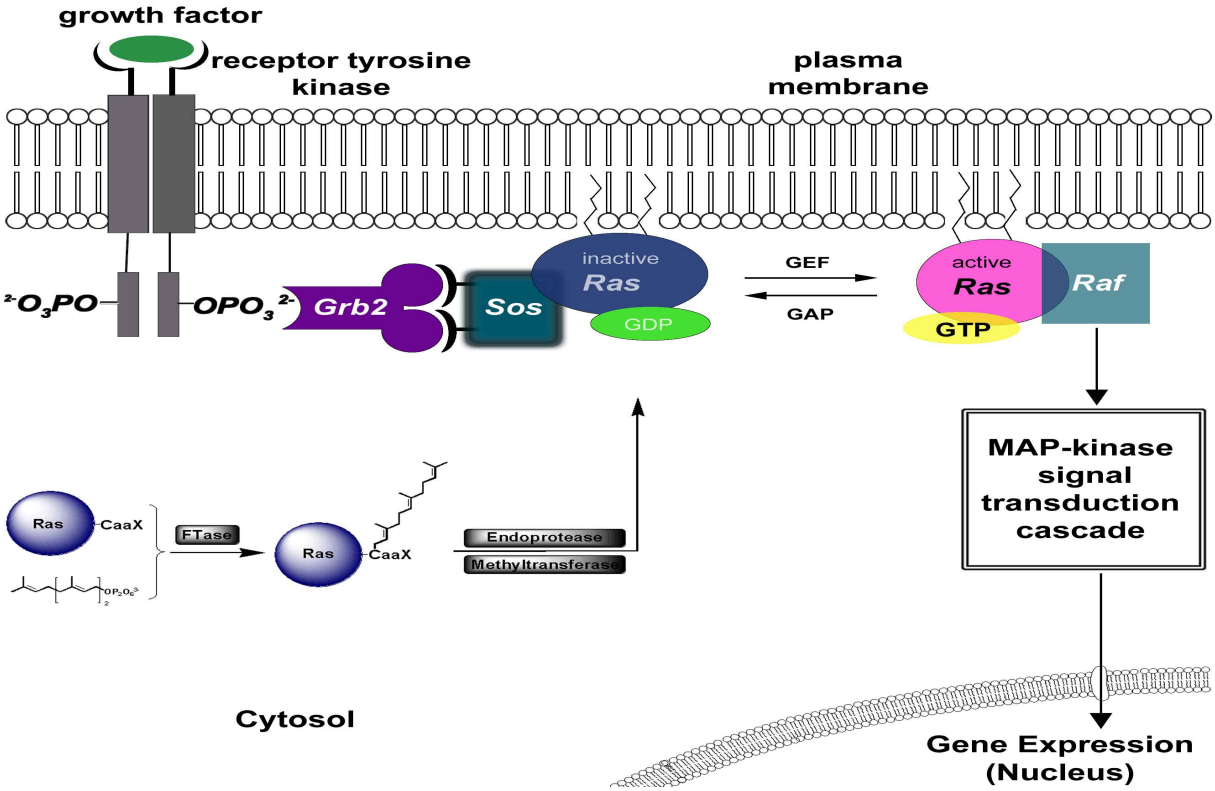
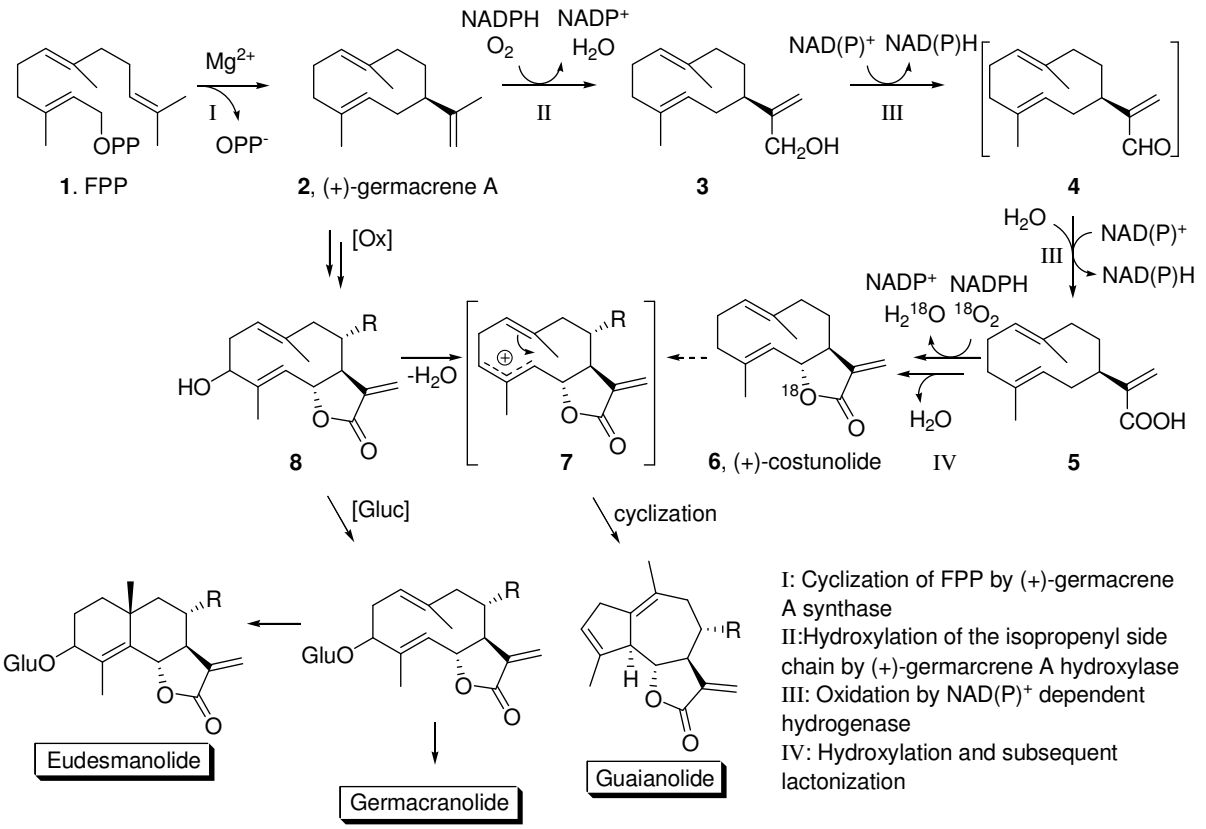


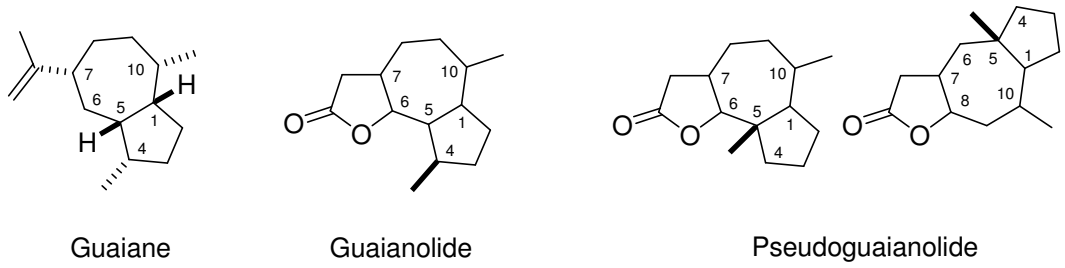
Figure 4. The post-translational modification of Ras and signal transduction pathway through MAP (Mitogen Activated Protein) kinase module.[25] (Modified from the reference)

Different kinds of FTIs (farnesyl transferase inhibitors) such as farnesyl diphosphate analogues, CaaX tetrapeptides, CaaX peptidomimetics, non-peptide CaaX, peptidomimetics, and natural products have been developed and clinically tested.[13,26] A natural product Arglabin (**96**) was tested in Phase II showing good efficiency of even monochemotherapy.[27] Arglabin belongs to the sesquiterpene lactones (SLs), guaiane lactones (guaianolide). Being specifically to the characteristic constituents of the *Asteraceae* and *Compositae*, guaianolides are biogenetically synthesized from *trans* farnesyl pyrophosphate **1** (Scheme 1).[28]



Scheme 1. The proposed biosynthesis of guaianolides, eudesmanolides and germacranolides in sprouts of chicory (*Cichorium intybus*).[28]

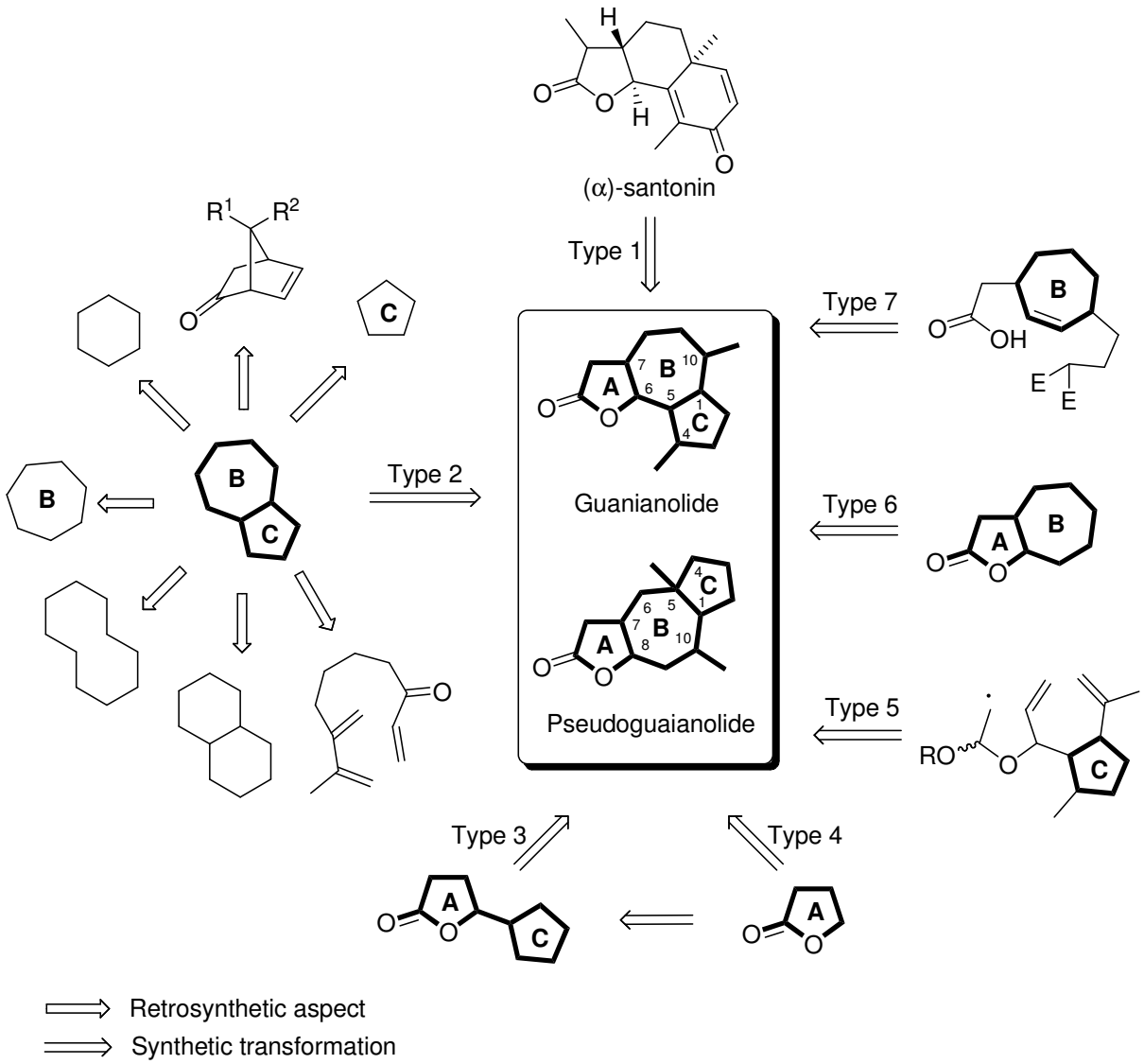
Guaianolides and pseudoguaianolides are composed with 5,7,5-tricyclic system. Since the guaianolides have methyl group in 4-position, while the pseudoguaianolides contain quaternary carbon at the 5-position (Scheme 2), they are separately classified.[29]



Scheme 2. The skeletal difference between guaianolide and pseudoguaianolide.

With only a few exceptions, guaianolides generally contain a 1,5-*cis* fused hydroazulene skeleton, for the cases in which there is no sp^2 hybridization at 1-C. Moreover the γ-butyrolactone ring is *trans* annulated at C-6 and C-7 in approximately 85% of all known guaianolides.[39] Many guaianolides with anti-tumor[30] and cytotoxic[31] activities have been reported.

4. The synthetic approaches towards guaianolides and pseudoguaianolides

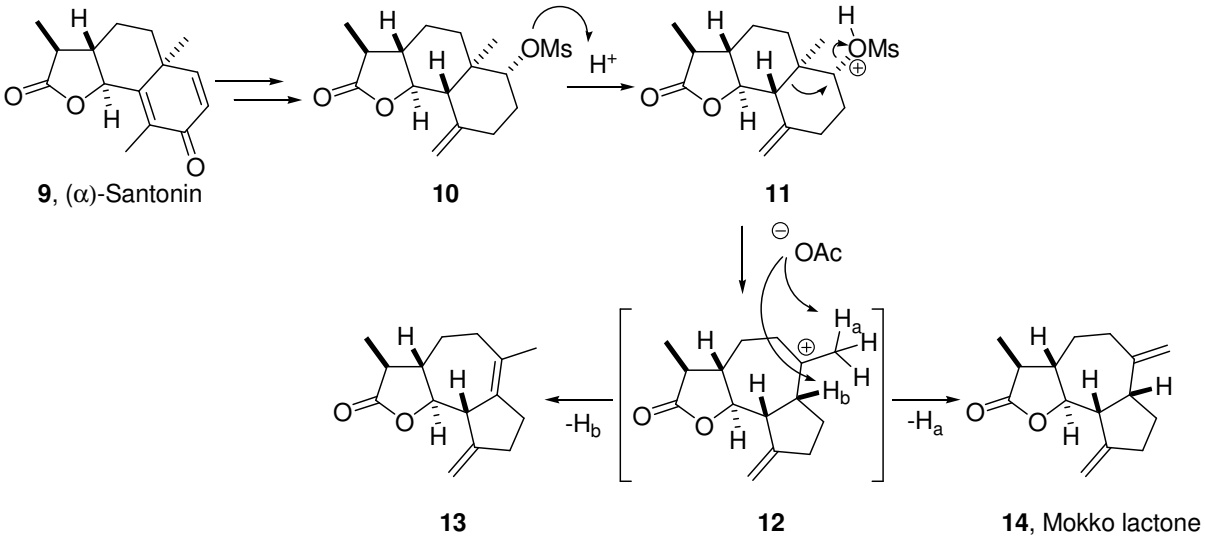


Scheme 3. Synthetic approaches towards guaianolide and pseudoguaianolide.

Largely, the synthetic approaches towards guaianolides and pseudoguaianolides can be classified into 7 types as shown in Scheme 3. A classical and well established method starts from (α)-Santonin, which is readily obtained naturally, or synthetically, by using a photochemical rearrangement[32] or a solvolytic rearrangement[33] of the 5,6,6-tricyclic system into the 5,7,5-tricyclic system (Type 1). The second approach is achieved by the formation of γ-butyrolactone moiety from hydroazulene skeleton. This type of approach was already explored by *Heathcock et al.*[34] The formation of the B-ring last from already containing rings AC substrates stands for type 3. Type 4 involves the concerted formation of B and C ring from γ-butyrolactone (ring A). The type 5 is the concerted A and B ring formation from highly functionalized C-ring *via* radical cyclization. In type 6, the C ring is formed

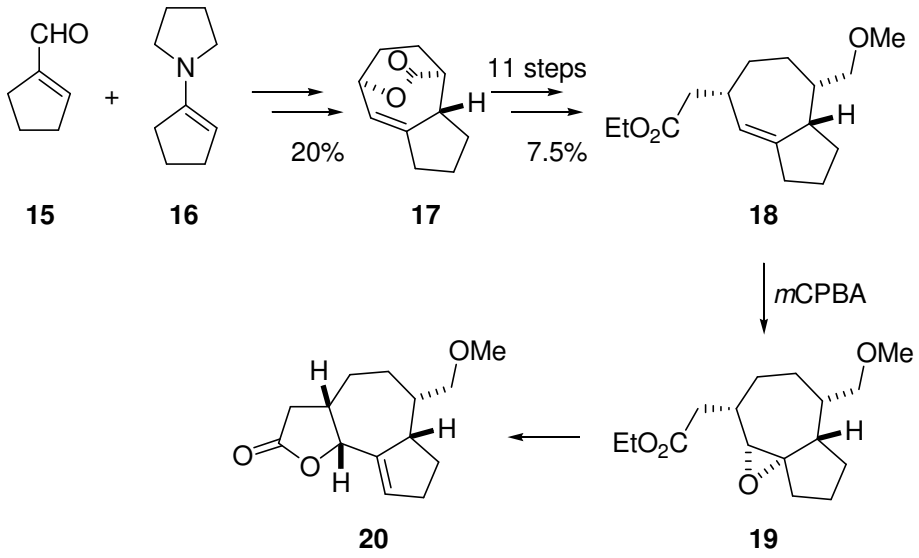
subsequently after the formation of A and B ring. Concerted A and C rings formation from 7-membered B-ring represents type 7 approach.

As an example of type 1, a photochemical rearrangement can promote the transformation of the 5,6,6-tricyclic system into the 5,7,5-tricyclic skeleton. *Yuuya et al.*[33a] reported the synthesis of guaianolide **13** and Mokko lactone (**14**) *via* solvolytic rearrangement of the cationic intermediate **12** which is supposed to be an intermediate of the biosynthesis (Scheme 4).



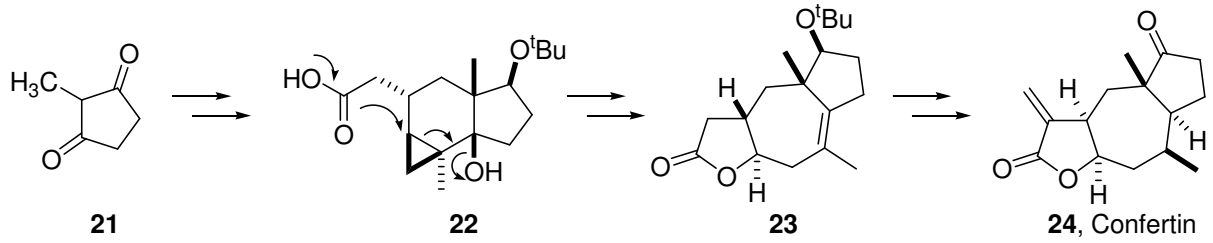
Scheme 4. Guaianolide synthesis from (α)-santonin *via* solvolytic rearrangement by *Yuuya et al.*[33a]

The most extensively developed method is the type 2 strategy using the B-C ring fused hydroazulene as a prerequisite building block. The synthesis of the 6,7-*cis* ring fused guaianolide **20** was reported by *Metz et al.*[35] They used hydroazulene **17**[36] containing a carboxylic ester bridge as key intermediate which is prepared from 1-cyclopenten carbaldehyde (**15**) and cyclopentenyl pyrollidine **16** in 20% yield (Scheme 5). Upon epoxidation of olefine **18** using *m*CPBA, **19** was obtained as 2 diastereomers (α:β=1.7:1), which was further transformed into **20** (18% yield).



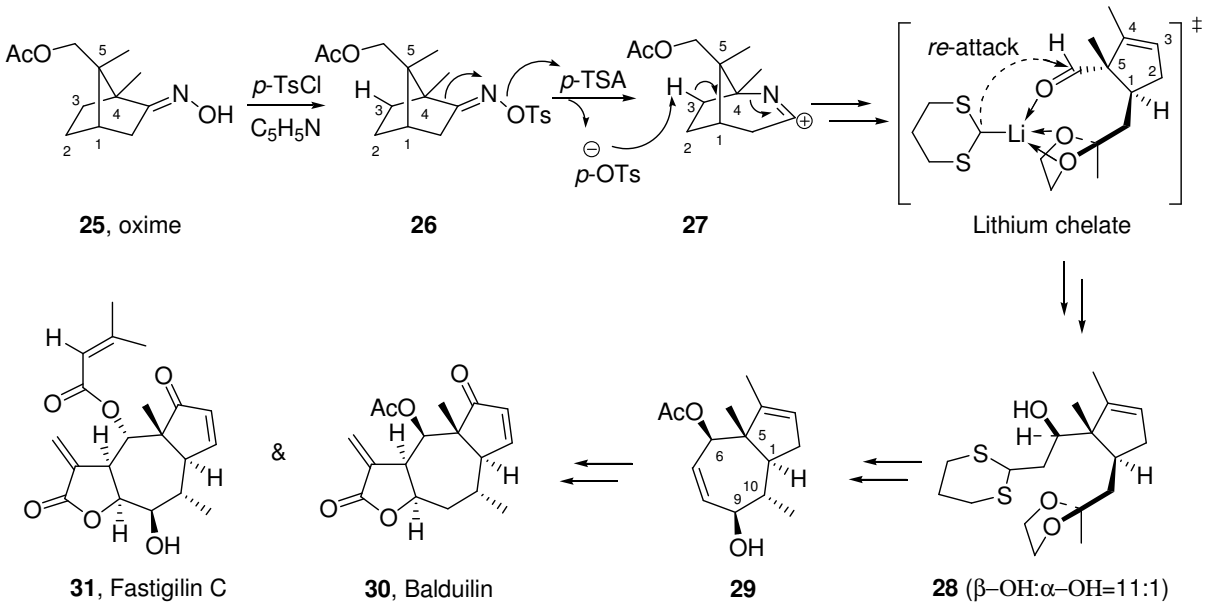
Scheme 5. Synthetic methodology for guaianolide **20** applied by *Metz et al.*[35]

The pseudoguaianolide Confertin (**24**) was synthesized by *Marschall et al.*[37] from 2-methyl-1,3-cyclopentadione (**21**) to give the corresponding 3,6,5-tricyclic intermediate **22** through a *Simmons-Smith* reaction (Scheme 6). The intermediate **22** was rearranged into hydroazulene lactone **23** upon treatment with aqueous perchloric acid as key step. Herein, the 5,7,5-tricyclic skeleton was achieved by concerted A and B ring formation.



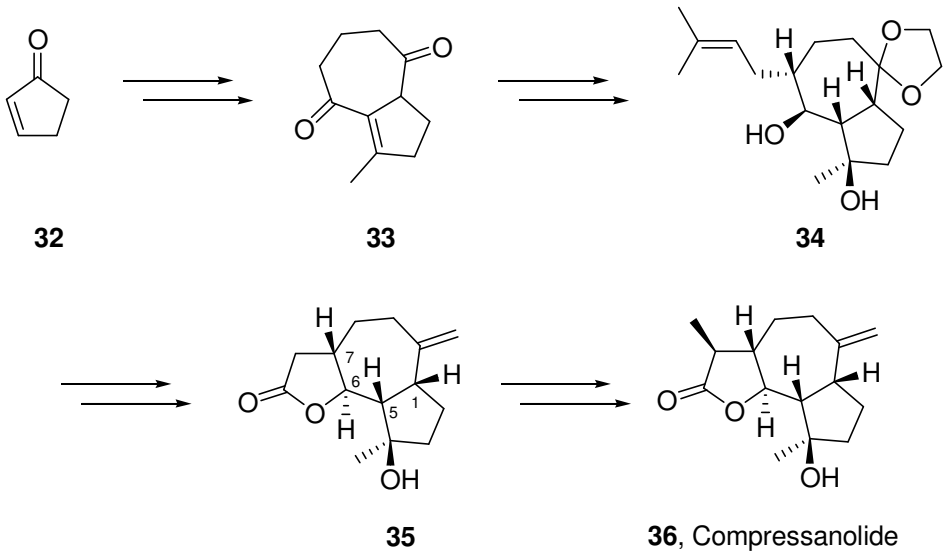
Scheme 6. The synthesis of Confertin (**24**) from **21** reported by *Marschall et al.*[37]

Lansbury et al.[38] synthesized Balduilin (**30**) and Fastigilin C (**31**) respectively. Fastigilin C (**31**) is a highly bioactive compounds due to three electrophilic α, β-unsaturated double bonds for trapping sulfhydryl enzymes. For the synthesis of **30** and **31**, the hydroazulene **29** was used as a key intermediate. **29** is readily prepared in an overall yield of 10% in 15 steps *via* a *Beckman* rearrangement of 9-acetoxycamphor derived oxime **25** and subsequent intramolecular aldol cyclization (Scheme 7). The highly diastereoselective (*dr*=11:1) nucleophilic addition of dithiane to the aldehyde group occurred predominantly from the *re*-face due to the rigid lithium chelate depicted in the transition state.



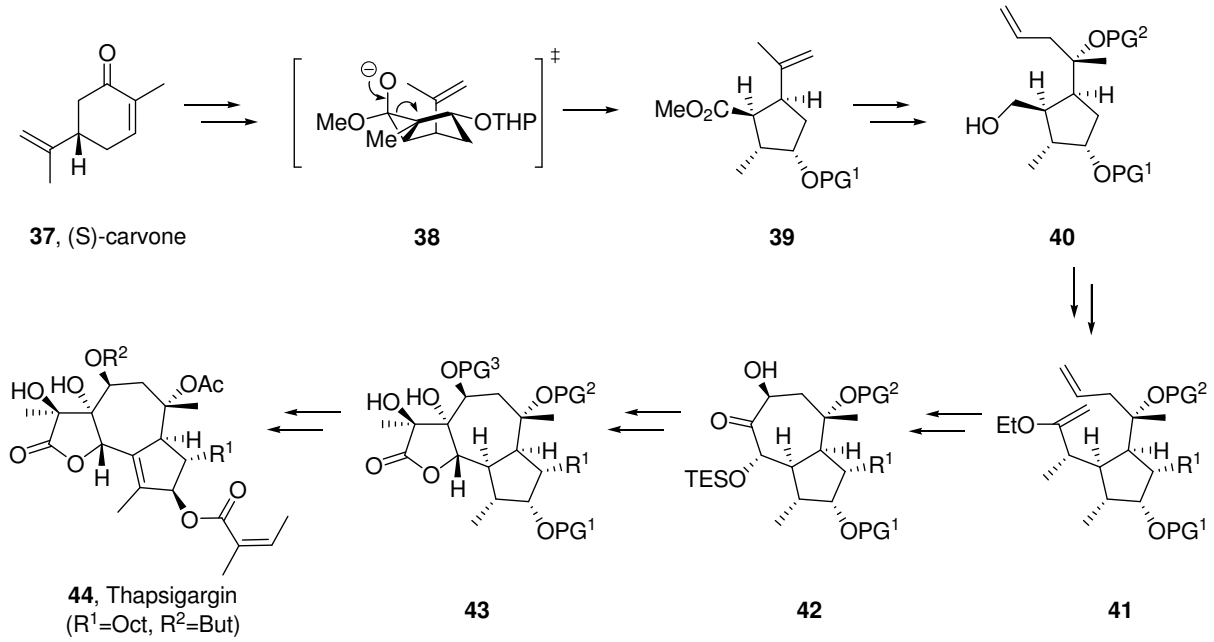
Scheme 7. Synthesis of Balduilin (**30**) and Fastigilin C (**31**) by *Lansbury et al.*[38] via Beckman rearrangement of oxime **25**.

Devreese et al.[39] synthesized Compressanolide (**36**) from diketohydroazulene **33** which is readily available from **32**.[40] The resulted guaianolide **35** contains a 1,5-*cis* hydroazulene ring and a 6,7-*trans* fused γ-butyrolactone ring as like most of guaianolides derived from nature. Over the 6 steps the guaianolide **35** was achieved to synthesize in 9% yield from **33** (Scheme 8).



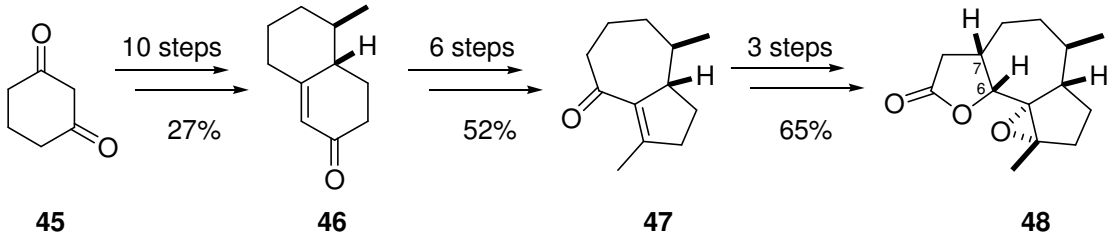
Scheme 8. Compressanolide (**36**) synthesis from diketohydroazulene (**33**) by *Devreese et al.*[39]

Ley et al.[41] synthesized thapsigargin analogues **43** from highly functionalized cyclopentane **39** which is synthesized *via* a *Favorskii* rearrangement of (S)-carvone (**37**). **39** was further transformed into **41**, and RCM using Grubbs (II) catalyst led to **42** and **43** as precursor of **44**. The synthesis took 23 steps up to **43** in 11% yield overall. Just 5 steps of purification are needed totally. In addition, this synthetic approach was amenable for scale-up, giving up to 30g of **43**.



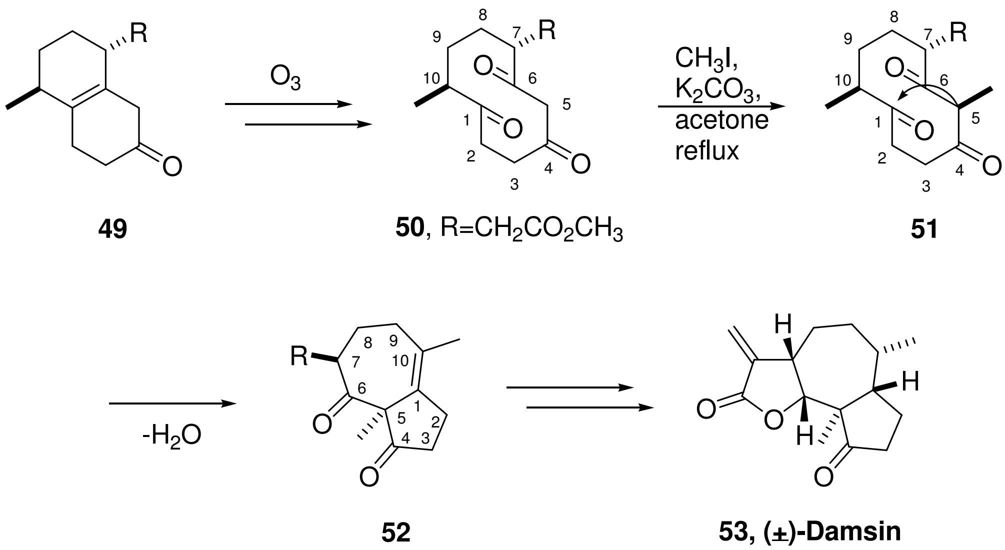
Scheme 9. The synthesis of Thapsigargin analogues (**43**) *via Favorskii* rearrangement and RCM established by *Ley et al.*[41]

The synthesis of 6,7-*cis*-annulated guaianolide **48** was reported by *Posner et al*[42] starting from 1,3-cyclohexanedione (**45**) *via* 19 steps in 8% overall yield. Key steps are the formation of decalin moiety **46** and solvolytic rearrangement into hydroazulene **47** (Scheme 10).



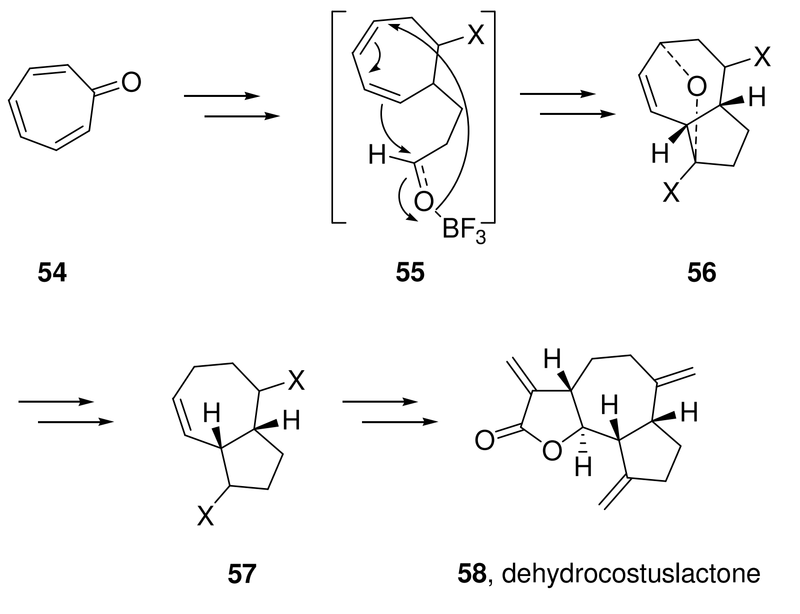
Scheme 10. Total synthesis of 4,5-epoxyosmitopsin analogue (**48**) by *Posner et al.*[42]

Kretchmer R. A. synthesized pseudoguaianolide (±)-Damsin (**53**) using hydroazulene **52** which is prepared from [4.4.0] bicyclic compound **49**. Ozonolysis of **49** afforded **50** and the transannulation of **51** gave intermediate **52** in 63% yield as 2:1 (β:α-R) mixture (Scheme 11).[43]



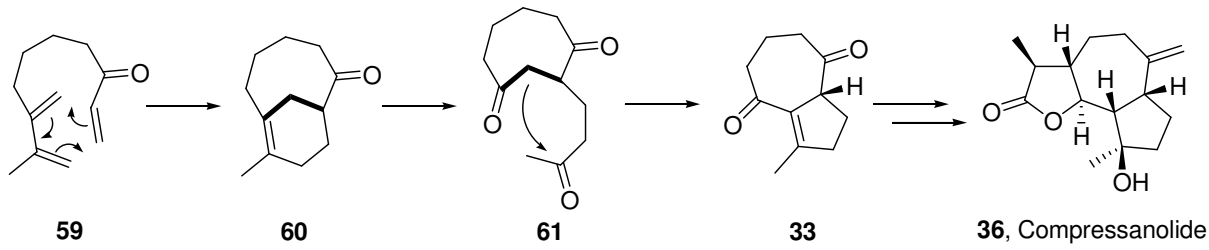
Scheme 11. Formation of hydroazulene **52** from hydronaphthalene **49** *via* transannular cyclization as key step by *Kretchmer R. A.*[43]

Rigby et al. synthesized (±)-dehydrocostuslactone **58**,[44] (±)-Grosshemin (**94**),[45] and (±)-Estafiatin ((±)-**80**)[45] from 2,4,6-cycloheptatrien-1-one (tropone, **54**) *via* Lewis acid mediated cyclization as key step (Scheme 12).



Scheme 12. Total synthesis of **58** from tropone **54** *via* $BF_3 \cdot Et_2O$ mediated cyclization, *Rigby et al.*[44]

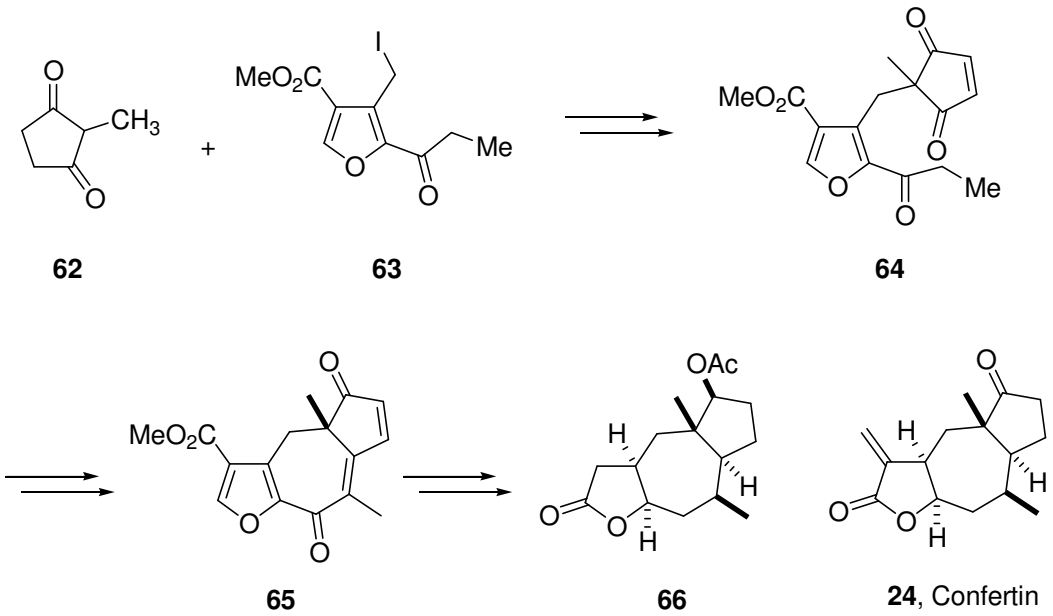
Acyclic triene **59** underwent cycloaddition to give the corresponding [5.3.1]-bicyclic compound **60**. **60** was subsequently transformed into the hydroazulene **33**, being the same building block as used by *Devreese et al.*[39] (Scheme 8) and in the *Vandewalle's* Compressanolide (**36**) synthesis,[46] *via* ozonolysis and intramolecular aldol cyclization reaction of **61** (Scheme 13).



59 **60** **61** **33** **36**, Compressanolide

Scheme 13. Intramolecular *Diels-Alder* reaction mediated guaianenolide synthesis reported by *Gwaltney et al.*[47]

With respect to type 3, *Schultz et al.*[48] introduced a 7-membered ring annulation using an intramolecular aldol reaction and subsequent dehydration of furan trione **64** towards the synthesis of (±)-Confertin (**24**). The precursor **66** was prepared in 10 steps from **62** and **63** (Scheme 14).



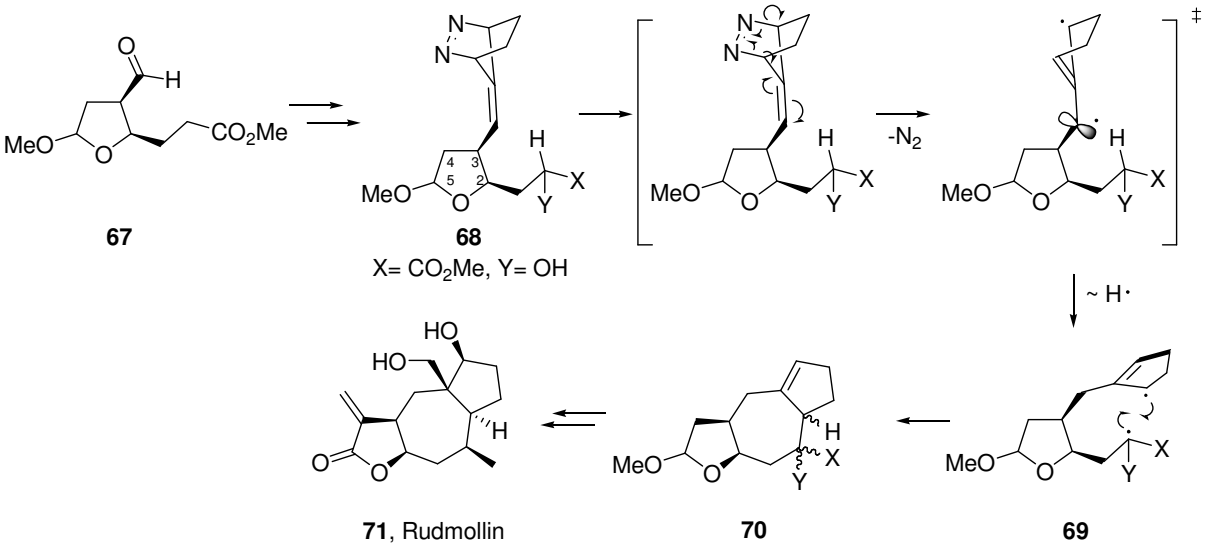
62 **63** **64**

65 **66** **24**, Confertin

Scheme 14. The synthesis of pseudoguaianolide analogue **66** by *Schultz et al.*[48]

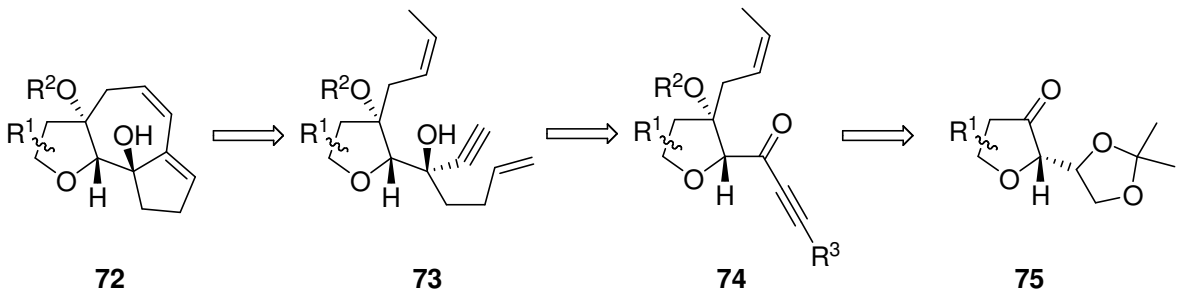
The antileukemia agent Rudmollin (**71**) is synthesized by *Carroll et al.*[49] (Scheme 15) from diazene **68**. When heated to reflux in toluene, **68** was efficiently (70%) converted to the

desired tricyclic hydroazulene **70** *via* atom transfer and subsequent 1,7-diyl recombination reaction. In the intermediate **69**, the radical can be stabilized by the substituents X and Y. It was also shown that the same reaction with the 2,3-*trans* substituted (*epi*)-diazene corresponding to **68** led to a complex mixture of compounds instead of **70**.



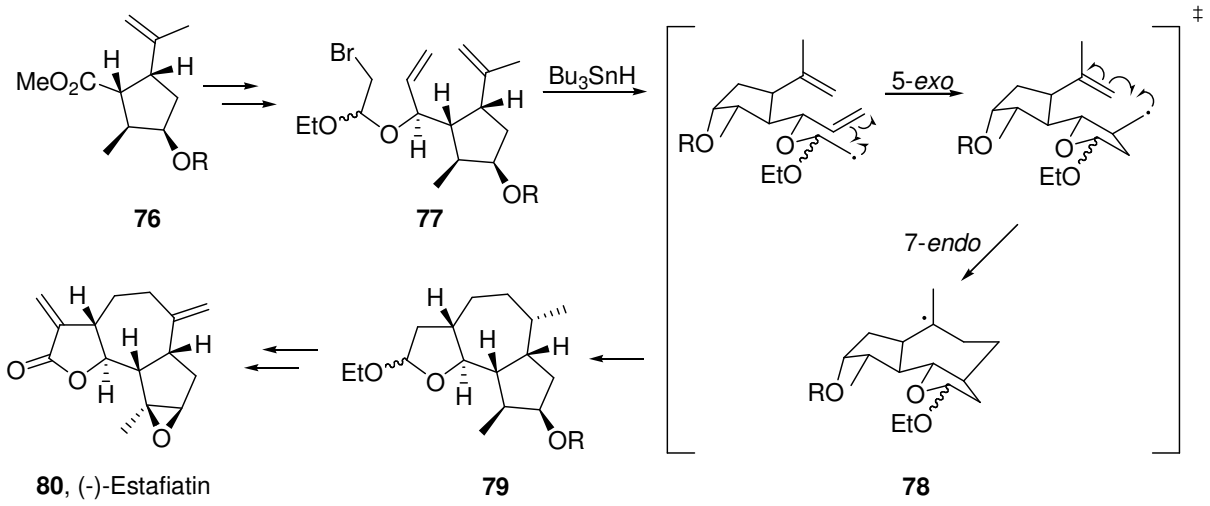
Scheme 15. *Carroll et al.*'s synthetic approach for pseudoguaianolide Rudmollin (**71**) from diazene **68** *via* hydrogen atom transfer-diyl recombination reaction.[49]

Since the metathesis reaction had been known as a powerful C-C bond formation method, ring closing metathesis (RCM) has been often used. Recently, *Kaliappan et al.*[50] reported the synthesis of guaianolide skeleton **72** *via* tandem domino enyne-RCM of the precursor **73** using Grubb's catalyst. They started from the sugar derived ketone **75** as an example of the type 4. This strategy can be useful to make just simple skeletal analogues of guaianolides starting from various sugar moieties (Scheme 16).



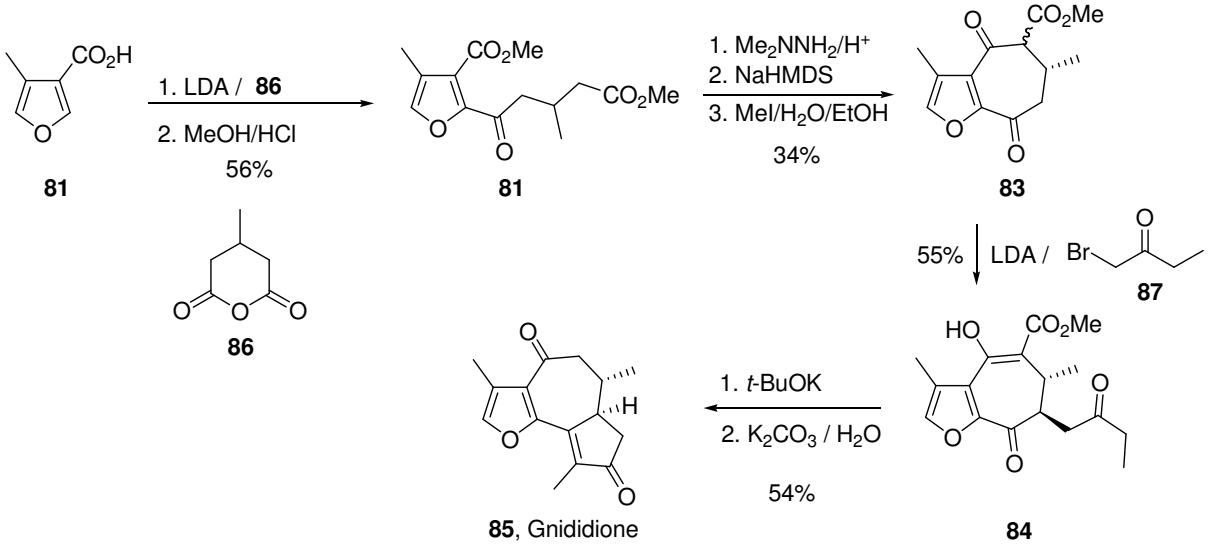
Scheme 16. Tandem domino enyne-RCM approach towards guaianolide skeleton by *Kaliappan et al.*[50]

As an example of type 5 methodology, *Lee et al.*[51] introduced 5-*exo* and 7-*endo* tandem radical cyclization as a key step to build up guaianolide skeleton. They prepared the bromoacetal **77** and subjected it to standard radical cyclization using Bu_3SnH and AIBN (Scheme 17).



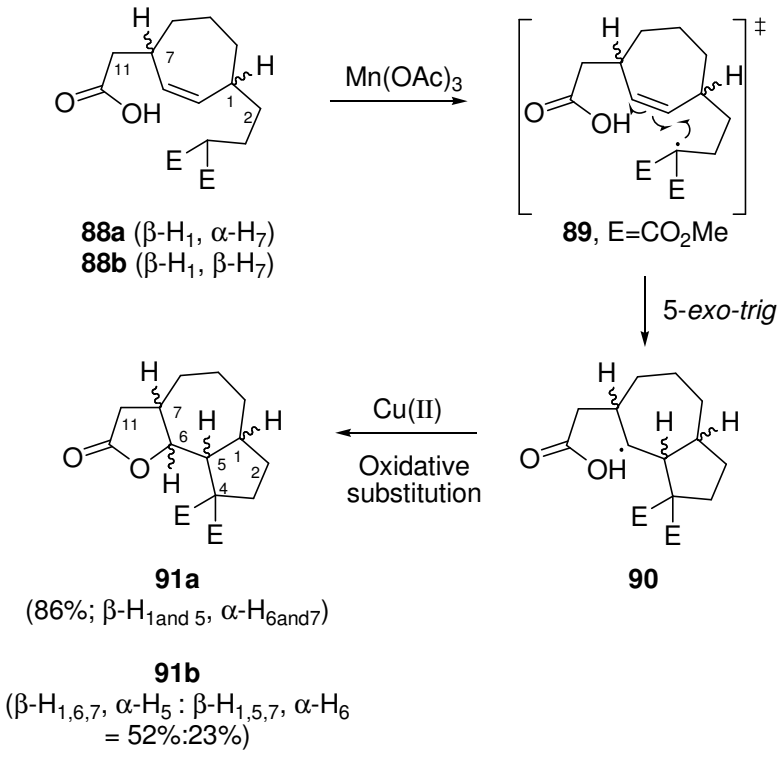
Scheme 17. The total synthesis of (-)-Estafiatin (**80**) *via* 5-*exo* and 7-*endo* tandem radical cyclization reaction by *Lee et al.*[51]

In this way, the corresponding guaianolide **79** was obtained in 99% yield from **77**. Looking in detail, a 5-*exo* radical cyclization had occurred first, followed by a subsequent 7-*endo* cyclization. During the B-ring cyclization, the 7-*endo* product was predominantly formed rather than 6-*exo* cyclization mode.



Scheme 18. *Knight et al.*'s synthetic approach towards Gnididione (**85**).[52]

The synthesis of Gnididione (**85**) by *Knight et al.*[52] is shown in Scheme 18. This method is an example of type 6. Acylation of 2-furyllithium using LDA / **86** and esterification gave **82**. The protection of the ketone group using hydrazone and *Dieckmann* cyclization afforded **83**, then C-ring formation *via* aldol condensation of **84** led to Gnididione (**85**) in 5.6% overall yield.

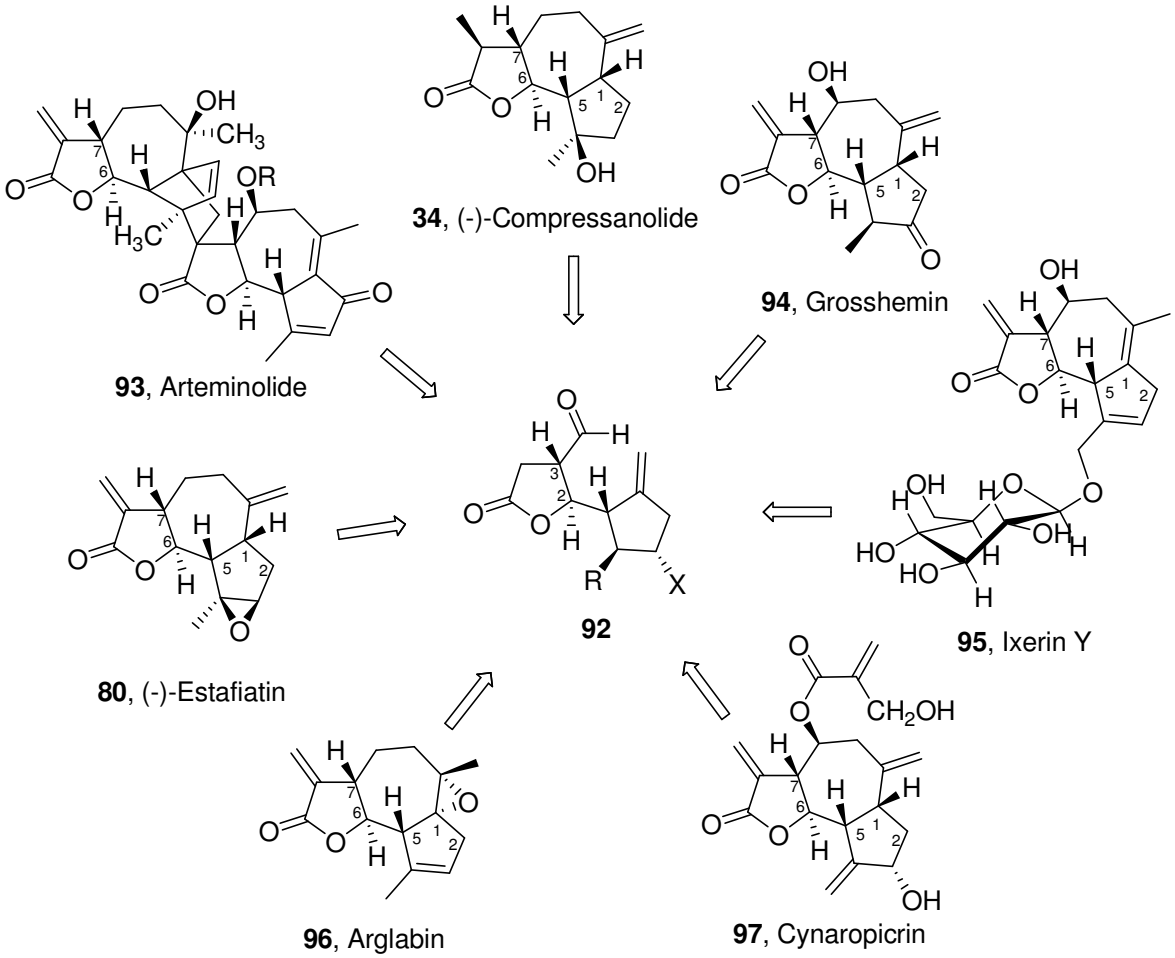


Scheme 19. *Burton et al.*'s synthetic approach towards guaianolide skeleton.[53]

As an example of type 7, *Burton et al.*[53] synthesized different tricyclic γ-butyrolactones (**91a**-**b**) *via* concerted formation of A and C-rings from 7-membered B-ring. $Mn(OAc)_3$ played a role as mild one electron oxidant which generates electrophilic *C*-centered radical from the malonates (**88a**-**b**). This radical intermediate underwent 5-*exo-trig* radical cyclization and subsequent oxidative substitution by $Cu(OTf)_2$ or $Cu(BF_4)_2$ to produce **91a** (86%) and diastereomeric mixture of **91b** (52%:23%) starting from **88a** and **88b** respectively. This synthetic approach using different size of B-ring can afford 5,5,5- and 5,6,5-tricyclic (*i.e.* eudesmanolide) γ-butyrolactone systems with high yields (71-94%) as well (Scheme 19).

5. 2,3-*anti* substituted γ-butyrolactone carbaldehyde as key building block for the guaianolide synthesis

The guaianolide analogues could also be built up from the 2,3-*anti* substituted γ-butyrolactone carbaldehyde **92**. Many biological active natural products based on guaianolide skeleton are shown in Scheme 20. Most of all, they are 6,7-*trans* substituted guaianolides.



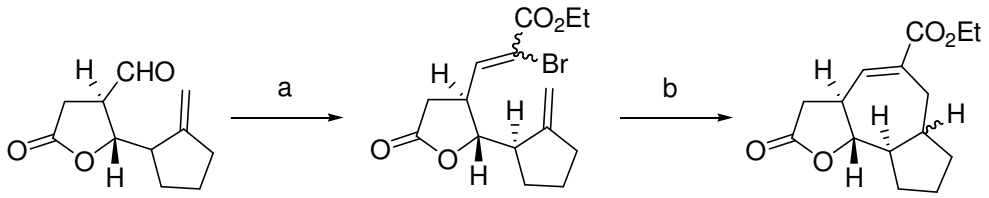
Scheme 20. The possible natural target products from 2,3-*anti* substituted γ-butyrolactone carbaldehyde **92**.

Ixerin Y (**95**), which was extracted from the *Ixeris denticulate f. pinnatipartita* plant, shows good inhibitory effects against the growth of human breast cancer MCF7 and MDA468 cell lines, with IC_{50} values of 6.36 μg/ml and 11.87 μg/ml, respectively.[54] Arteminolide (**93**) shows also very high inhibitory activity on farnesyltransferase (FTase) with IC_{50} values of 0.2-0.5 μg/ml.[55] Cynaropicrin (**97**) is extracted from *Cynara scolymus* L,[56] so called artichoke, and from *Saussurea lappa* as well.[57] Cynaropicrin is a useful agent not only for treatment of inflammatory diseases but also for the suppression of the proliferation of human

leucocyte cancer cells *via* induction of apoptosis.[57] (+)-Arglabin (**96**) was extracted by from aerial part of endemic plant *Artemisia glabella Kar. et Kir*. (Figure 5) in the early 1980s at Karaganda region of Kazakstan.

Figure 5. *Artemisia glabella Kar. et Kir.*

Arglabin and its synthetic derivatives have been demonstrated to show good antitumor activity and cytotoxicity against different tumor cell lines.[58] The most promising modification of Arglabin is dimethylamino arglabin hydrochloride (Arglabin-DMA) showing inhibitory activity on FTase with IC_{50} value of 7.28 μg/ml.



98 **99** **100**

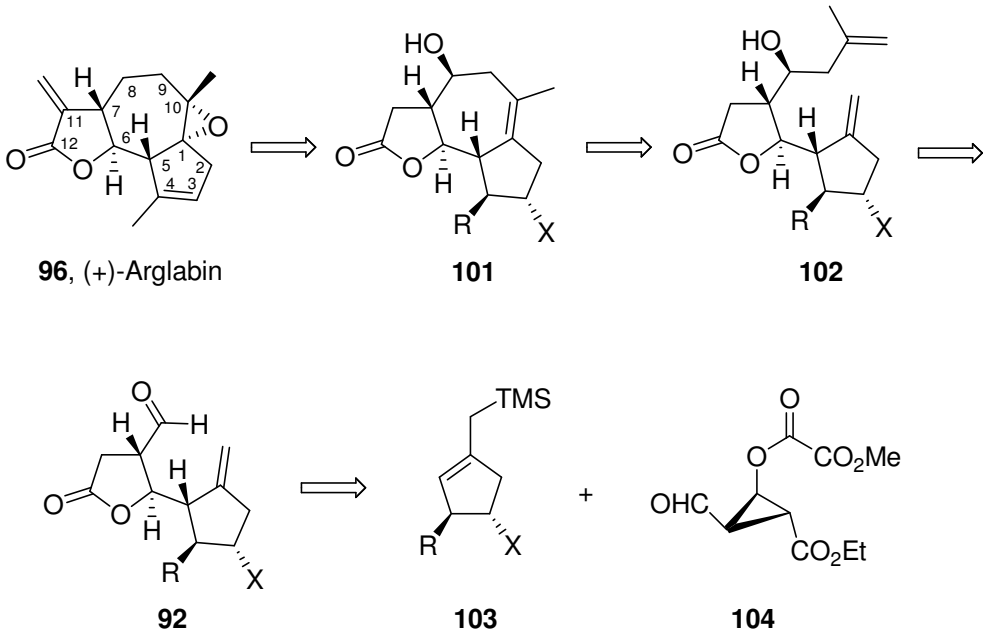
Reagents and conditions: a) $(Et_2O)P(O)CH_2CO_2Et$, NaH, Br_2, THF, 0 °C, 1.5 h, 83% (*E*/*Z*=20:80); b) *n*-Bu_3SnH (1.5 eq.), AIBN, benzene, 80 °C, 2 h, 83% (*cis*/*trans* = 4:1).

Scheme 21. The synthesis of guaianolide analogue **100** *via* radical cyclization by *Reiser et al*.[59]

Reiser et al.[59] has reported radical cyclization in order to make guaianolide analogue **100**. *Horner-Wadsworth Emmons* (*i.e.* HWE) reaction of **98** and the subsequent radical cyclization of **99** afforded predominantly **100** in 83% yield as 7-*endo-trig* radical cyclization product rather than 6-*exo-trig* cyclization (Scheme 21). This result is coincident with the results of tandem radical cyclization of *Lee et al*.[51]

6. Aim of this work

The guaianolide analogues **100** was synthesized by using the simple allylsilane **103** (R=X=H)[60] which was readily prepared from corresponding silylenolether.[61] However in order to build up guaianolides, the side C-ring containing a methyl group at 4-position is essential.



Scheme 22. Retrosynthetic outline towards (+)-Arglabin (**96**).

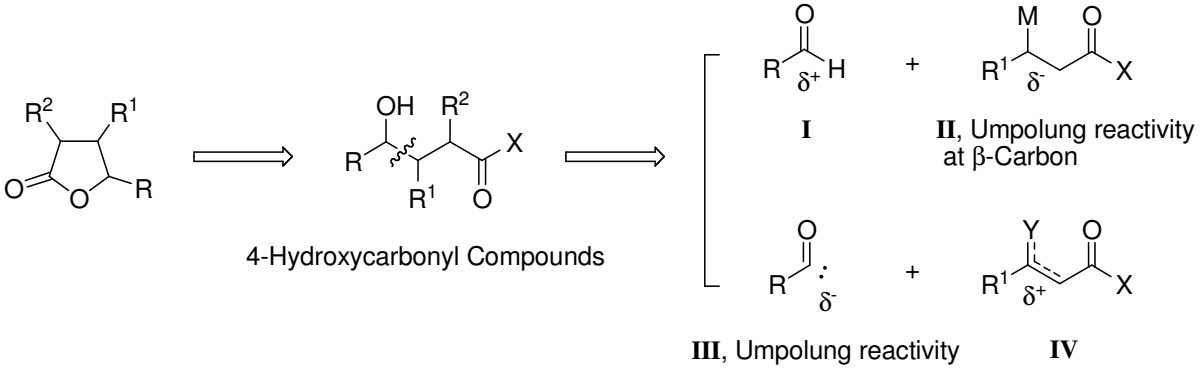
In order to achieve this, the allylsilane **103** should be synthesized and used in the reaction sequence, this way arriving at **92**. *Sakurai* allylation adduct **102** should be subsequently prepared. RCM of **102** should lead to the tricyclic guaianolide **101** as key step, which then was envisioned to be converted to Arglabin (**96**) as the target molecule (Scheme 22).

B. Main Part

1. Asymmetric synthesis of guaianolides towards Arglabin

1.1 Stereoselective synthesis of γ-butyrolactones (GBLs)

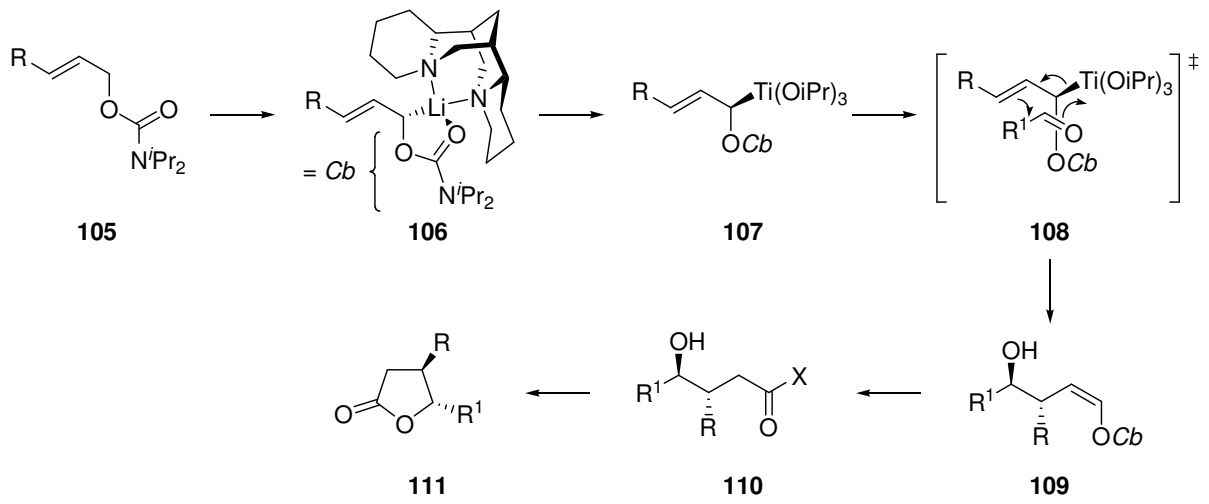
Natural products containing a γ-butyrolactone (*i.e.* GBL) moiety are abundant and they have a wide range of biological profiles.[62] Optical purity and absolute configuration of functionalities on the GBL are important for biological activity. For example, in the case of insect sex pheromones even small amounts of the opposite enantiomer can greatly reduce its biological activity.[63] Therefore, stereoselective synthesis of GBLs has received great attention in natural product synthesis. Most obvious, 4-hydroxycarbonyl compounds react as acyclic synthons of GBL. The synthesis of 4-hydroxycarbonyl compounds can be achieved by using carbonyl species (I or IV) having normal reactivity as electrophile and "*Umpolung*"[64] species (II or III) as nucleophile *via* homoaldol reaction (Scheme 23).



Scheme 23. GBL synthesis *via* homoaldol reaction by means of *Umpolung*.

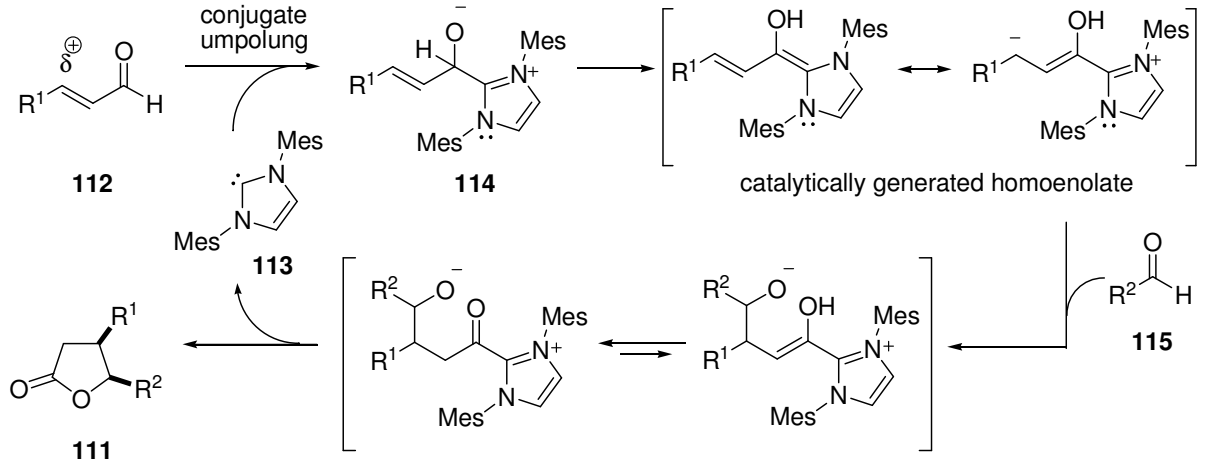
A homoaldol reaction for the synthesis of 4-hydroxycarbonyl compounds is much more difficult than the synthesis of 3-hydroxycarbonyl compounds by an aldol reaction because of the instability of homoenolates leading easily to self-condensation.[62a]

As an example of a homoaldol reaction, 2,3-*anti* disubstitued GBL **111** was synthesized by *Hoppe et al.* (Scheme 24).[65] The homoenolate reagent **105** was asymmetrically deprotonated, assisted by the *N,N*-diisopropylcarbamoyloxy (*Cb*) group, by treatment of *n*-BuLi/(-)-sparteine. Metal exchange occurred with inversion of configuration. The subsequent homoaldol addition of **107** to aldehydes gave the *anti*-configurated homoaldol adduct **109** *via* the *Zimmermann-Traxler* transition state **108**. Hydrolysis of **109** and subsequent lactonization afforded optically active GBL **111**.



Scheme 24. Synthesis of GBL by *Hoppe et al.*[65]

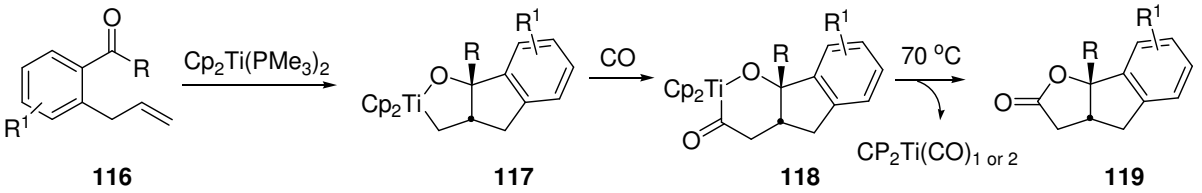
N-heterocyclic carbene-catalyzed homoenolate formation and subsequent addition to carbonyl compounds afforded GBLs, [66] a sequence that was discovered almost simultaneously by *Bode et al.*[66a] and *Glorius et al.*[66b] In just one reaction step using catalytic amounts of **113**, coupling of α,β-unsaturated enal **112** and aldehyde **115** led to GBL **111** in good yield with predominant *cis*-stereoselectivity (Scheme 25).



Scheme 25. Syntheses of GBL by *Bode et al.*[66a] and *Glorius et al.*[66b]

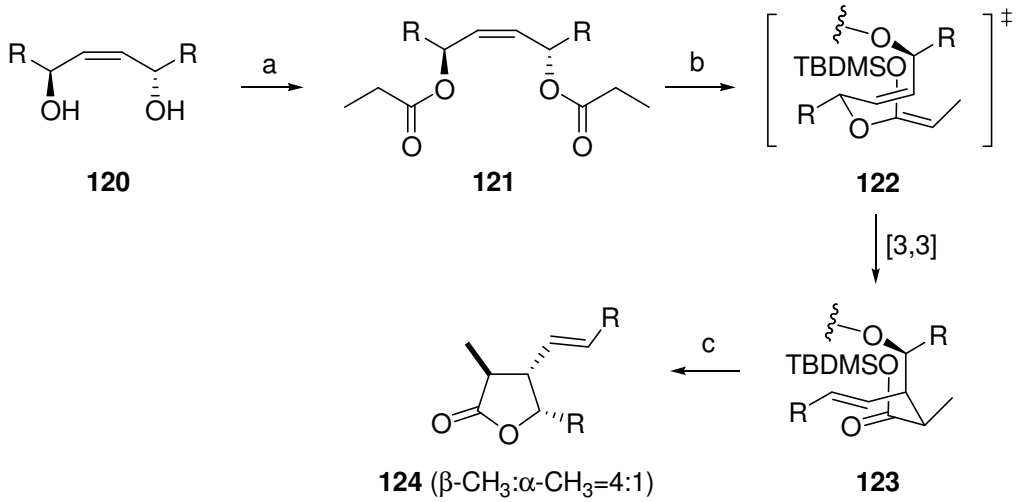
Early or late transition metal-catalyzed GBL syntheses have been extensively studied. *Evans et al.* synthesized 4-hydroxy carbonyl compounds as acyclic synthons of GBL in good yield and high enantioselectivity by means of C_2-symmetric bis(oxazolinyl)pyridine (*i.e.* pybox)-Cu(II) complex.[67] Besides, Ru-catalyzed oxidative cyclization of homopropargyl alcohols,[68] Pd-catalyzed intramolecular cyclization,[69] and chiral dirhodium(II)carboxamidate-mediated intramolecular C-H insertion are known as good methodologies toward GBLs since reaction steps are relatively short and a good yield and stereoselectivity can be achieved. An example

of a [2+2+1]-cycloaddition reactions[70] is shown in Scheme 26. This intramolecular "hetero *Pauson-Khand*" reaction of *o*-allyl aryl ketone **116** occurred *via* formation of titanacycle **117**, CO insertion into the Ti-C bond, and reductive elimination of the catalyst. The polycyclic GBLs **119** have been synthesized with complete diastereocontrol in a range of 74-96% yield by means of 5-20 mol% catalyst.



Scheme 26. GBL synthesis by *Buchwald et al.*[70a] *via* titanocene-catalyzed cyclocarbonylation.

Non-transition metal-catalyzed GBL synthesis is shown in Scheme 27. GBL **124** was synthesized by *Ariza and Garcia et al.*[71] *via* a desymmetrization of allylic 1,4-diacetates **121** using an *Ireland-Claisen* rearrangement as key step. [3,3] Thermal rearrangement of **122** lead to **123**, subsequent hydrolysis and lactonization afforded the GBL **124** as precursor of phaseolinic acid. This one pot reaction does not need any isolation of intermediates and a 85% overall yield (*de*=β-CH_3:α-CH_3=4:1) was obtained.



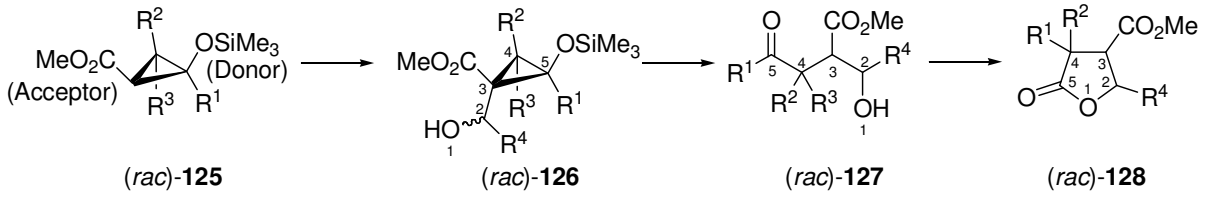
Reagents and conditions: a) $(EtCO)_2O$, Et_3N, DMAP, CH_2Cl_2, 100%; b) i) KHMDS, TBDMSCl, THF/30% DMPU, -78°C to rt. ii) toluene, Δ; c) i) LiOH, H_2O/THF, Δ. ii) aqueous HCl/THF, Δ, 85%.

Scheme 27. Synthesis of GBL by *Ariza and Garcia et al.*[71]

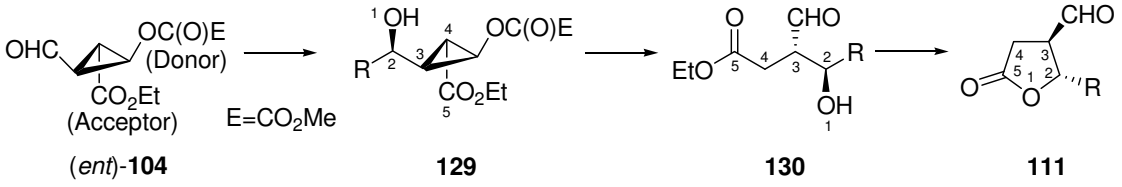
Donor-acceptor disubstituted cyclopropane (D-A cyclopropane) derivatives are used as attractive building blocks for various synthetic transformations.[72] Particularly, 1,2-vicinally substituted D-A cyclopropanes can react as electrophiles as well as nucleophiles due to their 1,3-dipolar properties upon cleavage of the cyclopropane ring. *Reissig et al.*[73] synthesized

(*rac*)-**128** from D-A substituted cyclopropane (*rac*)-**125** *via* deprotonation by using lithium base, followed by an aldol addition of the resulting enolate to carbonyl compounds giving (*rac*)-**126.** Upon ring-opening by fluoride reagents or acids and subsequent lactonization (Scheme 28) led to highly functionalized GBLs (*rac*)-**128**.

Reissig et al.



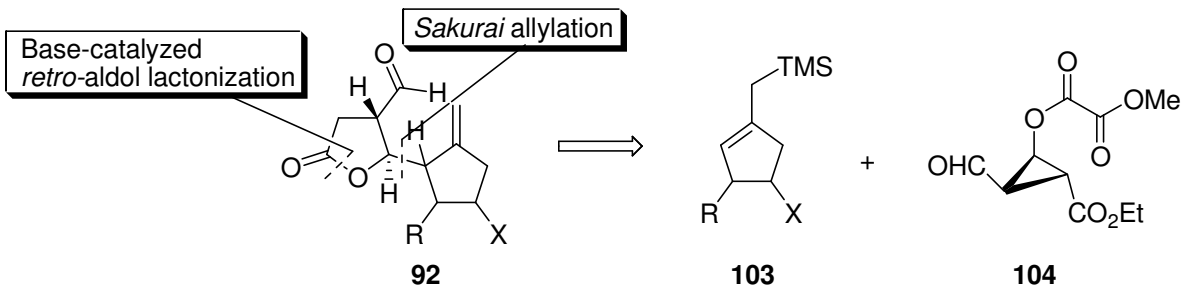
Reiser et al.



Scheme 28. Syntheses of GBL via D-A cyclopropane by *Reissig et al.* and *Reiser et al.*

Highly diastereoselective 2,3-*trans* disubstituted GBL synthesis using D-A substituted cyclopropane was also demonstrated by *Reiser et al.*[74] (Scheme 28). GBL **111** was synthesized from the enantiomerically pure (*ent*)-**104**, which is prepared by asymmetric cyclopropanation of furan-2-carboxylate using bis(oxazoline) ligand and ozonolysis. Diastereoselective nucleophilic addition to (*ent*)-**104**, D-A cyclopropane ring opening by base, and subsequent base-catalyzed retroaldol lactonization reaction sequence afforded the 2,3-*trans* disubstituted GBLs **111**.

Following this strategy, GBLs **92** containing 5-membered rings at 2-position were aimed to be synthesized as the first goal in this work in order to arrive at suitably functionalized precursors toward guaianolides. In order to achieve this goal, optically active cyclic 5-membered allylsilane **103** and enantiomerically pure **104** are necessary (Scheme 29).

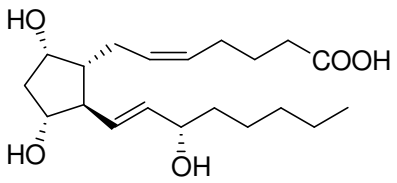


Scheme 29. Retrosynthetic overview toward GBL carbaldehydes **92**.

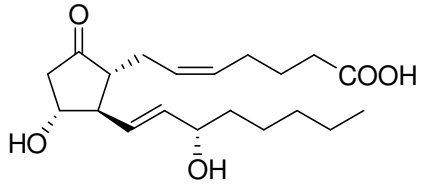
1.2 Synthesis of cyclic allylsilanes

1.2.1 Synthesis of optically active mono protected *cis*-2-cyclopenten-1,4-diol derivatives

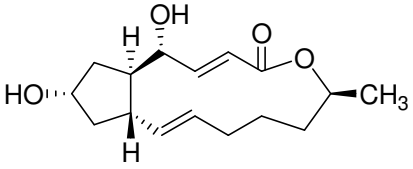
Mono protected optically active 4-hydroxycyclopent-2-enones **137** and chiral mono protected cyclopent-4-ene-1,3-diols **139** have been widely used for natural product syntheses containing cyclopentanoid[75] such as prostaglandins (**131**, **132**),[76] the macrolide antibiotic Brefeldin (**133**),[77] or Thromboxanes (**134**) (Scheme 30).



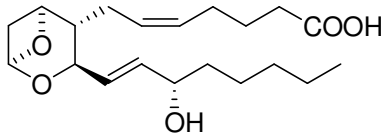
131. Prostaglandin ($PGF_{2\alpha}$)



132. PGE_2



133. Brefeldin A

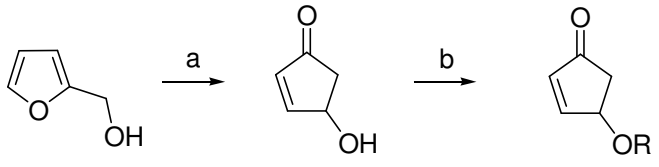


134. Thromboxane A_2

Scheme 30. Some examples of natural products containing cyclopentanoid.

Various methods to prepare mono protected cyclopent-4-ene-1,3-*cis*-diols **139**,[78] α,β-unsaturated optically active **137**,[79] and optically active **136**[80] have been reported. For the synthesis of optically active **139**, enzymatic kinetic resolution condition by *Curran et al.*[78e] was adopted to separate the two enantiomers of **138** as key step.

The synthesis started from fufuryl alcohol (**135**), which was rearranged to **136** in 43% yield by reflux for 43 h in aqueous phosphate buffer (pH 4.1) solution (Scheme 31).[78e]



135 **136** **137a-e**

Reagents and conditions: a) H_3PO_4, Na_2HPO_4 in H_2O, pH 4.1 under N_2, 100°C, 40 h, 43%; b) Et_3N, DMAP, TBDPSCl/TBDMSCl/TMSCl in THF, -20°C, 3 h for **137a**, **137b**, and **137d**, respectively. PTSA, 2-dihydropyran in CH_2Cl_2, 20°C, 14 h for **137c**. NaH, PMBCl in THF for **137e**.

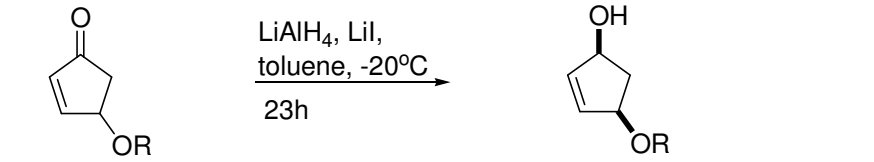
Scheme 31. Synthesis of mono protected 4-hydroxy-cyclopent-2-enones (**137a-e**).

Various protecting groups were used to subsequently protect the racemic 4-hydroxy-cyclopent-2-enone (**136**). TBDPS protection to **137a** was achieved in 97% yield, while THP protection yielded **137c** in 82% of yield as a mixture of two diastereomers.

Table 1. Protection of racemate **136**.

Entry	Product	R	Yield (%)
1	**137a**	TBDPS	97
2	**137b**	TBDMS	82 [a]
3	**137c**	THP	82 [b]
4	**137d**	TMS	45
5	**137e**	PMB	n.r. [c]

[a] Yield after 3rd column (78 % till 2nd column). [b] Two diastereomers *dr*=67:33 (δ 7.59: δ 7.65 on the ^{1}H-NMR). [d] No reaction under NaH, PMBCl reaction condition.

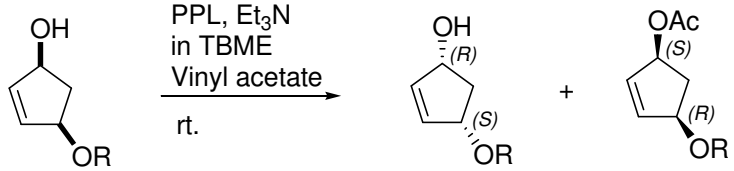


137a (R=TBDPS)
137b (R=TBDMS)

138a (46%, *dr*=82:18, R=TBDPS,)
138b (86%, *cis:trans*=92:8, R=TBDMS)

Scheme 32. Reduction of the racemates **137a**-**b**.

Reduction of **137a**-**b** using $LiAlH_4$ (0.65 eq.) afforded **138a** (46%) and **138b** (86%) yield, respectively (Scheme 32). The *cis/trans* ratio was determined by integration of the proton signals in the ^{1}H NMR spectrum of **138b** at δ=4.5 (*cis*) and δ=5.0 (*trans*), corresponding to the 1,3-hydrogens.



138a (R=TBDPS)
138b (R=TBDMS)

138a
(-)-**138b**

139a
(+)-**139b**

Reagents and conditions: PPL (0.12 g/mmol), Et_3N (0.68 eq.), TBME (1.25 ml/mmol), Vinyl acetate (5.0 eq.).

Scheme 33. Enzymatic kinetic resolution of racemate **138a-b** using PPL.

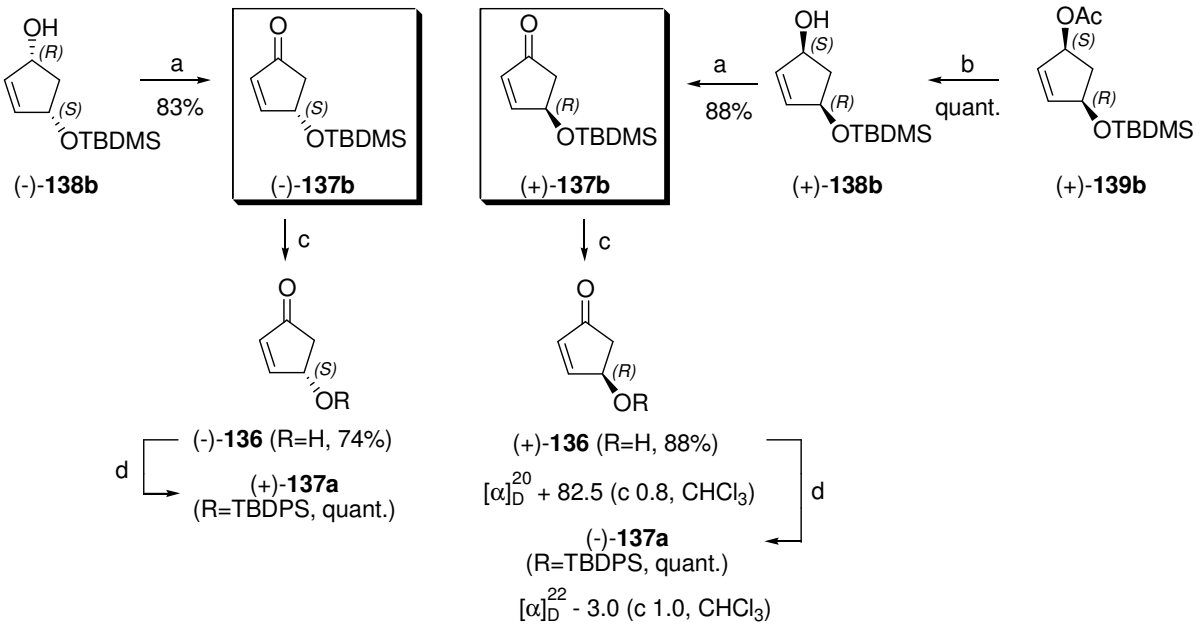
Each of the two enantiomers of **138a-b** was separated using PPL (Porcine Pancreatine Lipase) by an enzymatic kinetic resolution (Scheme 33). No significant conversion has been observed in case of **138a** even at long reaction times in Entry 1, but **138b** (Entry 2, Table 2) was smoothly acylated to yield (-)-**138b** and (+)-**139b** with high enantiomeric excess.

Table 2. Enzymatic kinetic resolution of **138a-b**

Entry	Starting material	R	Reaction time (h)	Product	Yield (%)	$[\alpha]_D$	*ee* (%) [d]
1	**138a**	TBDPS	84	(+)-**138a**	80 [a]	+0.4 (c 1.1) [b]	-
				(-)-**139a**	14	-1.4 (c 1.0) [b]	-
2	**138b**	TBDMS	14	(-)-**138b**	47	-18.4 (c 1.1) [c]	87.7
				(+)-**139b**	39	+0.6 (c 1.1) [c]	98.4

[a] The yield of recovered staring material. [b] Measured in $CHCl_3$ at 24°C. [c] Measured in $CHCl_3$ at 20°C. [d] *ee* value measured by GC using chiral column, RtβDexcst®(Restek).

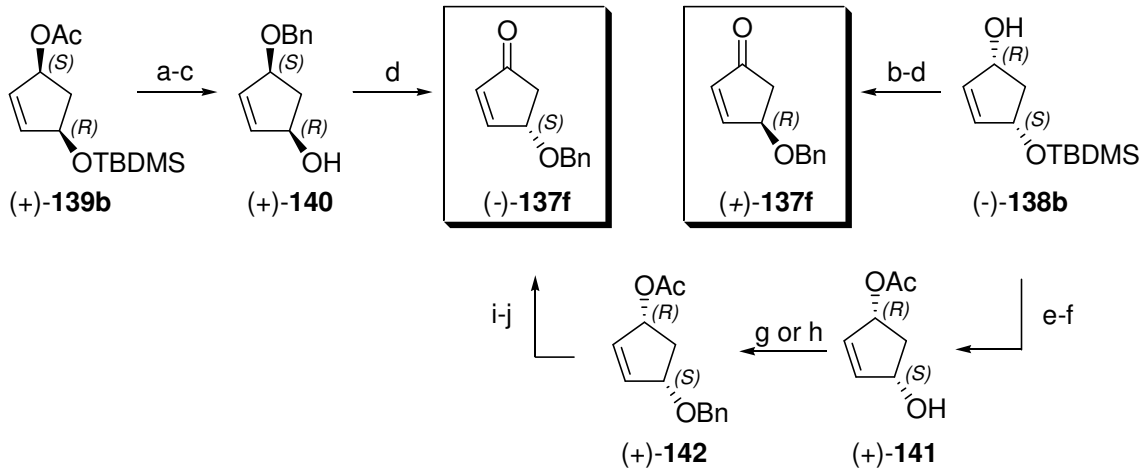
Optically active (-)-**138b** and (+)-**139b** were converted to the enantiomerically enriched (-)-**137b** *via* oxidation with PCC and to the enantiomerically pure (+)-**137b** *via* hydrolysis and subsequent oxidation with PCC respectively (Scheme 34).



Reagents and conditions: a) PCC, 3Å M.S. in CH_2Cl_2, rt., 15 h. b) LiOH in THF/MeOH/H_2O=3:1:1, 1 h. c) AcOH:THF:H_2O=3:1:1, 44 h, rt. d) DMAP, TBDPSCl, DMF, 12 h, rt., quant.

Scheme 34. Parallel synthesis of (-) and (+)-**137a-b**.

Due to poor kinetic resolution of TBDPS protected **138a** (Entry 1, Table 2), optically active (+) and (-)-**137a** were synthesized by deprotection of TBDMS ethers (-) and (+)-**137b** leading to (-) and (+)-**136**[80d] followed by immediate re-protection TBDPS ethers, respectively (Scheme 34). A first attempt to oxidize **138b** was carried out using *Dess-Martin* periodinane (1.1 eq.) in CH_2Cl_2. However **137b** was obtained in only 23%, whereas oxidation using PCC (1.0-2.0 eq.) proceeded efficiently (83-88%). Benzyl protected **137f** was also synthesized because benzyl ethers are relatively more tolerable than silyl ethers under more forcing reaction conditions. (-)-**137f** and (+)-**137f** were synthesized following the reaction sequence shown in Scheme 35 from (+)-**139b** and (-)-**138b**, respectively. Especially, the optically active (-)-**138b** could be transformed into both, (-)-**137f** as well as (+)-**137f** (Scheme 35).



Reagents and conditions: a) LiOH in THF/MeOH/H_2O=3:1:1, 1 h, quant.; b) NaH, BnBr, Bu_4NI in THF, 18 h, rt., 96%; c) AcOH(5*N*):THF=2:1, 65℃, 21 h, 98%; d) PCC, 3Å M.S. in CH_2Cl_2, rt., 94 %; e) pyridine (10 eq.), Ac_2O (4.5 eq.), rt., 3 h, 95%; f) Bu_4NF, Et_3N, THF, 1.5 h, 89%; g) NaH, BnBr, Bu_4NI in THF, 87% (racemized); h) $Cl_3C(=NH)OBn$, $Cu(OTf)_2$, CH_2Cl_2, rt., 83% (crude), $[\alpha]_D$ + 8.5 (c 1.1, $CHCl_3$, 21°C); i) LiOH in THF/MeOH/H_2O=3:1:1, 1 h; j) PCC, 3Å M.S. in CH_2Cl_2, rt., 94 % ((-)-**137f**, in two steps).

Scheme 35. Synthesis of (-) or (+)-**137f**.

This convergent synthesis of (-)-**137f** can offset the drawback of classical enzymatic kinetic resolution allowing to obtain only one enantiomer in a maximum yield of 50%. In this case, both enantiomers of the racemic compound can be converted to a single enantiomer, similar to a dynamic kinetic resolution (DKR).[81] During the convergent synthesis of (-)-**137f** *via* (+)-**142**, the benzylation of (+)-**141** under NaH, BnBr, Bu_4NI in THF condition caused the loss of optical activity of (+)-**142**. In contrast, the benzylation of (+)-**141** using $Cl_3C(=NH)OBn$ and $Cu(OTf)_2$ catalyst was achieved successfully without loss of optical activity of (+)-**142**.[82] The results in the synthesis of **137a-b** and **137f** are summarized in Table 3.

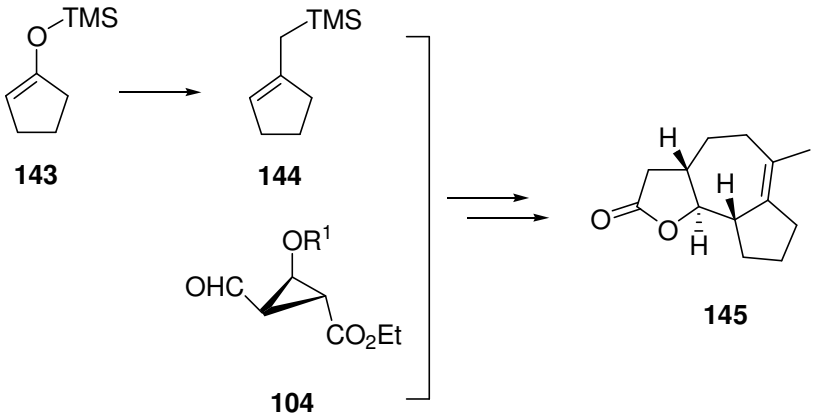
Table 3. Synthesis of optically active **137a-b** and **137f**.

Entry	Starting material	Product	R	Yield (%)	$[\alpha]_D$ [f]	*ee*[l] (%)
1	(-)-**138b**	(-)-**137b**	TBDMS	83 [a]	- 49.1(c 1.43, 20°C)	94.3
2	(+)-**139b**	(+)-**137b**	TBDMS	88 [b]	+ 53.1 (c 1.03, 21°C)	98.1
3	(+)-**139b**	(-)-**137f**	Bn	88 [c]	- 38.8 (c 0.95, 22°C)	90.6
4	(-)-**138b**	(+)-**137f**	Bn	82 [d]	+ 32.4 (c 1.02, 22°C)	78.9
5	(-)-**137b**	(+)-**137a**	TBDPS	74 [e]	-	-
6	(+)-**137b**	(-)-**137a**	TBDPS	88 [e]	-3.0 (c 1.02, 22°C)	-

[a] Yield of direct oxidation using PCC from (-)-**138b** (Scheme 34). [b] Yield in two steps (Scheme 34). [c] Yield in four steps (Scheme 35). [d] Yield in three steps (Scheme 35). [e] Yield in two steps (Scheme 34). [f] Measured in $CHCl_3$ [l] *ee* value measured by GC using chiral column, RtβDexcst®(Restek).

1.2.2 Synthesis of cyclic silyl enol ether

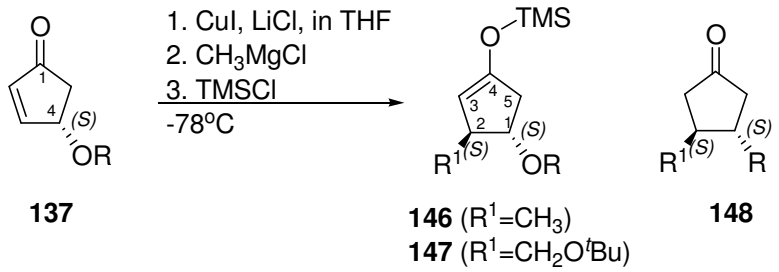
In our previous synthesis of 5,7,5-guaianolide-like tricyclic γ-butyrolactone **145**,[83] the simple cyclic allylsilane **144** prepared from the silyl enol ether **143** was used. **143** is readily prepared from cyclopentanone following the *House's* method (Scheme 36).[61]



Scheme 36. Synthesis of guaianolide-like tricyclic GBLs **145**.[61]

For the synthesis of guaianolides having methylated cyclopentane moiety at 4-position, a 1,4-conjugate addition onto **137** was envisioned. In general, conjugate 1,4-additions of α,β-unsaturated carbonyl substrates can be achieved by means of *Gilman* cuprates.[84] Additives such as TMSCl, $CuBr{\cdot}SMe_2$, HMPA, DMAP, DMPU, or TMEDA are known to have an accelerating effect on yield and regioselectivity of 1,4-conjugate addition reaction.[85] *Gilman* cuprates generally need stoichiometric amount of CuX to be prepared. *Hayashi et al.*

described Rh/BINAP-catalyzed asymmetric 1,4-conjugate addition of aryltitanium reagents to lead to chiral silyl enol ethers.[86] *Grignard* reagents are often used for 1,4-conjugate additions as well. Conjugate addition of *Grignard* reagents (RMgX) using catalytic amount of CuX was first reported by *Kharasch et al.*[87] Catalytic use of CuX_3Li_2 (X=halide),[88] which is inexpensive and easy to prepare, makes 1,4-conjugate additions of RMgX more effective. *Reetz et al.*[88a] achieved high yields and 1,4-selectivities (>99%) in different conjugated acyclic and cyclic enone systems by simply mixing of CuI and 2LiCl (10 mol%) in THF followed by treatment with RMgX.[88a] The resulting enolate can be either trapped as a silyl enol ether in the presence of excess of TMSCl *via* non-aqueous work-up[88b] or as desilylated keto adduct *via* aqueous work-up. Difficulties occurred during the synthesis since the silyl enol ethers were prone toward hydrolysis to the corresponding keto adducts **148** (Scheme 37). The Results are shown in Table 4. Due to the instability, most of the silyl enol ethers **146** were subjected immediately to the next step.



137 **146** (R^1=CH_3) **148**
147 (R^1=CH_2O^tBu)

Reagents and conditions: CuI (0.15 eq.), LiCl (0.3 eq.), CH_3MgCl (3M in THF solution, 4.5 eq.) and TMSCl (5.0 eq.) in abs. THF (5.5 ml/mmol) at -78°C for 1-2 h and quenching with anhyd. Et_3N (12 eq.).

Scheme 37. CuX_3Li_2 catalyzed conjugate 1,4-addtion of *Grignard* reagent in the presence of TMSCl.

The *Gilman* reagent Me_2CuLi and TMSCl in CH_2Cl_2 (Entry 1, Table 4)[89] was used for a synthesis of (*rac*)-**146a**. For the attempted synthesis of **147**, which could be used as side chain of Ixerin Y, $(Bu^tOCH_2)_2CuLi$ was prepared *in situ* from Bu^tOCH_2Li and $CuBr{\cdot}(CH_3)_2S$ (Entry 3, Table 4),[90] however, the desired product could not be obtained.

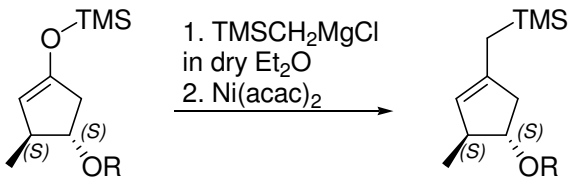
Table 4. Synthesis of silyl enol ethers **146** and **147**.

Entry	Starting material	R	R^1	Product	Yield (%)
1 [a]	(*rac*)-**137a**	TBDPS	CH_3	(*rac*)-**146a**	-
2	(*rac*)-**137a**	TBDPS	CH_3	(*rac*)-**146a**	71 [c]
3 [b]	(*rac*)-**137a**	TBDPS	CH_2O^tBu	**147**	-
4	(*rac*)-**137b**	TBDMS	CH_3	(*rac*)-**146b**	64 [c, d]
5	(+)-**137a**	TBDPS	CH_3	**146a**	90 [c]
6	(-)-**137b**	TBDMS	CH_3	**146b**	40 [c]
7	(-)-**137a**	TBDPS	CH_3	(*ent*)-**146a**	56 [e]
8	(+)-**137b**	TBDMS	CH_3	(*ent*)-**146b**	42 [f]
9	(*rac*)-**137c**	THP	CH_3	(*rac*)-**146c**	66 [g]
10	(*rac*)-**137d**	TMS	CH_3	(*rac*)-**146d**	52 [h]
11	(-)-**137f**	Bn	CH_3	**146f**	95 [c]
12	(+)-**137f**	Bn	CH_3	(*ent*)-**146f**	94 [c]

[a] CH_3Li, CuI in Et_2O, TMSCl. -78°C. [b] K^tOBu, *sec*-BuLi, TBME, LiBr, $CuBr_2 \cdot SMe_2$, diisopropylsulfide, TMSCl. -78°C. [c] Crude yield after non aqueous work-up. [d] CuI (1.0 eq.), LiCl (0.5 eq.), CH_3MgCl (3M in THF solution, 1.5 eq.) and TMSCl (4.2 eq.) were used. [e] Among 56% of mixture, (-)-**137a**:(*ent*)-**146a**:(*ent*)-**148a**=11:19:70 calculated by the integration of ^{1}H-NMR. [f] Isolated yield after column on alumina-N; CuI (2.0 eq.), LiCl (1.0 eq.), CH_3MgCl (3M in THF solution, 4.5 eq.) and TMSCl (4.2 eq.) were used. [g] Crude yield. CH_3MgCl (1.1 eq.), CuI (0.15 eq.), LiCl (0.3 eq.), TMSCl (5.0 eq.), THF, -78°C, 3 h. [h] Isolated yield. *dr*=(*rac*)-**146d**:(*rac*)-**148d=**67:33 calculated by the integration of ^{1}H-NMR.

1.2.3 Synthesis of cyclic allylsilanes

Silyl enol ethers are usually inert toward *Grignard* reagents. However under drastic condition such as reflux in dimethoxyethane, the silicon-oxygen bond is cleaved slowly to form magnesium enolates.[91] $Ni(acac)_2$ catalyzes the cross-coupling between silyl enol ethers and *Grignard* reagents (Scheme 38).



146 **103**

Reagents and conditions: $TMSCH_2MgCl$ (2.0-6.4 eq.) in Et_2O, $Ni(acac)_2$ (0.15-0.3 eq.) reflux at 35℃ for 1-2 days.

Scheme 38. Synthesis of cyclic allylsilanes **103**.

Consequently, a silicon-carbon bond in silyl enol ethers can be converted into a carbon-carbon bond of allylsilanes.[61]

Table 5. Cross-coupling reactions of silyl enol ethers **146** and *Grignard* reagent under $Ni(acac)_2$ catalyst.

Entry	Starting material	R	Product	Yield (%)	$TMSCH_2$-MgCl (eq.)	$[\alpha]_D$ [d]
1	(*rac*)-**146a**	TBDPS	(*rac*)-**103a**	29	5.0	-
2	(*rac*)-**146b**	TBDMS	(*rac*)-**103b**	42	6.4	-
3	**146a**	TBDPS	**103a**	48	2.0	n.d. [e]
4	**146b**	TBDMS	**103b**	25 [a]	5.0	n.d. [e]
5	(*ent*)-**146b**	TBDMS	(*ent*)-**103b**	56 [b]	5.6	- 44.3 (c 0.75, 22°C)
6	**146f**	Bn	**103f**	97	3.5	+ 49.4 (c 3.16, 21°C)
7	(*ent*)-**146f**	Bn	(*ent*)-**103f**	55 [c]	3.5	- 5.9 (c 0.29, 20°C)

[a] Yield in two steps starting from (-)-**137b** [b] Crude yield in two steps starting from (+)-**137b**. 0.57 eq. of $Ni(acac)_2$ was used. [c] Yield based on the amount of (*ent*)-**146f** which is calculated by the integration of crude ^{1}H-NMR. [d] Measured in $CHCl_3$. [e] n.d.=not determined.

1.3 Asymmetric cyclopropanation and ozonolysis

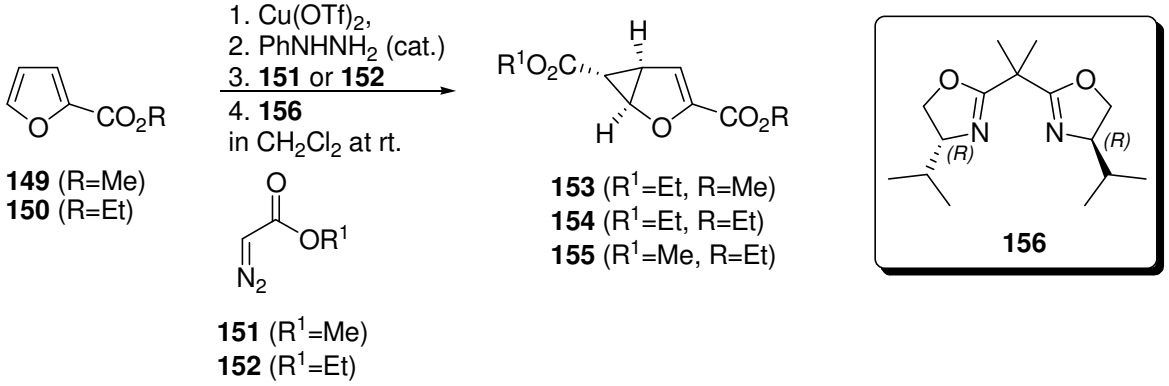
1.3.1 Asymmetric cyclopropanation

Cyclopropanation is an important tool not only for the synthesis of complex molecules but also for the development of synthetic methodologies.[92]Among known methodologies[93] for the enantioselective synthesis of cyclopropanes, carbene-transition metal complex-mediated cyclopropanation reactions are widely used.[94] Carbenes formed by decomposition of diazoalkanes are normally too reactive that good stereoselectivities are difficult to achieve. Such a vigorous reactivity of diazoalkanes is reduced somewhat by introducing electron withdrawing groups such as carboxylic esters. Moreover, carbenes are further stabilized by complexation with transition metals (*i.e.* carbenoid). *Nozaki*, *Noyori* and coworkers developed the first enantioselective and homogeneous copper-catalyzed cyclopropanation of styrene with salicylaldimino ligands in 1966, although the resulting cyclopropanes contained

low enantioselectivities.[95] Since this finding, several chiral ligands have been synthesized and tested in copper-catalyzed cyclopropanation reactions including substituted salicylaldimines, semicorrins, bis(oxazolines), bypyridines.[93]

1.3.2 Cyclopropanation of furan-2-carboxylic ester

Wenkert et al. reported the cyclopropanation of furan-2-methyl carboxylic ester (**149**) under $Rh_2(OAc)_4$ catalyst in 55% yield leading to *exo*-cyclopropane furoic ester **153**.[96] In the previous work by *Böhm*, the copper catalyzed cyclopropanation in the presence of chiral bis(oxazoline) ligands was studied.[97]



Reagent and conditions: $PhNHNH_2$ (2 droplets), rt. (Entry 1-3, Table 6); $PhNHNH_2$ (0.9 mol%), 0°C (Entry 4, Table 6).

Scheme 39. Cyclopropanation of furan carboxylic esters with diazocarboxylic esters.

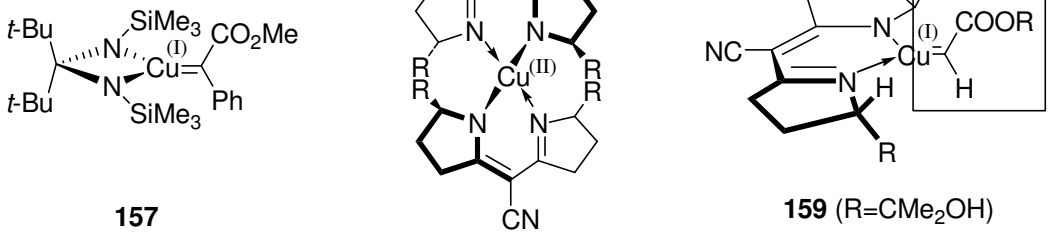
The chemical yield of the cyclopropanation depends on the addition time and the concentration of diazocarboxylic esters **151** and **152**.[98] The asymmetric cyclopropanation of **149** with **152** using chiral ligand **156** afforded **153** with high enantioselectivity (Entry 4, Table 6).

Table 6. Cyclopropanation of the furan carboxylic esters **149** and **150**.

Entry	Starting material	Diazocarboxylic esters (eq.)	$Cu(OTf)_2$ (mol %)	Product	Yield (%)
1	**149**	**152** (1.0)	0.2	(*rac*)-**153**	12
2	**150**	**151** (0.8)	0.13	(*rac*)-**155**	20
3 [a]	**149**	**152** (4.7)	0.5	**153**	23 (20) [b]

[a] With **156** (0.67 mol %). [b] Yield in parenthesis is estimated after recrystallization; 100% *ee* was estimated by chiral HPLC after single recrystallization with CH_2Cl_2/*n*-Pentane.

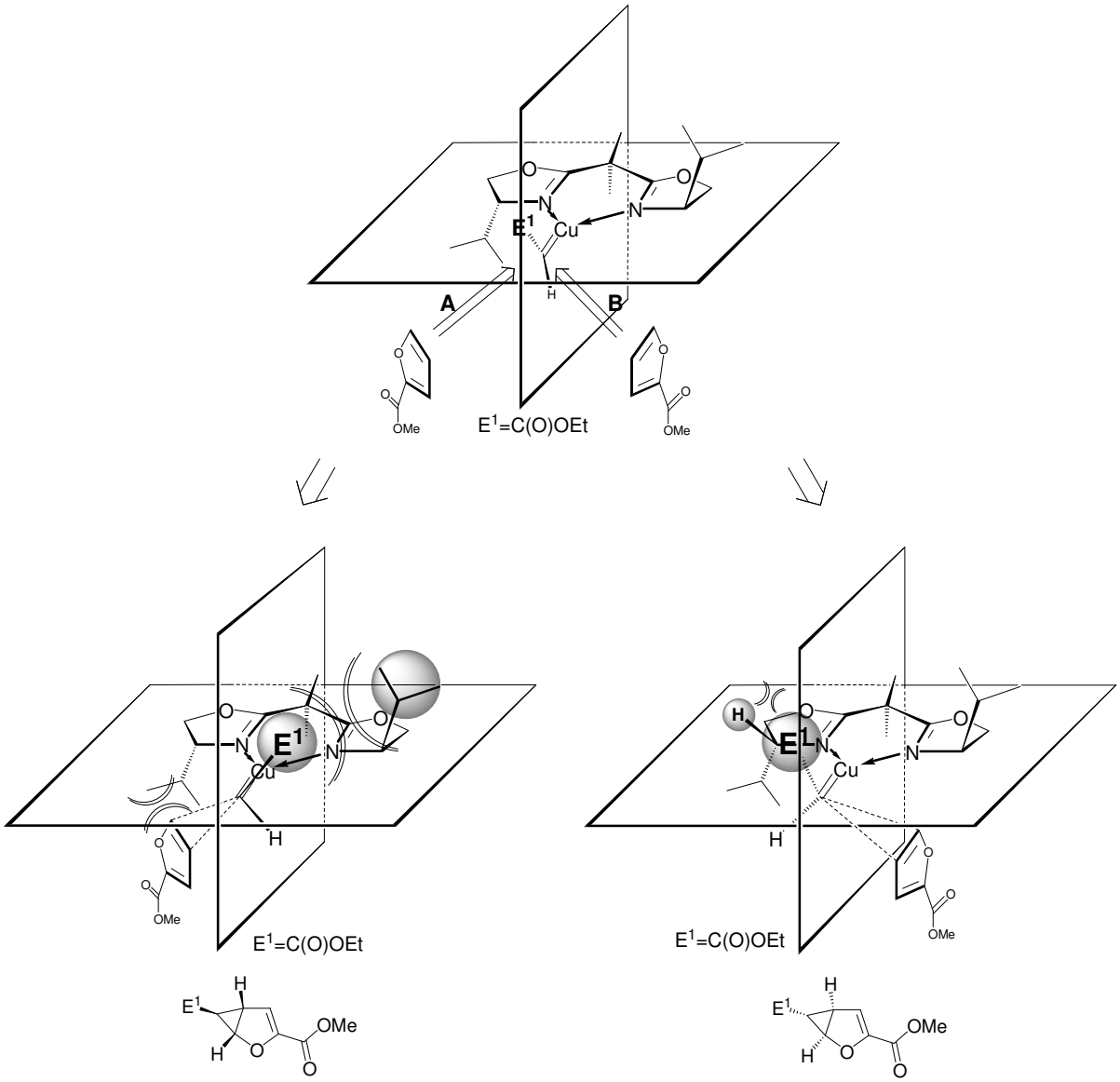
Different from other metal-carbene complexes such as pybox ruthenium carbene[99] and phorphyrin-osmium[100]carbene, copper-carbene complexes have never been characterized by X-ray crystallography. However, *Hofmann et al.*[101] succeeded to study the carbene **157** by NMR in solution, which is entirely consistent with the mechanistic postulation by *Pfaltz et al.* [102] for mono(semicorrinato)copper(I) complex (**159**)-mediated cyclopropanations. According to the *Pfaltz et al.*, cyclopropanation is carried out using bis(semicorrinato) copper(II) complex (**158**) as a precatalyst. On activation of **158** with heating in the presence of alkyldiazoacetate or phenylhydrazine, **158** is reduced to lose one semicorrin ligand. The resulting **159** reacts as an active catalyst for cyclopropanation (Scheme 40).



157 **158** **159** (R=CMe_2OH)

Scheme 40. Characterization of geometry in copper(I)-carbene complex bound to asymmetric ligand by *Hoffmann et al.*[101] (**157**) and *Pfaltz et al.*[102] (**158** and **159**).

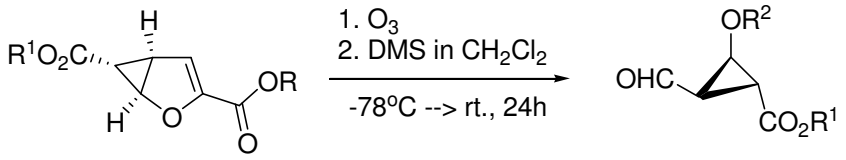
Similarly with *Pfaltz et al.*'s postulation, C_2-symmetric BOX-copper(I) complex-mediated asymmetric cyclopropanations can be visualized as shown in Scheme 40. The BOX-Cu(I) carbene complex provides two enantiotopic faces in the trigonal carbon center of Cu(I)-carbene. Upon approaching the double bond of furan carboxylic ester **149** from the left side of the carbenoid carbon center (approach A, Scheme 41), the tetrahedral bulky ester group (E^1) experiences relatively larger repulsive steric interactions with the isopropyl group than with the proton in the case of approach B (Scheme 41).



Scheme 41. Visualization of asymmetric cyclopropanation of furan-2-carboxylate **149** using BOX (**156**)-Cu(I) complex.

1.3.3 Ozonolysis of the cyclopropyl furan-2-carboxylic esters

Ozonolysis of the cyclopropane adducts **153-155** and subsequent reductive work-up with DMS led to the vicinally D-A disubstituted cyclopropane carbaldehydes **104** in good yield (Scheme 42 and Table 7).



153 (R=Me, R^1=Et)
155 (R=Et, R^1=Me)

104
160

Scheme 42. Ozonolysis of the cyclopropane furan-2-carboxylic esters **153** and **155**.

Table 7. Ozonolysis of the cyclopropyl furan-2- carboxylic esters.

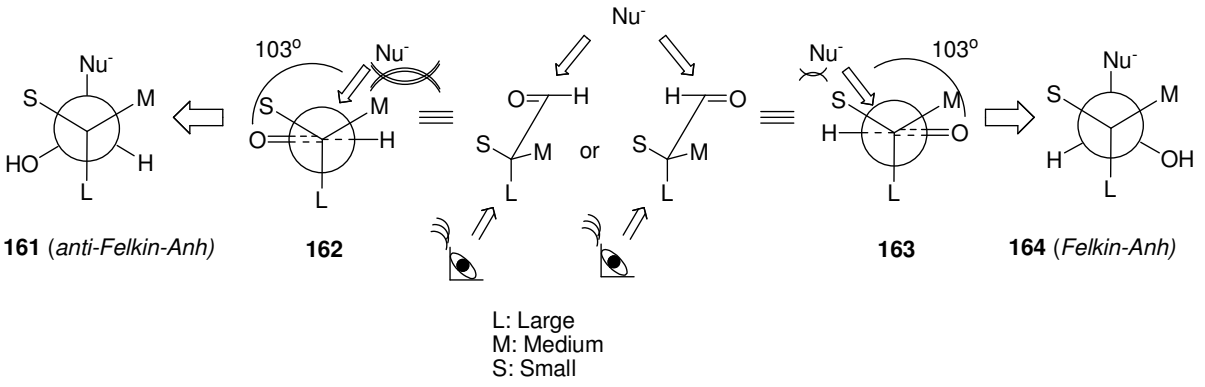
Entry	Starting material	R	Product	R^1	R^2	Yield (%) [a]
1	(*rac*)-**153**	Me	(*rac*)-**104**	Et	$C(O)CO_2Me$	37 [b]
2	**153**	Me	**104**	Et	$C(O)CO_2Me$	quant.
3	(*rac*)-**155**	Et	(*rac*)-**160**	Me	$C(O)CO_2Et$	69

[a] Crude yield before recrystallization. [b] Yield after recrystallization with ethyl acetate.

1.4 Formation of γ-butyrolactone carbaldehyde

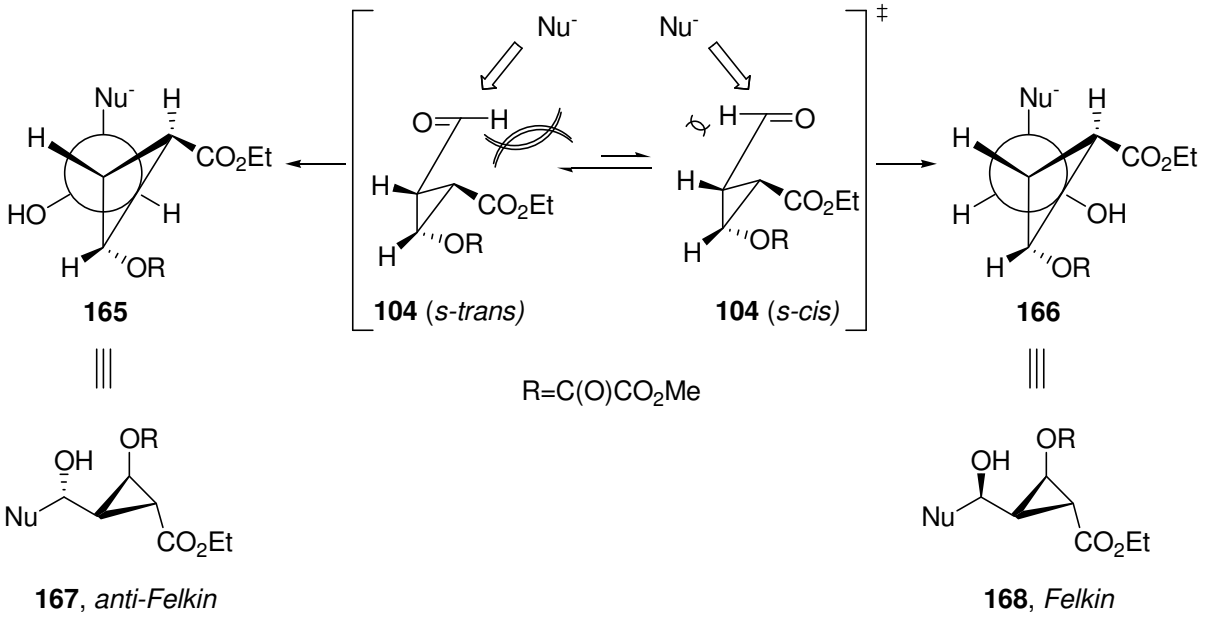
1.4.1 Determination of stereochemistry on nucleophilic addition to carbonyl compounds: *Cram's* rule and *Felkin-Anh* rule

The influence of an adjacent chiral center on a prochiral reaction center within the same molecule is an important issue for asymmetric organic synthesis. The *Cram*'s rule[103] contributed to the understanding diastereoselective 1,2-induction upon a nucleophilic attack into prochiral center of α-chiral carbonyl compound. Subsequently, based on the principles, a new model was introduced by *Felkin, Anh*, and *Eisenstein*, the so-called *Felkin-Anh* rule.[104] According to the *Felkin-Anh* rule, the carbonyl group orients orthogonally to the adjacent large group (L), resulting in two possible conformations **162** and **163** (Scheme 43). The priority of the L group is determined normally by steric bulkiness. However substituents exhibiting an electron-withdrawing effect are regarded as L independent of their steric bulkiness in the *Felkin-Anh* model. Compared with *Cram's* rule, the *Felkin-Anh* rule is advantageous since addition of the nucleophile leads directly to a staggered conformation in the product. According to calculation of *Bürgi* and *Dunitz*, the nucleophile attacks the carbonyl group with an angle of 103°.[104] The transition state **162** give rise much bigger steric repulsive interaction between the approaching nucleophile and medium group (M) group at the α-chiral center than the transition state **163** (Scheme 43).



Scheme 43. Diastereoselective 1,2-induction by *Felkin-Anh* model.

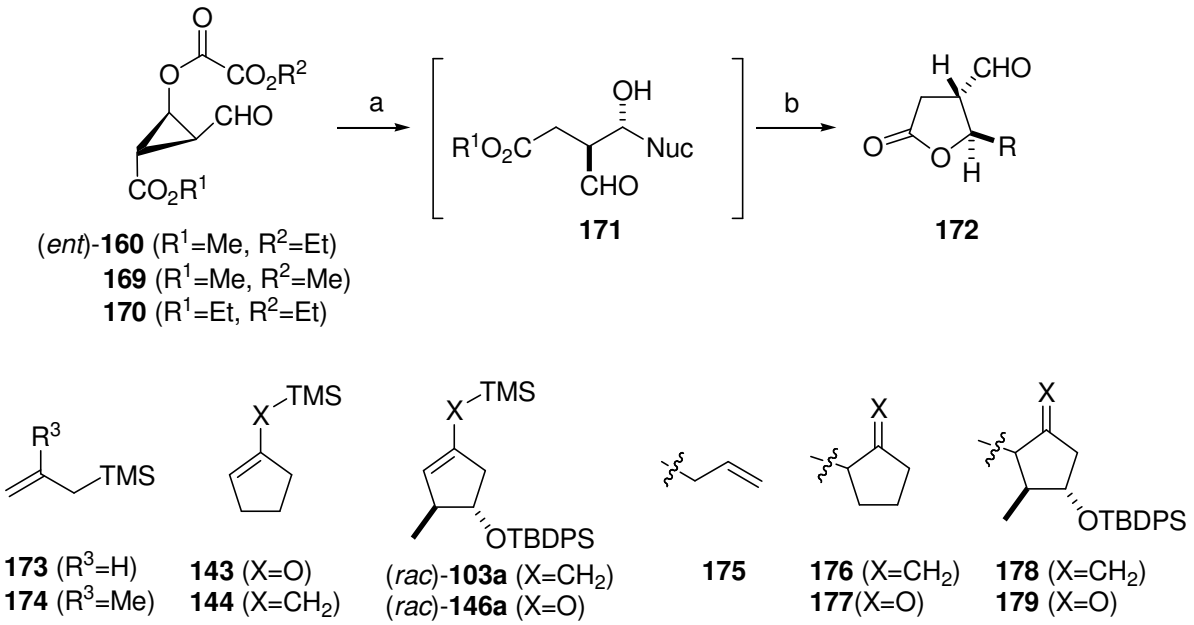
Nucleophilic attacks to sterically restricted α-chiral cyclopropane carbaldehydes[105] and ketones[106] are complicated. Of the two distinct conformations of the cyclopropyl carbaldehyde **104**, the *s-trans* conformation is preferred rather than the *s-cis* because in the latter case a steric repulsion occurs between the carbonyl group of aldehyde and cyclopropane moiety (Scheme 44). Upon approaching of nucleophile to **104**, however, the *s-cis* conformation give rise to less steric repulsive interactions than the *s-trans* one. Consequently, addition to the *s-cis* conformer leads to *Felkin-Anh* product **168**, whereas the *s-trans* conformer leads to *anti-Felkin-Anh* product **167**. Generally, the diastereoselectivities of nucleophilic additions to α-chiral cyclopropyl carbaldehydes depend highly on substituents and nucleophiles.[104]



Scheme 44. Postulation of diastereoselectivity on nucleophilic attack to cyclopropane carbaldehydes.

Although the *s-trans* conformation of cyclopropane carbaldehyde **104** is favored, when bulky nucleophiles approach the **104**, the steric repulsive interaction between nucleophile and cyclopropyl group dominates its diastereoselectivity (Scheme 44).

1.4.2 Synthesis of GBLs incorporating racemic nucleophiles



Reagents and condition: a) $BF_3{\cdot}Et_2O$ in CH_2Cl_2, Nucleophile, -78°C, 1-2 h; b) $Ba(OH)_2{\cdot}8H_2O$ (1.1 eq.) in MeOH, 0°C.

Scheme 45. GBL synthesis using different racemic allylsilanes and silyl enol ethers.

Table 8. Synthesis of GBLs incorporating racemic nucleophiles.

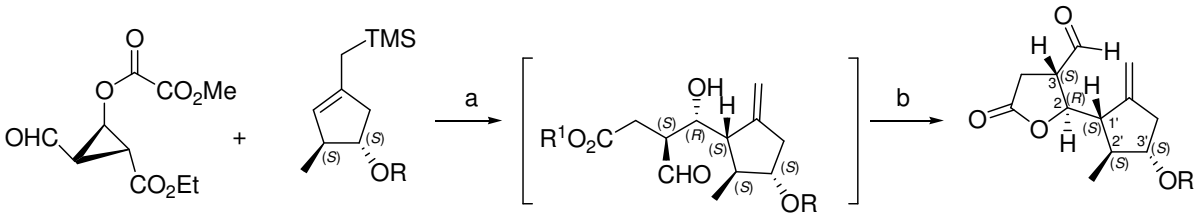
Entry	Aldehyde	Nucleophile		L.A. [a]	Rxn.time	Product (**172**)	Yield
		type	(eq.)	(eq.)	(h)	R	(%)
1	(*ent*)-**160**	**144**	1.0	1.0	12	**176**	33 [b]
2	**169**	**173**	1.1	1.0	12	**175**	42 [c]
3	**169**	**143**	1.1	1.1	12	**177**	n.r. [d]
4	**169**	(*rac*)-**146a**	1.1	1.1	1	**179**	n.r. [d]
5	(*rac*)-**170**	(*rac*)-**103a**	1.0	1.1	2	**178**	79 [e]

[a] $BF_3{\cdot}Et_2O$. [b] *dr*=92:8. 0.5 eq. of $Ba(OH)_2{\cdot}8H_2O$ was used. [c] *dr*=96:4. [d] n.r.=no reaction. [e] Crude yield. *dr* was not determined.

GBLs **172** were synthesized *via Sakurai* allylation of (*ent*)-**160**, **169**, and **170** using various acyclic and cyclic nucleophiles, followed by base-catalyzed cyclopropane ring opening and retroaldol lactonization sequence (Scheme 45 and Table 8). Attempts to do *Mukaiyama* aldol reaction of **169** with the silyl enol ether **143** and (*rac*)-**146a** were not successful (Entry 3 and 4, Table 8).

1.4.3 Synthesis of GBLs using optically active nucleophiles

With the same reaction sequence, the enantiomerically pure **104** was the starting point to synthesize GBLs **181-183** using optically active cyclic nucleophiles **103a-b** and **103f** (Scheme 46 and Table 9).



104

103a (R=TBDPS)
103b (R=TBDMS)
103f (R=Bn)

180

181 (R=TBDPS)
182 (R=TBDMS)
183 (R=Bn)

Reagents and condition: a) $BF_3{\cdot}Et_2O$ in CH_2Cl_2, allylsilanes **103**, -78°C, 1-2 h; b) $Ba(OH)_2{\cdot}8H_2O$ in MeOH, 0°C.

Scheme 46. Synthesis of GBLs incorporating optically active cyclic allylsilanes.

Different protecting groups on the allylsilane moiety were investigated. The inefficiency of the kinetic resolution step on the TBDPS protected allylsilane **138a** (Entry 1, Table 2) shifted the protecting strategy into TBDMS. However, TBDMS ether protection on **103b** was not able to survive under $Ba(OH)_2{\cdot}8H_2O$ lactonization condition. As shown in Table 9, the yields of lactone carbaldehydes ((*epi*)-**181** and **182**) went down at longer reaction time (Entry 1-2 and 3-4), respectively. Accordingly, benzyl ether protection was chosen allowing better tolerance in various reaction conditions.

Table 9. Synthesis of GBLs using optically active allylsilanes **103a-b**, and **103f**.

Entry	Aldehyde	Allylsilane	L.A. [a] (eq.)	Base (eq.)	Rxn time (h)	Product	Yield (%)	*dr*
1	**104**	(*rac*)-**103a**	1.1	1.5	39	(*epi*)-**181**	24	50:45:4:1
2	**104**	(*rac*)-**103a**	1.0	1.1	20	(*epi*)-**181**	50	53:42:3:2
3	**104**	**103b**	1.1	1.1	48	**182**	3	97:2:2
4 [b]	**104**	**103b**	1.0	1.5	15	**182**	12	88:7:5
5	(*ent*)-**104**	(*ent*)-**103b**	1.0 [c]	- [d]	4	(*epi*)-**182**	n.r. [e]	-
6	**104**	**103a**	1.1	1.5	39	**181**	24	60:40
7	**104**	**103f**	0.5	0.5	2	**183**	39	95:2:3
8	**104**	**103f**	1.2	0.4	17	**183**	65	96:2:2
9	**104**	**103f**	1.9	0.5	17	**183**	72	96:2:2
10	**104**	(*ent*)-**103f**	1.9	0.5	17	(*epi*)-**183**	50	80:20 [f]
11	**104**	**103f**	1.1	0.5	17	**183**	63	n.d. [g]
12	**104**	**103f**	1.1	0.5	3.5	**183**	68	n.d. [g]

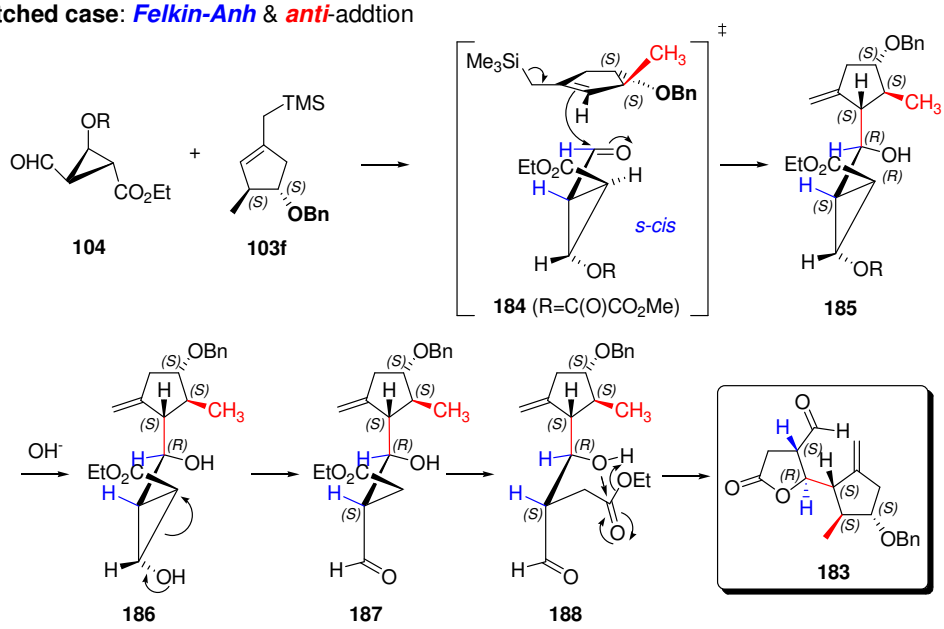
[a] $BF_3{\cdot}Et_2O$ as Lewis Acid. [b] Desilylated byproduct (**182-1**) was also obtained in 16% yield. [c] $SnCl_4$. [d] 5 mol% of *Otera* catalyst as base (see ref. 97). [e] n.r.=no reaction. [f] Just two major diastereomers were able to be determined. [g] n.d.=not determined.

1.4.4 Explanation of diastereoselectivity during the synthesis of GBLs using enantiomerically pure allylsilanes

As a result of *Sakurai* allylation of enantiomerically pure allylsilanes **103** to cyclopropane carbaldehydes **104** and subsequent base-catalyzed retroaldol lactonization, four potential diastereomers can be produced according to the conformations of **104** and the orientations of **103**. In principle, bulky substituent (OPG) of allylsilanes **103** should be located as far away as possible from the cyclopropane moiety. When the enantiomerically pure **103f** is used, **183** can be obtained predominantly as major diastereomer controlled by *Felkin-Anh* model, reacting from the *s-cis* conformation of **104**, and *anti*-addition to the methyl group of the allylsilane (matched case A, Scheme 47). Besides, three mismatched cases are possible as shown in Scheme 47. The mismatched case B is caused by *anti-Felkin-Anh* attack and *anti*-addition leading to 2,3-*syn* disubstituted GBL carbaldehyde **191**.

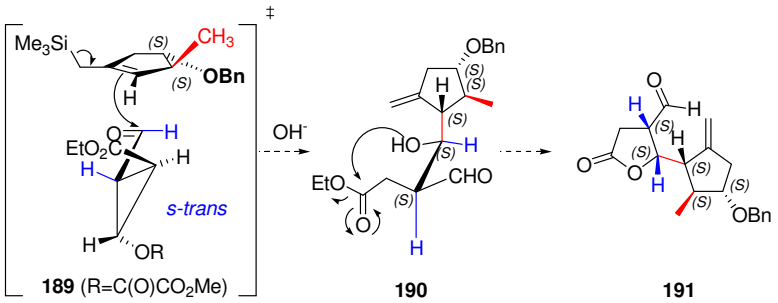
1. GBL carbaldehyde **104** + enantiomerically pure allylsilane **103f**.

A. **matched case**: ***Felkin-Anh*** & ***anti***-addtion



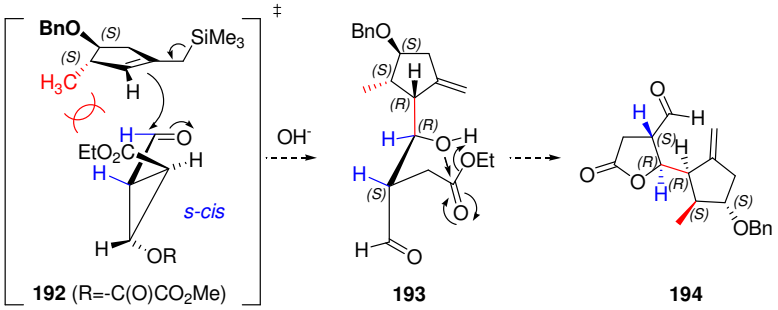
B. mismatched case

anti-Felkin-Anh
& *anti*-addtion



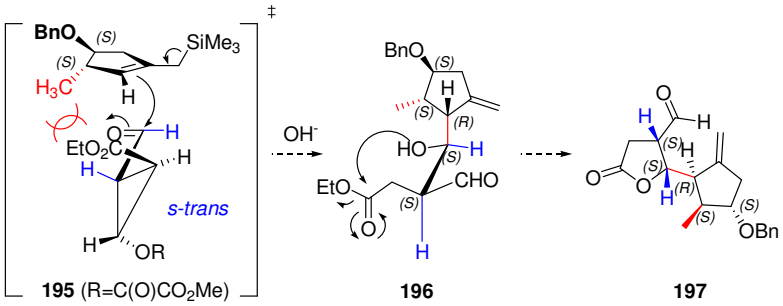
C. mismatched case

Felkin-Anh
& *syn*-addtion



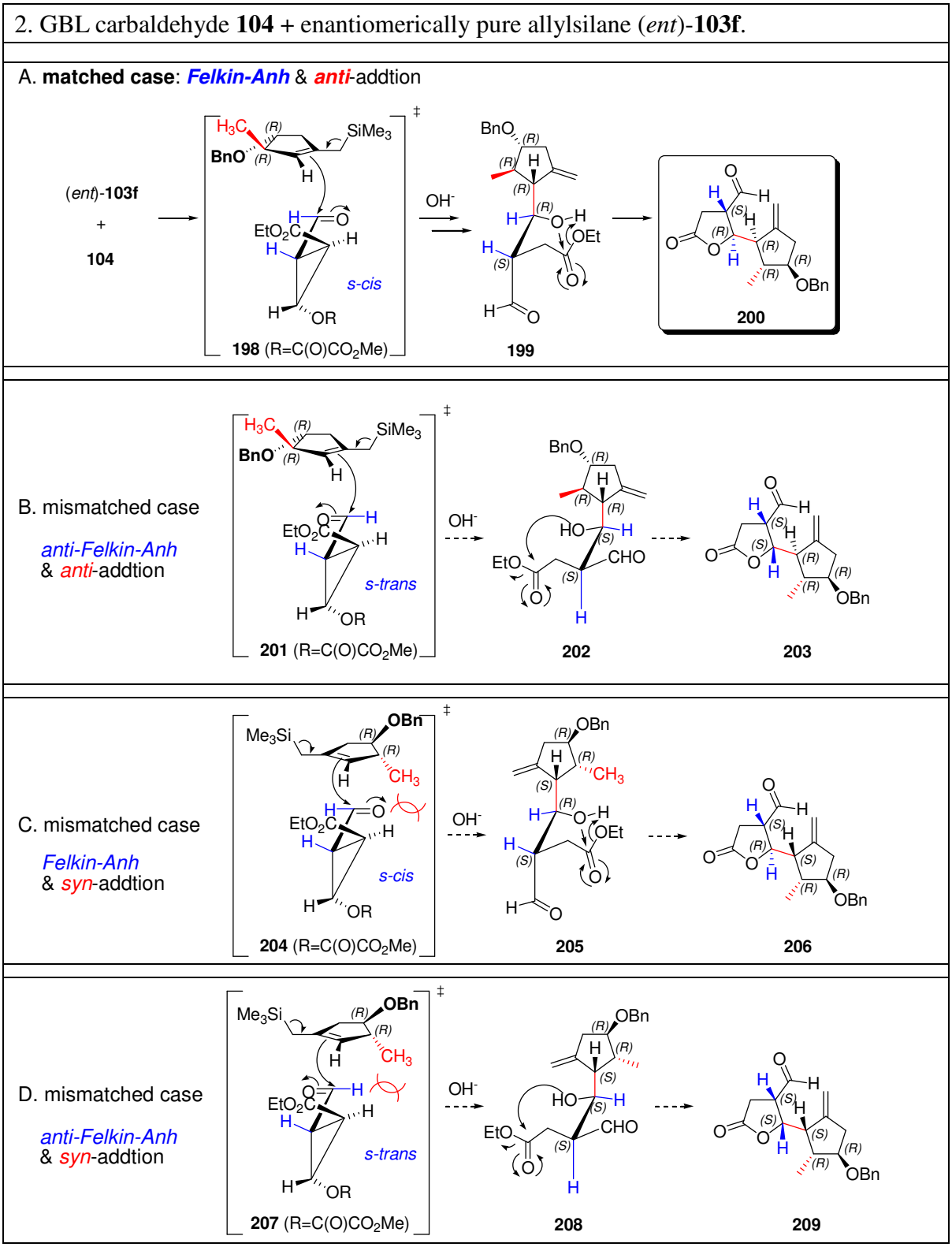
D. mismatched case

anti-Felkin-Anh
& *syn*-addtion



Scheme 47. Matched (**183**) and mismatched (**191**, **194**, and **197**) cases on using the enantiomerically pure **103f**.

The mismatched cases C and D are derived from *syn*-addition to the methyl group of the allylsilane, which give rise to steric repulsive interaction between the downward methyl group and cyclopropane carbaldehyde moiety (Scheme 47).



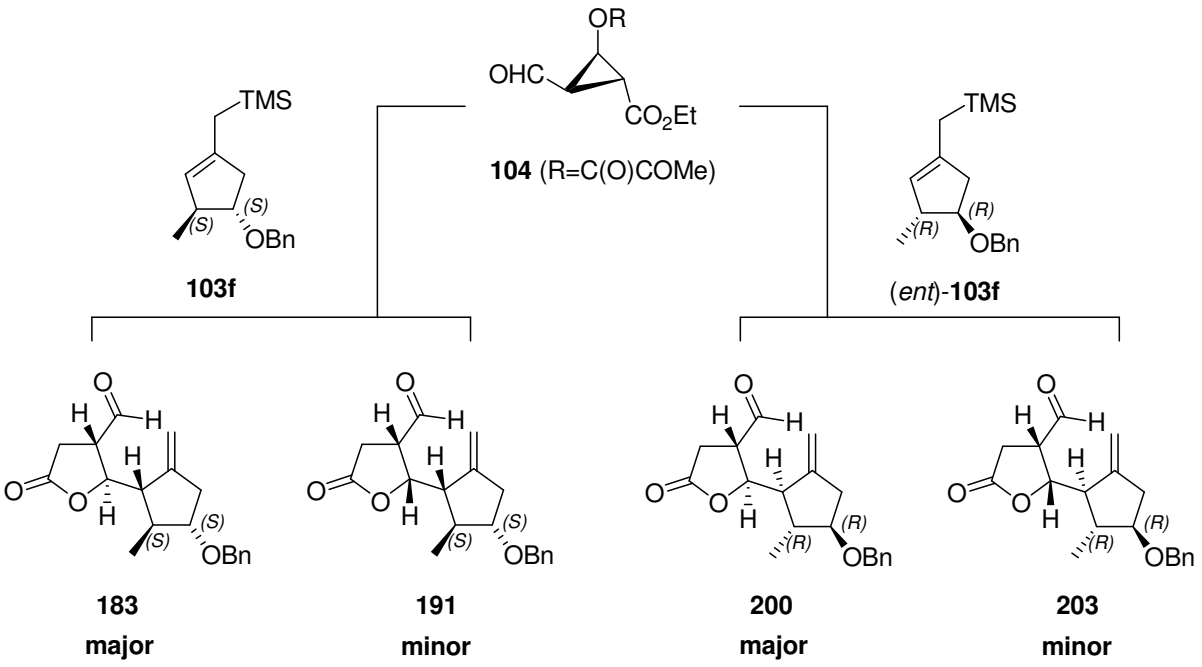
Scheme 48. Matched (**200**) and mismatched (**203**, **206**, and **209**) cases on using the enantiomerically pure (*ent*)-**103f**.

With respect to the (*ent*)-**103f**, *Felkin-Anh*-control and *anti*-addition leads to diastereomer **200** *via* corresponding transition state **198** as the matched case (Scheme 48). Three mismatched cases can occur as shown in Scheme 48 according to the same reasons explained for **103f**.

The stereochemistry of the chiral centers in **183** coincides with guaianolide-based natural target compounds such as Arglabin (**96**), Ixerin Y (**95**), and Grosshemin (**94**) (see the Scheme 20).

1.4.5 Explanation of diastereoselectivity of GBLs using enantiomerically enriched allylsilanes

Allylsilanes **103f** and (*ent*)-**103f** were not obtained with 100% *ee* but enantiomerically enriched. Consequently, reactions can lead to small amounts of diastereomers resulting from the small portion of the minor enantiomer present. The enantiomeric excess (*ee*) of **103f** and (*ent*)-**103f** was indirectly estimated from the *ee* of the corresponding precursors (-)-**137f** (91% *ee*) and (+)-**137f** (79% *ee*). Given the high preference for *anti* addition of the allylsilane, four possible diastereomers can be expected with enantiomerically enriched **103f** being controlled by *Felkin-Anh*/*anti*-addition and *anti-Felkin-Anh*/*anti*-addition (Scheme 49).



Scheme 49. An empirical set of diastereomers of GBLs using the enantiomerically enriched allylsilanes **103f** or (*ent*)-**103f**.

Table 10. Diastereomeric ratio of GBLs obtained by using enantiomerically enriched allylsilanes.

Entry	Allylsilane [a]	Diastereomeric ratio of GBLs [b]			
		183	**191**	**200**	**203**
1	**103f** (91% *ee*)	96	2	2	-
2	(*ent*)-**103f** (79% *ee*)	20 [c]	-	80 [c]	-

[a] Enantiomeric enriched allylsilanes. The *ee* were indirectly assumed from the corresponding precursors (-)-**137f** and (+)-**137f**. [b] Measured the integration of ^{1}H-NMR. [c] Just two diastereomers were determined.

Indeed, in the reaction of **104** and the enantiomerically enriched **103f** (Entry 1, Table 10), the ^{1}H-NMR at aldehyde region shows clearly the existence of three diastereomers at δ 9.57 (2%, J = 1.6 Hz), 9.64 (96%, J = 1.1 Hz), and 9.68 (2%, J = 1.4 Hz) as a doublet peak, respectively.

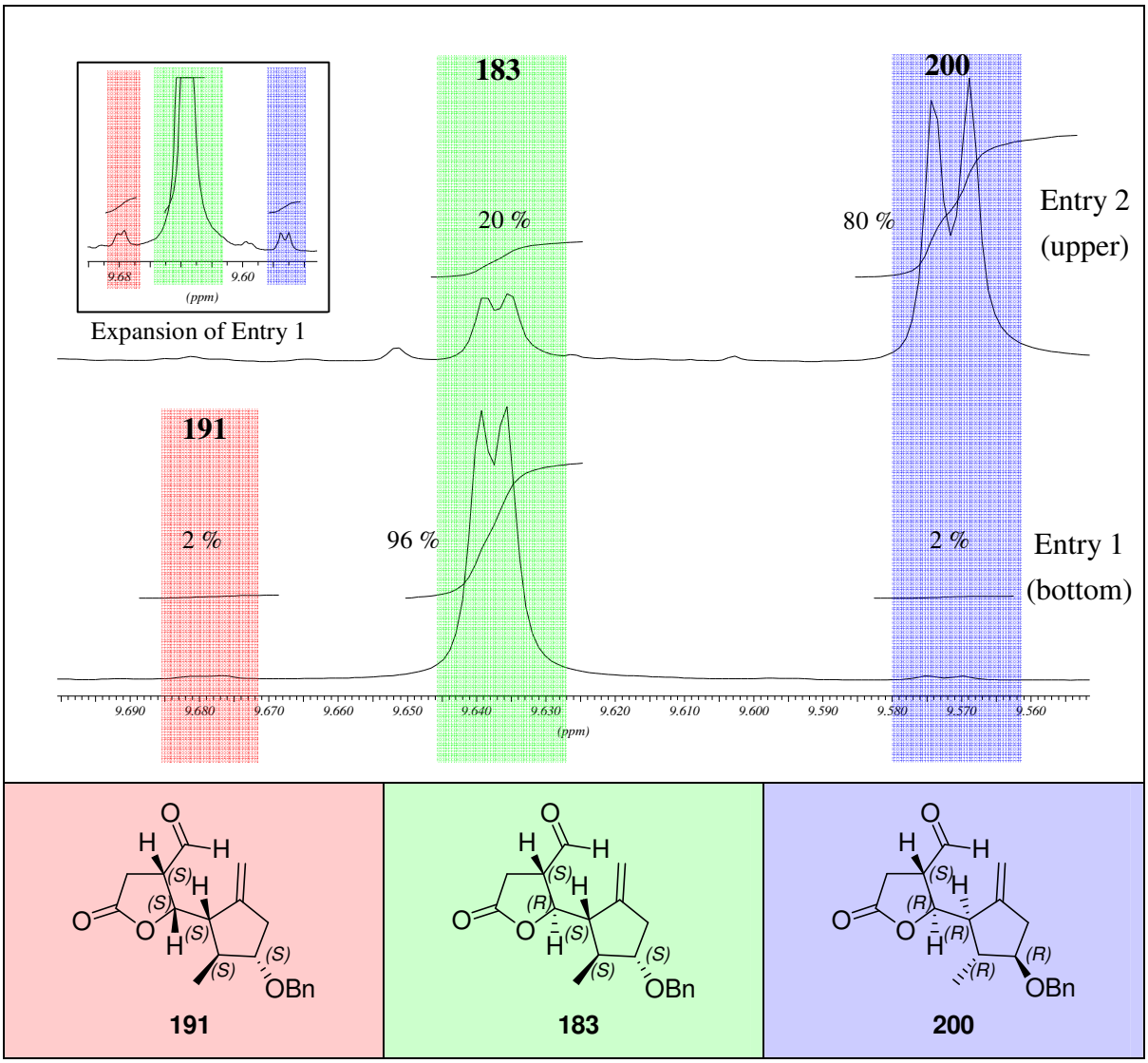
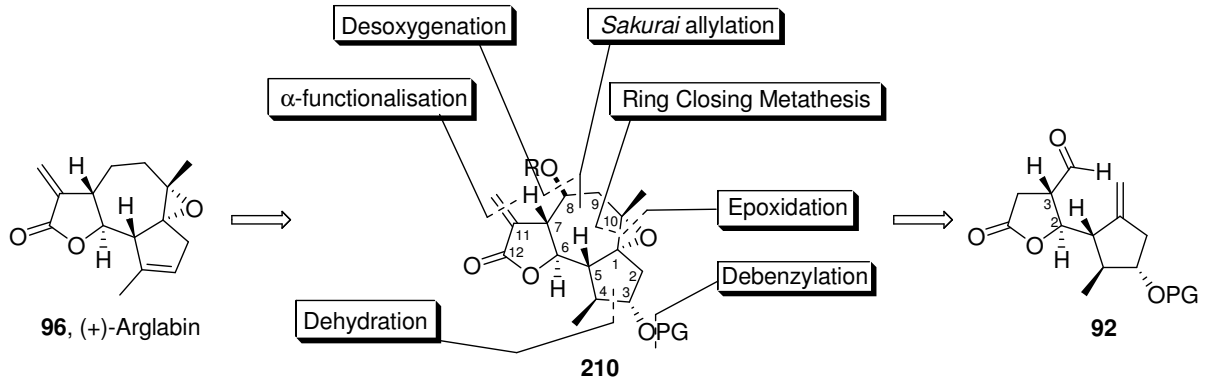


Figure 6. Assignment of diastereomers by comparison of ^{1}H-NMR in Entry 1 (bottom), and Entry 2 (upper) of Table 10. The magnified intensity of Entry 1 is shown in a small rectangle.

The major peak at δ 9.64 (J = 1.1 Hz) can be assigned to **183** corresponding to the matched case A in Scheme 47. Of the remaining two peaks, the peak at δ 9.57 (J = 1.6 Hz) is assigned as **200** being the major product in the reaction between **104** and (*ent*)-**103f** (Entry 10, Table 9). The third peak at δ 9.68 (J = 1.4 Hz) must be **191**. The remaining possible diastereomer **200** (*anti-Felkin-Anh*/*syn*-addtion) could not be found.

In the reaction of **104** and the enantiomerically less pure (*ent*)-**103f** (Entry 10, Table 9), **200** appeared at δ 9.57 as major diastereomer and **183** was found at δ 9.64 as 2nd major one. In this case, just 2 major diastereomers were determined.

1.5 Towards the total synthesis of Arglabin

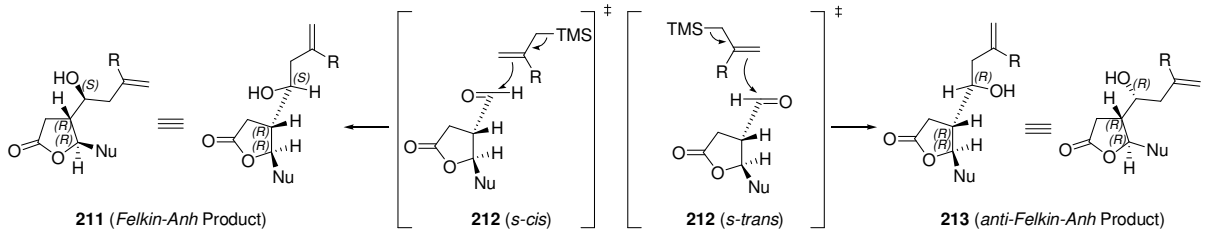


Scheme 50. Retrosynthetic analysis of Arglabin (**96**) from GBL carbaldehyde **92**.

The asymmetric synthesis towards Arglabin (**96**) is composed of multi-step transformations starting from the 2,3-*trans* disubstituted GBL carbaldehyde **92**: Elongation of the aldehyde functionality of **92** *via Sakurai* allylation, a ring closing metathesis reaction (*i.e.* RCM), desoxygenation, debenzylation, and diastereoselective epoxidation. Additionally, formation of the double bond at C3-C4 in **210**, and α-functionalization at C11 have to be carried out (Scheme 50).

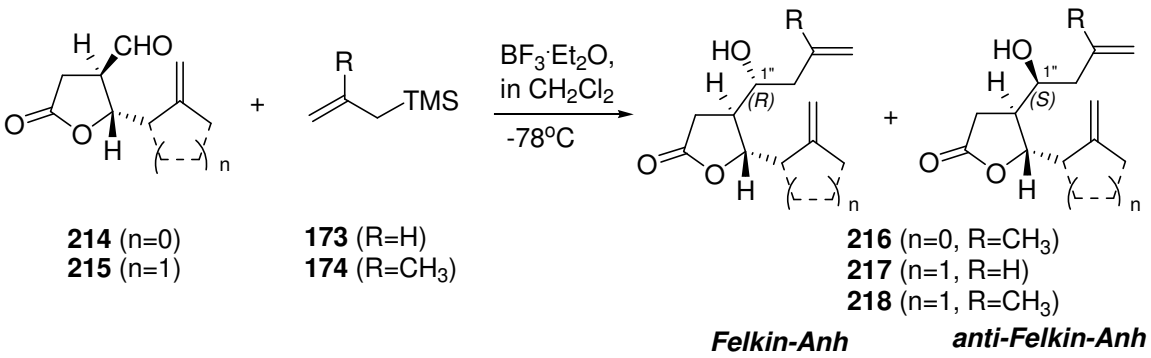
1.5.1 Model study for the synthesis of Arglabin

Upon a nucleophilic attack to GBL carbaldehydes of type **212** *via Sakurai* allylation, a new chiral center is generated. Consequently, two new diastereomers, *i.e.* **211** in agreement with the prediction of the *Felkin-Anh* rule or **213**, can be formed (Scheme 51).



Scheme 51. Diastereoselectivity during *Sakurai* allylations with GBL carbaldehydes.

The GBLs **214** and **215** containing no chiral centers in their side chain were applied in *Sakurai* allylations with **173** and **174** mediated by $BF_3{\cdot}Et_2O$ (Scheme 52).[83] The results are shown in Table 11. In these cases, the diastereomeric ratios are merely determined on the basis of newly formed chiral center C1" (Table 11).



214 (n=0)
215 (n=1)

173 (R=H)
174 ($R=CH_3$)

216 (n=0, $R=CH_3$)
217 (n=1, R=H)
218 (n=1, $R=CH_3$)

Felkin-Anh ***anti-Felkin-Anh***

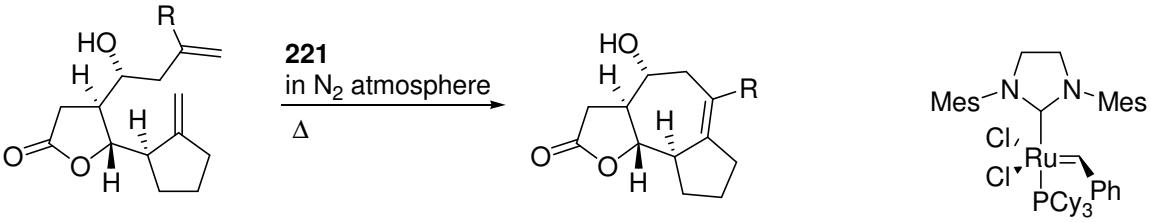
Scheme 52. *Sakurai* allylation of **214** and **215**.

Table 11. *Sakurai* allylation of **214** and **215**

Entry	Starting material	Allylsilane (eq.)	Rxn. Time (h)	Product	Yield (%)	*dr* (1"R:1"S)
1	**214**	2.0 [a]	11	**216**	50	72:28
2	**215**	1.1 [b]	12	**217**	33	80:20
3	**215**	1.1 [a]	16	**218**	20	72:28

[a] **174**. [b] **173**.

Subsequent RCM of **217** and **218** was attempted using **221** as catalyst, which was synthesized by following the synthetic procedure of *Hoveyda et al.*[107] RCM of the unprotected homoallylic alcohols **217** and **218** was not successful.



217 (R=H)
218 ($R=CH_3$)

219 (R=H)
220 ($R=CH_3$)

221

Scheme 53. RCM of **217** and **218** under conventional thermal heating.

Conversion was hardly observed even at long reaction time under conventional thermal heating using oil bath (Scheme 53 and Table 12). The desired RCM products **219** and **220** could not be obtained, although a number of examples have shown that unprotected hydroxyl group do not disturb or even accelerate ruthenium-based RCM reactions.[108]

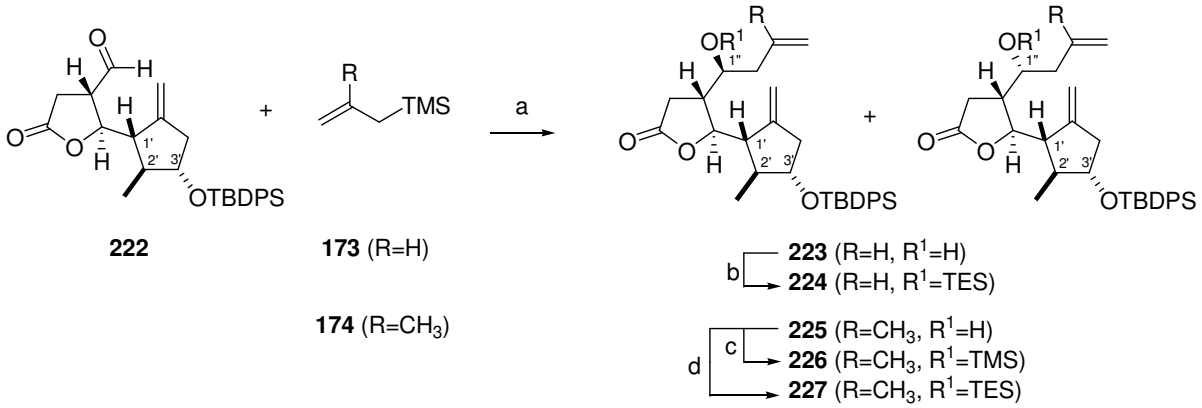
Table 12. Attempts to do RCM of the unprotected homoallylic alcohol **217** and **218**.

Entry	S.M. (mM)	Solvent	**221** (mol %)	Rxn. Time (h)	Product	Yield (%)
1 [a]	**217** (8.5)	Toluene	5.0	48	**219**	- [b]
2 [a]	**218** (10.1)	CH_2Cl_2	10.0	288	**220**	- [c]

[a] Conventional thermal heating using oil bath. Under N_2 atmosphere. [b] 45% of starting material was recovered. [c] 76% of starting material was recovered.

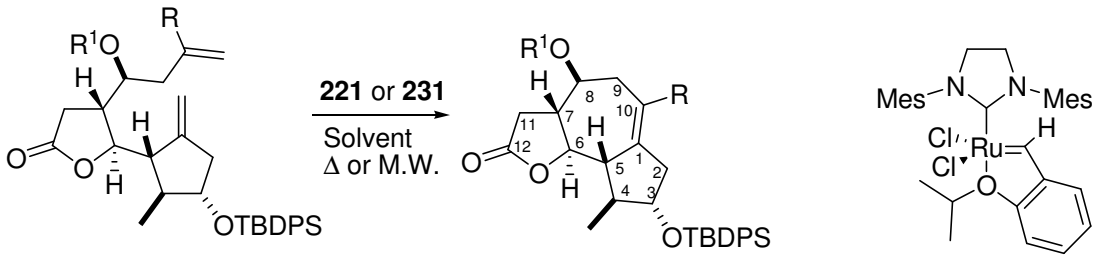
Therefore, silyl protection of alcohol was done before RCM reactions because the adjacent hetero atom to the double bonds such as allylic alcohols can affect adversely in the following RCM reactions via coordination of hetereoatoms and double bonds with catalysts.[109]

Another closer model study for the synthesis of Arglabin (**96**) was carried out using **222** containing the epimeric side chain as the starting point. The addition of allylsilanes to **222**, being a mixture of two diastereomers in the beginning, led more complicated four diastereomers (Scheme 54). The diastereomeric ratio could be analyzed by NMR, using the signal of the methyl group at C-2' showing typical doublet peak (J = 6.9 Hz). Subsequent silyl protection of alcohols was performed successfully using TMSCl and TESCl under Et_3N and DMAP condition (Scheme 54).



Reagents and conditions: a) **173** (3.0 eq.), $BF_3{\cdot}Et_2O$ (2.0 eq.), CH_2Cl_2, -78°C, 26 h, 95% (**223**, crude, *dr*=54:26:12:8): **174** (2.0 eq.), $BF_3{\cdot}Et_2O$ (1.1 eq.), CH_2Cl_2, -78°C, 60 h, 62% (**225**, *dr*=40:36:14:10); b) Et_3N (2.0 eq.), TESCl (1.5 eq.), 63.5 h, rt., 65% (**224**, *dr*=49:39:12); c) Et_3N (3.0 eq.), TMSCl (5.0 eq.), 3.5 h, rt., 54% (**226**, *dr*=42:37:14:7); d) Et_3N (10 eq.), TESCl (3.0 eq.), 44.5 h, rt., 65% (**227**, *dr*=38:36:13:13)

Scheme 54. *Sakurai* allylation of **222** and subsequent silyl protection of alcohols.



224 (R=H, R^1=TES)
226 (R=CH_3, R^1=TMS)
227 (R=CH_3, R^1=TES)

228(R=H, R^1=H)
229 (R=CH_3, R^1=TMS)
230 (R=CH_3, R^1=H)

231

Scheme 55. RCM of **224** and **226**-**227**.

RCM of **224** using **221** as catalyst afforded **228** in 48 % yield as four diastereomers, which were isolated by column chromatography and analyzed separately (Entry 2, Table 13). Recrystallization yielded the mono diastereomer in pure form which could be characterized by an X-ray crystal structure (Figure 7). RCM of **227** to yield the tetrasubstituted **230** (Entry 3, Table 13) proceeded in a lower yields than the trisubstituted **224** (Entry 2, Table 13) under the same reaction condition. Compared with conventional thermal heating using oil bath, RCM of **224** under microwave irradiation was achieved within 1 h employing 20 mol % of **221** (Entry 4, Table 13). Unspecific desilylation using TBAF led to deprotection of both silyl groups and the major diastereomer of **231** could be obtained as a crystal in pure form shown in Figure 8.

Table 13. RCM of the silyl protected alcohols **224** and **226**-**227**.

Entry	S.M.	Catalyst (mol %)	Rxn. Condition [a]	Rxn Time (h)	Desilylation (eq.)	Prod.	Yield (%)
1	**226**	**231** (20)	$ClCH_2CH_2Cl$ T.C. (84°C)	300	-	**229**	16 [b]
2	**224**	**221** (10)	toluene T.C. (110°C)	360	$ZnBr_2/H_2O$	**228**	48 [c]
3	**227**	**221** (10)	toluene T.C. (110°C)	550	$ZnBr_2/H_2O$	**230**	28 [d]
4	**224**	**221** (20)	toluene M.W.	1	TBAF	**232**	32 [e]

[a] T.C.=Thermal conduction using oil bath: M.W.=Microwave irradiation. [b] *dr* is not determined. 60% of starting material was recovered. [c] *dr*=51:20:17:12. [d] Three diastereomers were observed (*dr*=76:15:9). 22% of **225** was recovered. [e] *dr* is not determined. X-ray crystal of **232** is shown in Figure 8.

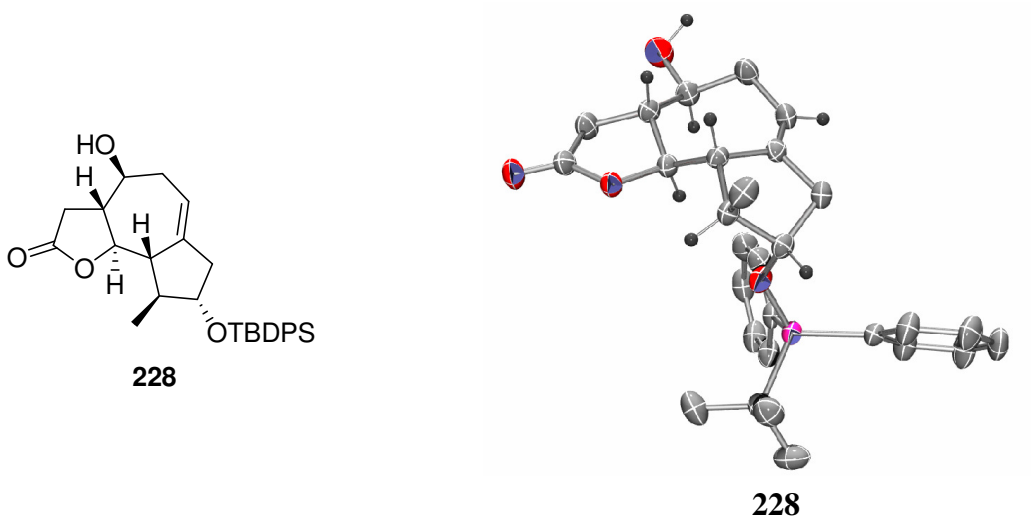


Figure 7. X-ray crystal structures of **228** (Thermal Ellipsoid, 50% probability. Some H-atoms were hidden).

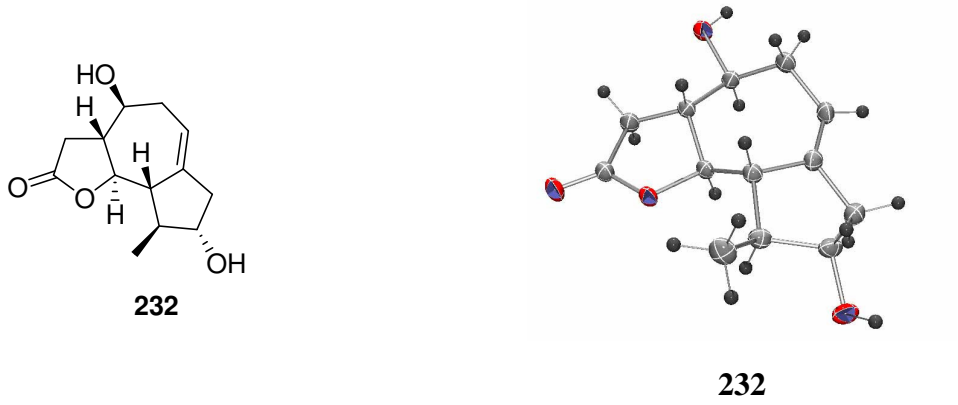
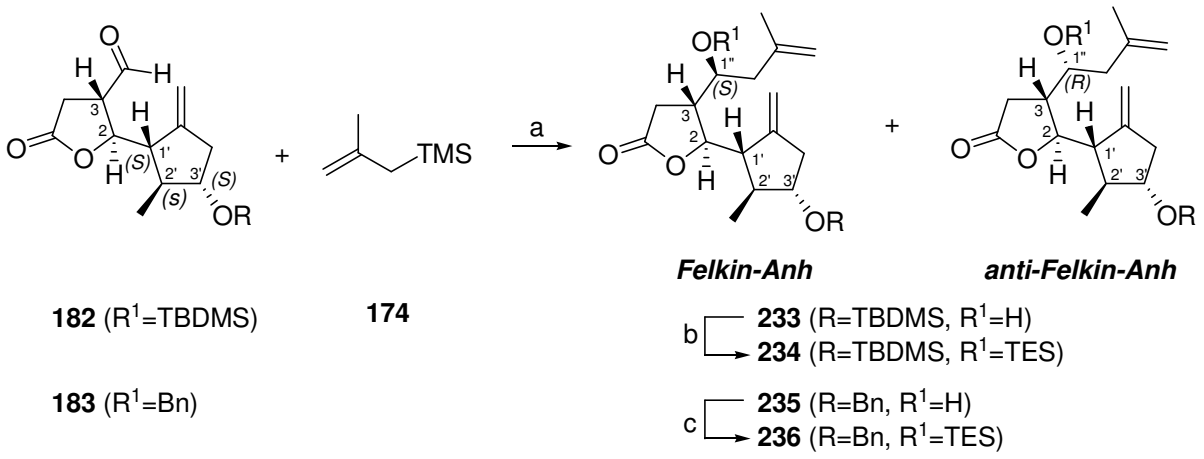


Figure 8. X-ray crystal structures of **232** (Thermal Ellipsoid, 50% probability).

1.5.2 Towards the total synthesis of Arglabin (96)

The sequence of the model studies **228**-**230** was repeated with optically active GBLs **182** and **183** towards the asymmetric synthesis of Arglabin (**96**). *Sakurai* allylation of **183**, subsequent silyl protection and RCM were carried out. However, **182** could not be obtained in sufficient amounts due to the loss of compound *via* desilylation of TBDMS protecting group during the *retro*-aldol lactonization of **104** and **103b** under $Ba(OH)_2$ condition. Therefore, this derivative was only studied in one allylation with **174**, giving rise rise to **233** in 40 % yield as a 86:4 mixture of diastereomers (Entry 1, Table 14). The silyl protected RCM precursor **236** was synthesized in good yield from **235** (Scheme 56) being obtained from the allylsilane addition of **183** with **174** (Entry 2, Table 14). Three diastereomers (*dr*=75:22:3) were observed in **235**, which could be analyzed as shown in Figure 9.



Reagents and conditions: a) see table 14; b) Et_3N (1.7 eq.), TESCl (2.0 eq.), DMAP (cat.), 96 h, rt., 49% (**234**, *dr*=73:27); c) Et_3N (1.5 eq.), TESCl (2.0 eq.), DMAP (1.1 eq.), 64 h, rt., 95% (**236**, *dr*=70:30).

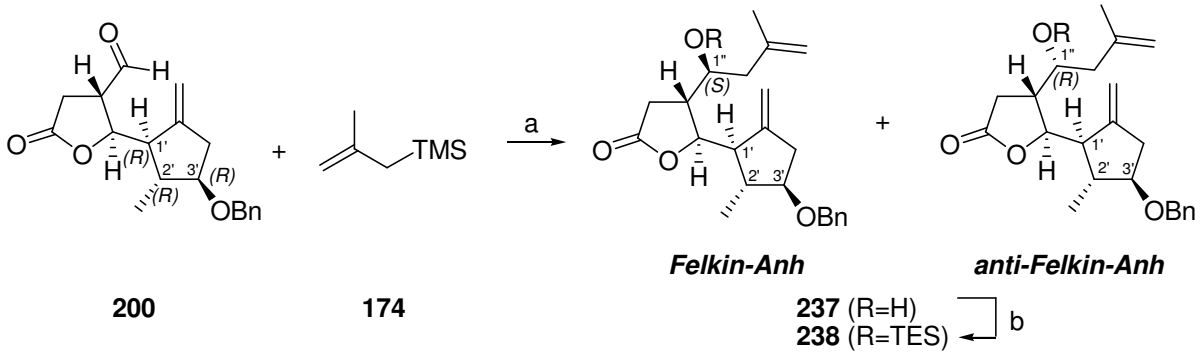
Scheme 56. *Sakurai* allylation of optically active **182** and **183** and subsequent silyl protection.

Table 14. *Sakurai* allylation of optically active GBL carbaldehydes **182** and **183**.

Entry	Starting material	Allylsilane (eq.)	L.A. (eq.) [a]	Rxn. Time (h)	Product	Yield (%)	*dr*
1	**182**	2.0	1.0	12	**233**	40	86:14 [b]
2	**183** [c]	2.0	1.0	50	**235**	80	75:22:3 [d]

[a] $BF_3{\cdot}Et_2O$. [b] Three diastereomers were observed; two major diastereomers (86%) and one minor diastereomer (14%). [c] **183** contained 3% of minor diastereomers either **191** or **194**. [d] 3% of diastereomer (1"S)-**237** coming from the reaction with **200** was also observed.

Allylation of **200**, employed as a mixture of **200** and **183**, was also performed to prepare the RCM precursor **238** (Scheme 57).



Reagents and conditions: a) $BF_3{\cdot}Et_2O$ (1.1 eq.), **174** (2.0 eq.), -78°C, 80 h, 72% (**237**, *dr*=57:19:17:7); b) Et_3N (1.5 eq.), TESCl (2.0 eq.), DMAP (1.1 eq.), 48 h, rt., 80% (**238**, *dr*=68:12:10:9).

Scheme 57. *Sakurai* allylation of optically active **200** and subsequent silyl protection of **237**.

As shown in Figure 9, allylsilane addition to **183** afforded two main diastereomers (1”S)-**235** (75%) and (1”R)-**235** (22%) *via Felkin-Anh* control and *anti-Felkin-Anh* control, respectively. The third diastereomer (3%), showing a distinct signal at δ 1.68, was assigned to be (1”S)-**237** by comparison with ^{1}H-NMR of the major product in the reaction between **200** and **174** (bottom, Figure 9). In the case of less diastereomerically pure **200**, more than four diastereomers were observed (bottom, Figure 9), however only four diastereomers could be assigned as follows. The major diastereomer (57%) showing a signal at δ 1.67 can be assigned to (1”S)-**237** as a *Felkin-Anh* controlled adduct. The second diastereomer showing a signal at δ 1.72 is (1”S)-**235** (19%). The third diastereomer, showing a signal at δ 1.73, was assigned to be (1”R)-**235**. The peak at δ 1.76 (17%) was assigned to be the *anti-Felkin-Anh controlled* adduct (1”R)-**237**.

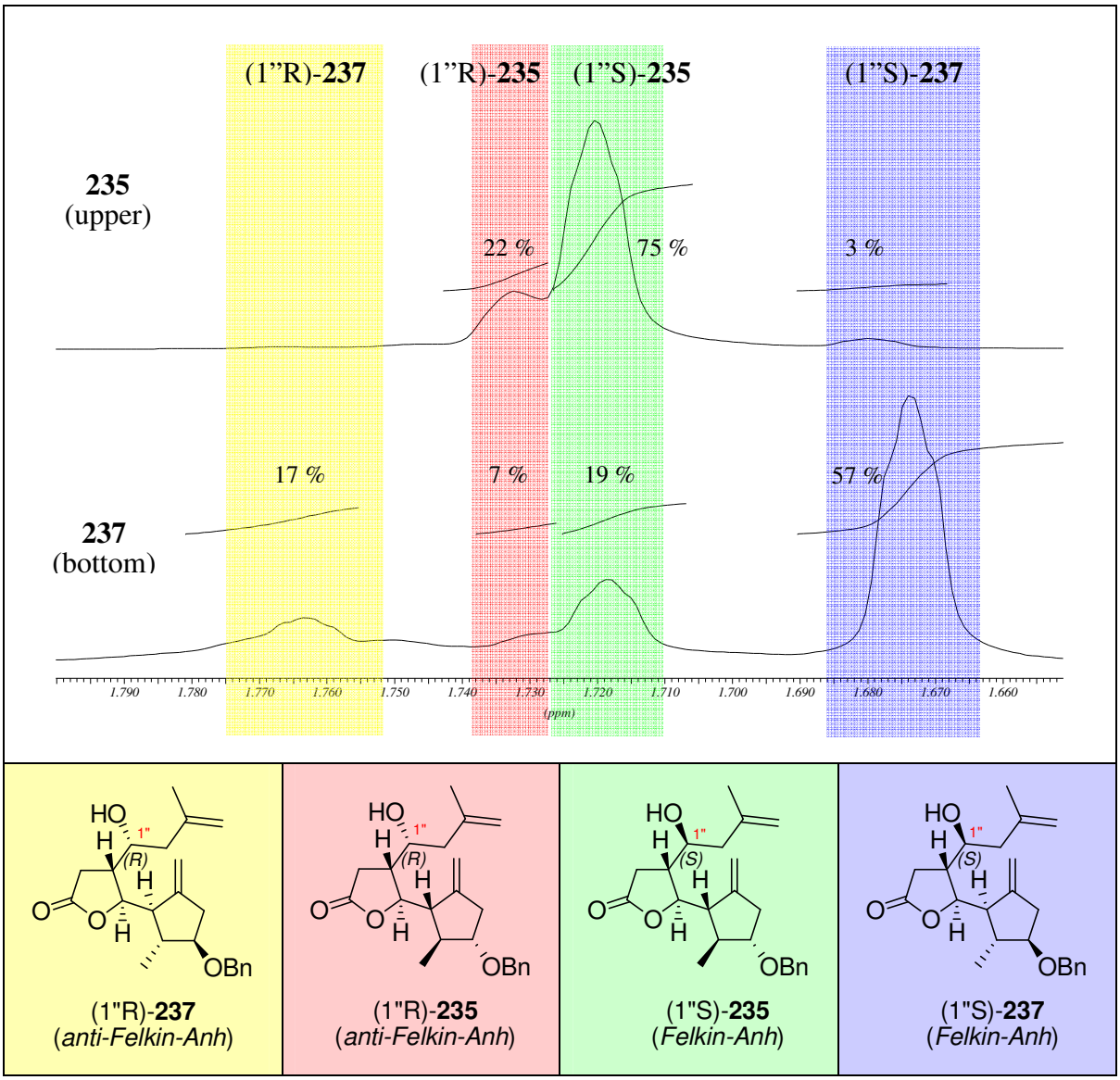


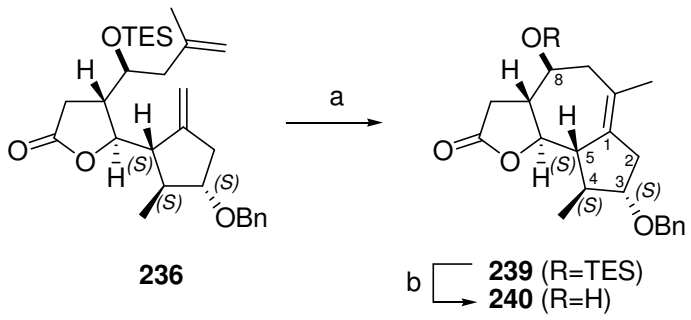
Figure 9. The assignment of the diastereomers by comparison with ^{1}H-NMR of **235** (Entry 2, Table 14) and **237** (Scheme 57).

1.5.3 RCM under microwave irradiation

Microwave dielectric heating is an appropriate method to drive reaction media rapidly to chemical reactions *via* the transformation of electromagnetic radiation into heat. Compared with conventional thermal conductions, such as Bunsen burners, oil baths, and hot plates, microwave irradiations have advantages of decreasing reaction time and improving yields.[110] Microwave ovens came to markets in the 1950s with a view to heating foodstuffs rapidly, but utilizations of microwave for chemical reactions not so far remote. Since the mid-1980s microwave assisted organic synthesis (MAOS) has been used more and more in many different reactions.[111]

Microwave radiation consists of two components, a magnetic field and an electric field being responsible for dielectric heating. Molecules having dipoles align themselves along with the oscillating external electric field. At a given frequency of electric field, not all the molecules rotate unified manner but they make phase differences. This phase differences cause energy to be lost from the dipoles by molecular frictions and collisions, giving rise to dielectric heating.[111c] Among a number of applications in MAOS, ring closing metathesis (RCM) reaction is still a recent field of research. Compared with RCM using conventional thermal heating, microwave irradiation makes the reaction media homogeneous so rapid as to achieve the optimal activities of catalysts, resulting in the less thermal decomposition of catalysts caused by direct contact with reaction vessel, so called walleffect.[111a] Many metathesis reactions are known as considerable improvements of yields under microwave irradiation.[112]

In this work, microwave assisted RCM reactions were performed using a mono-cavity microwave synthesizer (SYNLAB®, ν = 2.45 GHz, max. 300W) with quartz reaction vessel equipped water cooling system under open ambient pressure and inert argon gas sparging conditions. In all cases, the catalyst **221** was added as solution in toluene using Teflon tube connected to syringe.



236

Reagents and conditions: a). **221** (10-22 mol %), toluene, M.W., Ar sparging; b). TBAF, THF, rt.

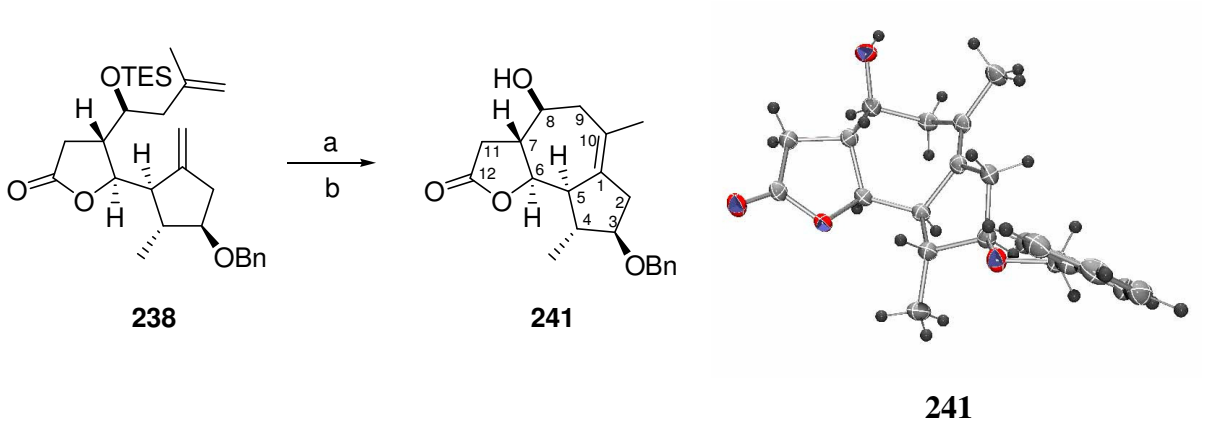
Scheme 58. RCM of **236** under microwave irradiation.

RCM reaction of **236** was carried out under microwave irradiation, varying the amounts of catalyst employed (Scheme 58). Addition of 15 mol% of catalyst **221** at once (Entry 1, Table 15) showed a lower yield of **240** than three separate addition of 5 mol% catalyst each over a total time of 35 min (Entry 2, Table 15) under the same reaction condition. When the catalysts were added as powder, the yield was reduced drastically (Entry 3, Table 15). The slight reduction of yield was observed in the case of Entry 4, being added 10 mol% of catalyst first and the last 5 mol% at 120 min, comparing with additions of 5 mol% of **221** over three times (Entry 2, Table 15). The reaction could be scaled up, converting **236** on scale of 1g to **240** as well (Entry 6, Table 15).

Table 15. RCM of **236** under microwave irradiation.

Entry	**236** (mM)	Catalyst [a] (mol %)	Rxn. Time (min)	TBAF (eq.)	Yield (%) [g]
1	37	15	60	1.25	50
2	62	5+5+5 [b]	75	1.25	61
3	78	5+5+5+5 [c]	65	1.25	30
4	120	10+5 [d]	180	1.0	57
5	126	5+5+5+7 [e]	460	1.25	61
6	69	5+5+5+5 [f]	480	1.25	72

[a] Grubbs(II) catalyst **221**. [b] Addition at 0 min, 20 min, and 35 min. [c] Direct addition of **221** as powder at 0 min, 15 min, 45 min, and 65 min. [d] Addition at 0 min and 120 min. [e] Addition at 0 min, 120 min, 240 min, and 340 min with 10 min of breaks. [f] Addition at 0 min, 100 min, 185 min, and 320 min. [g] In all cases, *dr*=4:1 is observed.



238 **241**

241

Reagents and conditions: a). **238** (194 mM), **221** (four separate additions of 5+5+5+5 mol % at the reaction time of 5 min, 120 min, 260 min, and 400 min), toluene, M.W., Ar sparging; b). TBAF, THF, rt. 69% (*dr*=69:12:8:6:5).

Scheme 59. RCM of **238** under microwave irradiation and the X-ray crystal structure of **241** (Thermal Ellipsoid, 50% probability).

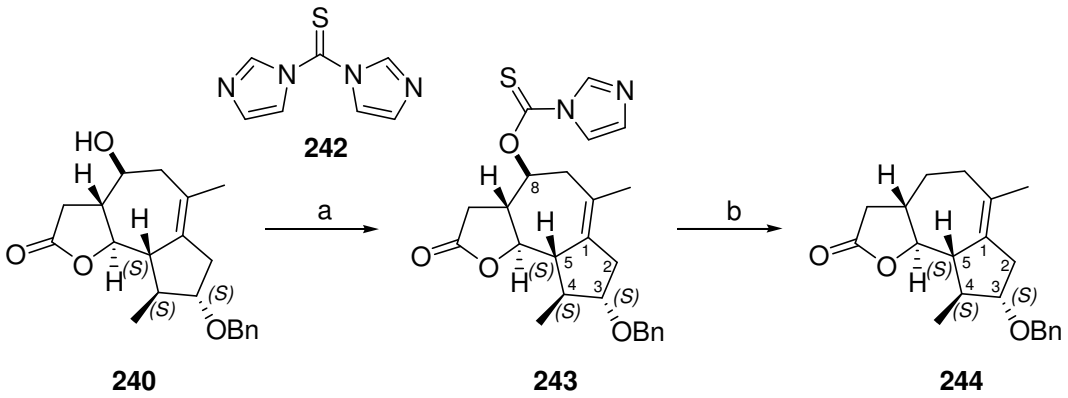
In the RCM of **238**, a complex mixture of diastereomers was obtained due to the mixture of diastereomers. Upon recrystallization the major diastereomer could be obtained in pure form and analyzed by X-ray crystallography. The structure confirmed the *syn* relationship between C4-Me and H5 (Scheme 59).

Different from heterogeneous addition of Grubbs (II) catalysts in conventional thermal conductions, the homogeneous addition of **221** as solution in toluene under microwave irradiation and inert Ar gas sparging techniques led RCM reactions to success in good yield, although the substrates were structurally-constrained tetrasubstituted olefin systems.[113]

1.5.4 *Barton-McCombie* desoxygenation

Desoxygenaton of secondary alcohols, known as *Barton-McCombie* reaction,[114] is an important transformation in the synthesis of deoxy-carbohydrate compounds, [115] carbocycles, [116] natural products containing GBL. [117] Besides, biologically active guaianolide-based natural products such as Compressanolide (**34**), Estafiatin (**84**), and Arglabin (**96**), do not contain hydroxyl group at C8. For such a transformation, different kinds of xanthates[118] can be introduced first, followed by reduction of radical intermediates using Bu_3SnH/AIBN, [119] Bu_3SnH/Et_3B, [120] or alternative to toxic Bu_3SnH; tris(trimethylsilyl)silane /AIBN,[121] phosphine-borane/AIBN,[122] or $(Bu_4N)_2SO_8/HCO_2Na$.[123]

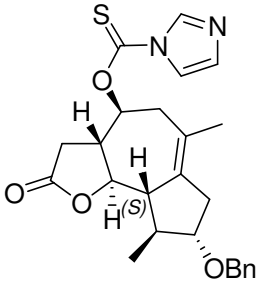
In the course of the synthesis towards Arglabin (**96**), the *O*-imidazolylthiocarbonated compound **243** was synthesized in quant. yield (*dr*=4:1) from **240** by the reaction with thiocarbonyldiimidazole (**242**) using DMAP as catalyst. Without DMAP formation of **243** was not efficient (37% yield). By the column chromatography, the major diastereomer, the X-ray crystal structure of **243** was obtained as shown in Figure 10.



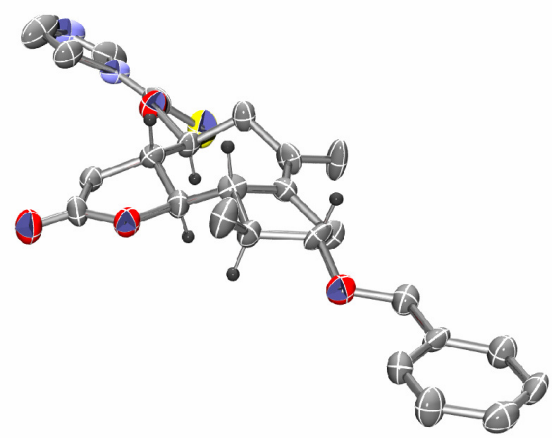
Reagents and conditions: a) **242** (3.5 eq.), DCE, DMAP (0.4 eq.), reflux, 50 h, quant. (*dr*=4:1); b) Bu_3SnH (3.0 eq.), AIBN (0.4 eq.), toluene, reflux, 4 h, 77%.

Scheme 60. *Barton-McCombie* desoxygenation of **240**.

The subsequent radical reduction of **243** using Bu_3SnH/AIBN afforded **244** in 77% yield as single diastereomer (Scheme 60) *via* typical *Barton-McCombie* desoxygenation mechanism.[124]



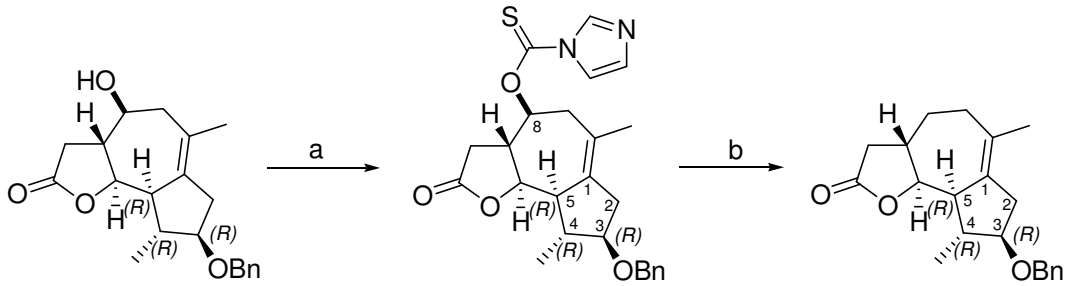
243



243

Figure 10. The X-ray crystal structure of **243** (Thermal Ellipsoid, 50% probability. Some H-atoms were hidden).

The same reaction was achieved with the mixture of diastereomers containing **241** as the major component (Scheme 61). The corresponding xanthate **245** was yielded in 92%, and subsequent radical reduction of **245** afforded **246** in 75% as a mixture of diastereomers.

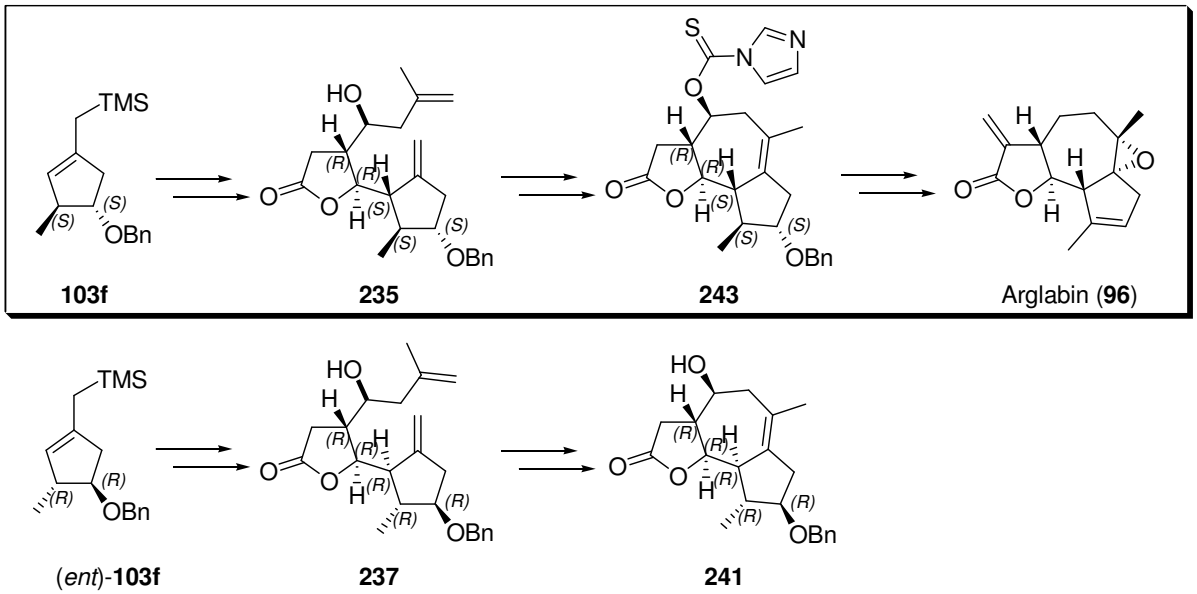


241 **245** **246**

Reagents and conditions: a) **242** (3.6 eq.), DCE, DMAP (0.5 eq.), reflux, 36 h, 92% (**245**, *dr*=67:14:13:6); b) Bu_3SnH (3.0 eq.), AIBN (0.4 eq.), toluene, reflux, 60 h, 75% (**246**, *dr*=67:18:14).

Scheme 61. *Barton-McCombie* desoxygenation of **241**.

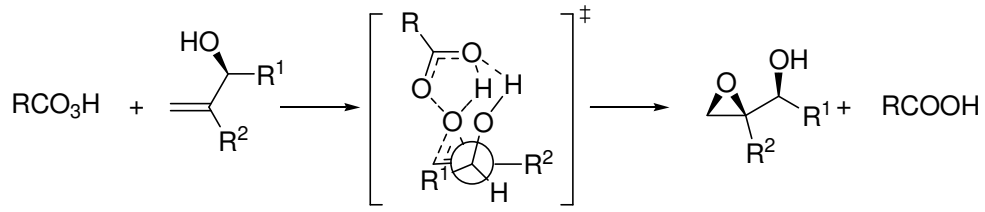
The X-ray crystal structures of **241** and **243** proved that only **235**, derived from **103f**, coincides with the stereochemistry of Arglabin (**96**) as shown in Scheme 62. Accordingly, the allylsilane **103f** was chosen for the further synthetic processes towards Arglabin (**96**).



Scheme 62. Ultimate selection of allylsilane towards Arglabin (**96**).

1.5.5 Epoxidation and debenzylation

As a crucial step towards Arglabin (**96**), diastereoselective α-epoxidation of **244** is necessary. A number of natural products contain epoxide within their skeletons, and diverse approaches to achieve asymmetric epoxidation are known.[125] Epoxides functionalities can be synthesized by either epoxidation of olefins or intramolecular S_N2 reactions such as halohydrins. For asymmetric epoxidations of electron-rich alkenes, various oxidants can be available. For examples, *m*CPBA,[126,127a] dimethyldioxirane (DMDO),[127b] and peroxometal complexes[128] of transition metals such as Ti, V, Cr. Mo, W, Mn. Epoxidations of electron-deficient olefins such as conjugated *Michael* systems can be achieved by means of nucleophilic reagents.[129] Electronic properties play an important role in diastereoselective epoxidation of alkenes. Electrophilic oxidants such as *m*CPBA and dimethyldioxirane (DMDO) react faster with electron-rich alkenes which are more substituted by alkyl groups.[127a-b] Steric interactions and solvent effects are also important since *trans*-alkenes are approximately eight times less reactive than their corresponding *cis*-isomer[127b] and the epoxidation rates in Et_2O or ethyl acetate are about one tenth of those in benzene or chloroform owing to intermolecular H-bonds between solvents and oxidants.[127b]



Scheme 63. Postulated transition state of epoxidation of allylic alcohols using peroxyacids.[130]

Epoxidations of olefins using peroxyacids, allylic alcohols contribute to the diastereoselectivities of epoxidations *via* intermolecular H-bonds with oxidants in their transition states (Scheme 63).[130]

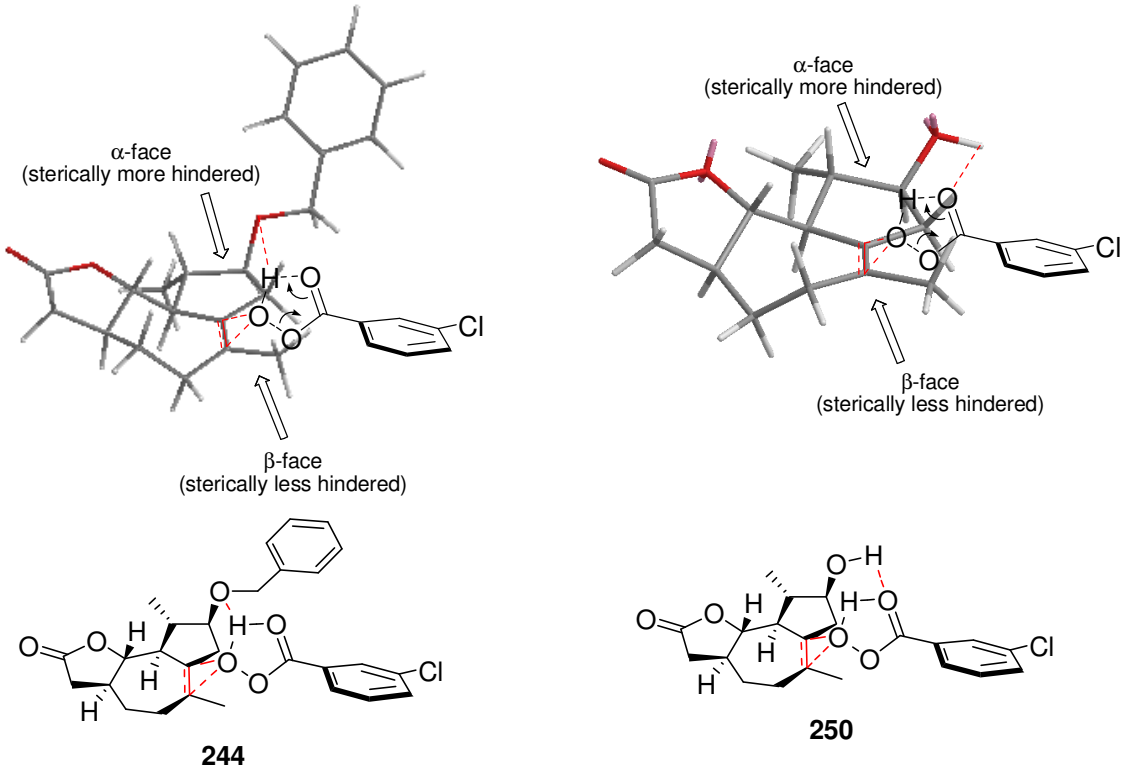
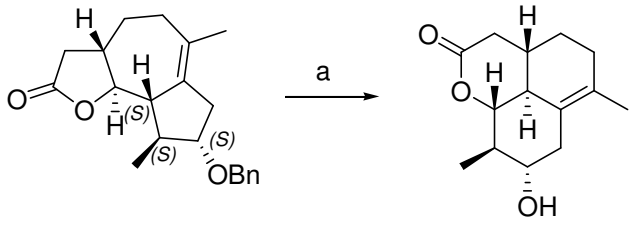


Figure 11. Putative coordination between *m*CPBA and homoallylic alcohols of **244** and **250** (Operation: MM2 minimized energy).

Epoxidations of **244** and **250** were envisioned with *m*CPBA in hopes to get the α-epoxide preferentially due to the coordination effect of homoallylic alcohol (Figure 11). Therefore, debenzylation in **244** was attempted. Anhyd. $FeCl_3$,[131] $Pd(OH)_2/C$ and H_2,[132] DDQ,[133] or BCl_3 [134] were considered as the debenzylation reagents for **244**. The most widely used method, *i.e.* hydrogenolytic removal of benzyl, was thought to be not compatible with the double bond between C1-C10. Therefore, anhyd. $FeCl_3$ was used for the debenzylation of **244** (Scheme 64), which surprisingly led to the undesired rearrangement product **247** (see

Chapter C.1).

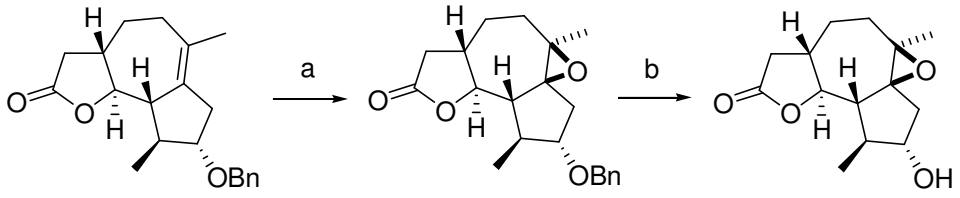


244 **247**

Reagents and conditions: a) anhyd. $FeCl_3$ (4.5 eq.), CH_2Cl_2, 0°C, Ar atmosphere, 2.3 h, 56%. (see Chapter C.1).

Scheme 64. Debenzylation of **244** using anhyd. $FeCl_3$.

Therefore, epoxidation of **244** was envisioned to be carried out first, followed by removal of the benzyl group by hydrogenolysis (Scheme 65). Epoxidation of **244** with *m*CPBA led to **248** as a mixture of two diastereomers (β:α=3:1).



244 **248** **249**

Reagents and conditions: a) *m*CPBA (1.2 eq.) in CH_2Cl_2, -10°C, 13 h, quant. yield (*dr*=3:1=β:α); b) $Pd(OH)_2$/C (100 wt. %), H_2 in abs. EtOH, rt., 4 h, 77%.

Scheme 65. Epoxidation of **244** using *m*CPBA and subsequent debenzylation by hydrogenolysis.

The absolute configuration of **248** was manifested by the X-ray crystal structure of **249** after debenzylation (Figure 12). Debenzylation of **248** using $Pd(OH)_2$/C and H_2 afforded **249** in 77% yield, which was recrystallized by CH_2Cl_2/Et_2O.

This result shows that the benzyl protected homoallylic alcohol does not direct the epoxidation by coordination but steric hindrance shields the α-face for steric reason. The elucidated configuration of the major epoxide in **249** differs from the target natural product Arglabin (**96**).

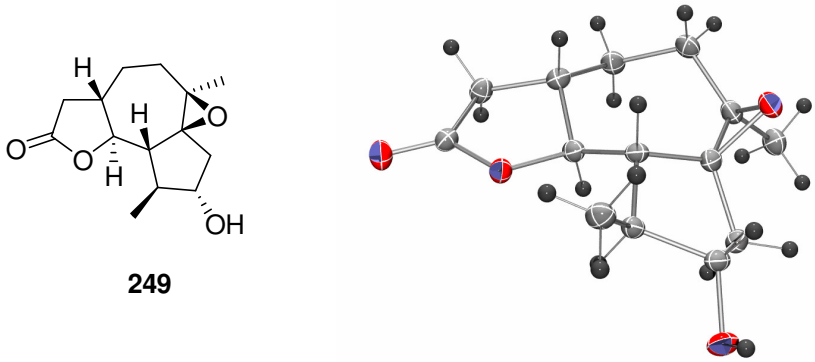
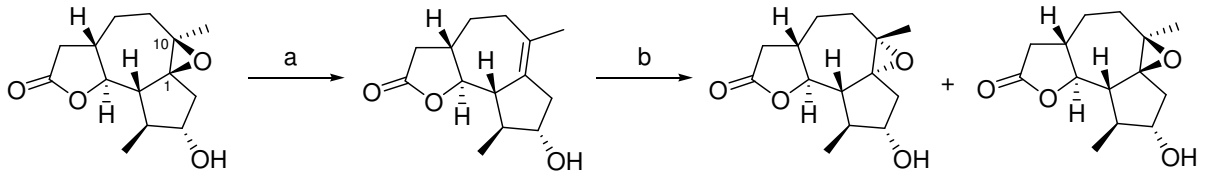


Figure 12. X-ray structure of **249** (Thermal Ellipsoid, 50% probability).

To investigate the coordination effect of the unprotected homoallylic alcohol, the β-epoxide of **249** was reduced into **250** in 35% yield using PPh_3 and I_2 (Scheme 66). Subsequent epoxidation of **250** with *m*CPBA led to the mixture of **249** and (*epi*)-**249** in 69% yield in which, however, again the undesired **249** had favored as the major product (**249**:(*epi*)-**249**=2:1) (Scheme 66). Consequently, the homoallylic alcohol group of **250** does not direct the epoxidation with *m*CPBA, although the slight improvement from *dr*=3:1 in **244** to *dr*=2:1 in **250** could be observed. The epoxidations of **244** and **250** are controlled by steric factors rather than by coordination to the homoallylic alcohol. The X-ray structure of **243** shows a convex shape on the β-face of the ring structure. It is therefore plausible that the epoxidations of **244** and **250** occur preferentially at the less steric hindered β-face.



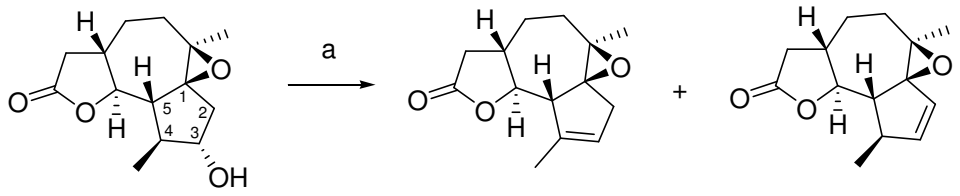
Reagents and conditions: a) PPh_3 (1.1 eq.), I_2 (0.6 eq.), in CH_3CN, 6.5 h, 35%. b) *m*CPBA (1.2 eq.), CH_2Cl_2, 0 °C, 1.4 h, 69% (**249**:(*epi*)-**249**=2:1) **.**

Scheme 66. Epoxidation of the unprotected homoallylic alcohol **250** using *m*CPBA.

As disclosed by *Sharpless et al.*, epoxidations of homoallylic alcohols show low enantioselectivities and slow reaction speed even at low temperature comparing with epoxidations of allylic alcohols.[135] This result is compatible with epoxidation of guaianolides with *m*CPBA by *Fischer et al.* as well.[136]

1.5.6 Formation of double bond at C3-C4 *via* dehydration

Double bond formation at C3-C4 of **249** can be achieved by *syn*-elimination using pyrolysis, [137] piperidinium acetates, [138] or *anti*-elimination after alteration of the stereochemistry of the hydroxyl group at C-3 by *Mitsunobu* reaction.[139] However, forcing reaction conditions can affect other functionalities. Therefore, dehydration of **249** was carried out using pyridine and Tf_2O under Ar atmosphere *via syn*-elimination (Scheme 67).[140] In this reaction condition, reaction temperature played decisive role in regioselection between the *Zaitsev* product **251** and the *Hofmann* product **252**.



249 **251** **252**

Reagents and conditions: a) Pyridine (10 eq.), Tf_2O (3.0 eq.), CH_2Cl_2, Ar, 0°C→rt.

Scheme 67. Dehydration of **249** *via syn*-elimination using Tf_2O and pyridine.

The reaction of **249** with Tf_2O at 0°C yielded the *Zaitsev* product **251** as the only diastereomer, which could be detected by ^{1}H-NMR whti the signal at δ=5.56, showing one multiplet peak (Entries 1 and 3, Table 16). A mixture of two regioisomers, not only **251** but also **252** showing doublet of doublet peaks at δ=5.41 (*J* = 5.8 Hz, 1.4 Hz) and δ=6.19 (*J* = 5.8 Hz, 2.7 Hz), was obtained as shown in Figure 13, when the reaction was carried out at room temperature (Entry 2, Table 16).

Table 16. Dehydration of **249** *via syn*-elimination using Tf_2O and pyridine.

Entry	Rxn time (h)	Rxn. Temp. (°C)	Yield (%)	*dr* (**251**:**252**)
1	19	0 → rt.	41	100:0
2	1	rt.	28	64:36
3	16	0 → rt.	31	98:2

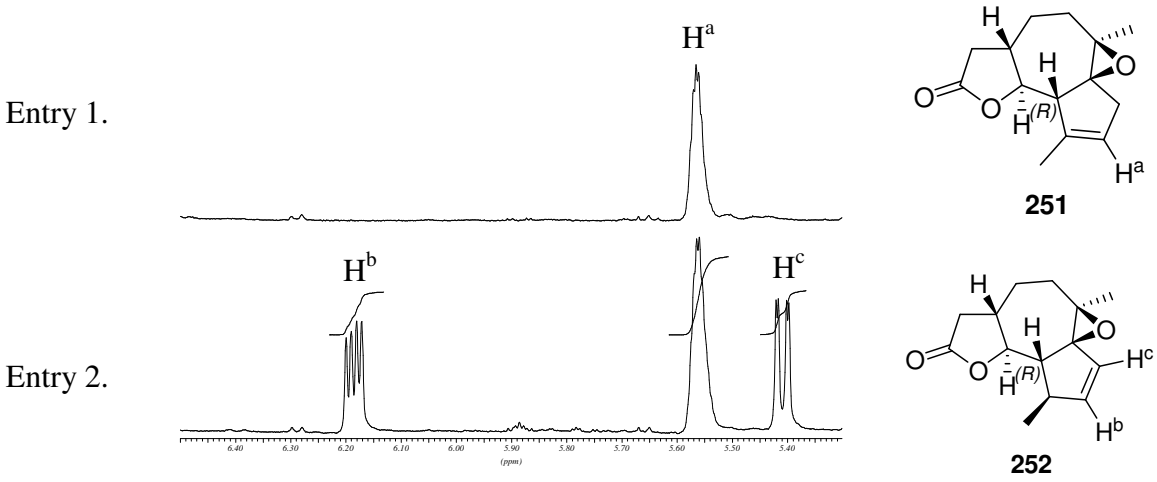
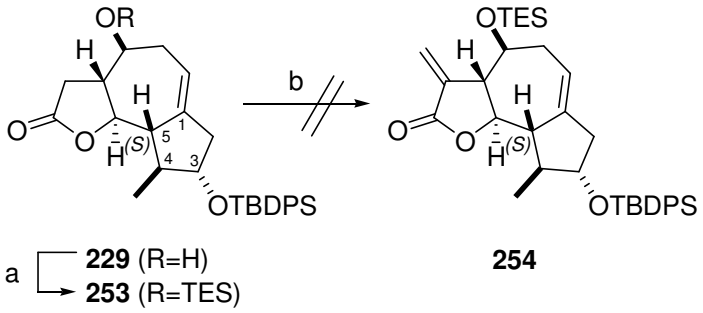


Figure 13. Regioselection by reaction temperature during dehydrations (Table 16).

1.5.7 α-functionalization of GBLs

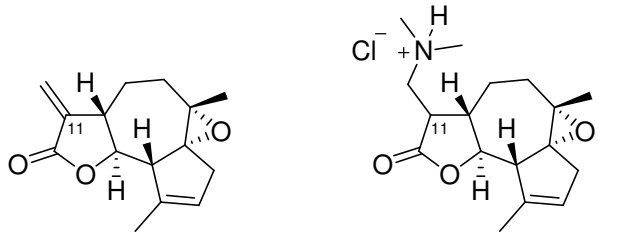
Many of biologically active natural products based on GBL contain α,β-unsaturated *exo*-methylene functionalities as *Michael* acceptors toward various cellular nucleophiles.[141] Moreover, the relationship between biological activities and structures of guaianolides, containing *exo*- or *endo*- double bonds, was reported by *Yuuya et al*.[142] For the formation of *exo*-methylene moieties, the following methods are commonly known such as hydroxyl methylenation-elimination, [143] organosulfur reagents, [144] organoselenium reagents, [145] reductive amination of α-formyl lactones,[146] decarboxlative methylenation,[147] and one-pot procedure using reduction of thiophosphates by $NaBH_4$.[148] As a first attempt for the formation of *exo*-methylene GBL, one-step synthesis was tried using excess of paraformaldehyde and NaH (Scheme 68).[149] However, no change was observed neither at 0°C nor at 100°C.



Reagents and conditions: a) Et_3N (1.5 eq.), DMAP (1.0 eq.), TESCl (2.0 eq.), CH_2Cl_2, 56 h, 86%; b) NaH (1.7 eq.), paraformaldehyde (10 eq.), THF, at 0°C or 100°C, 1 h.

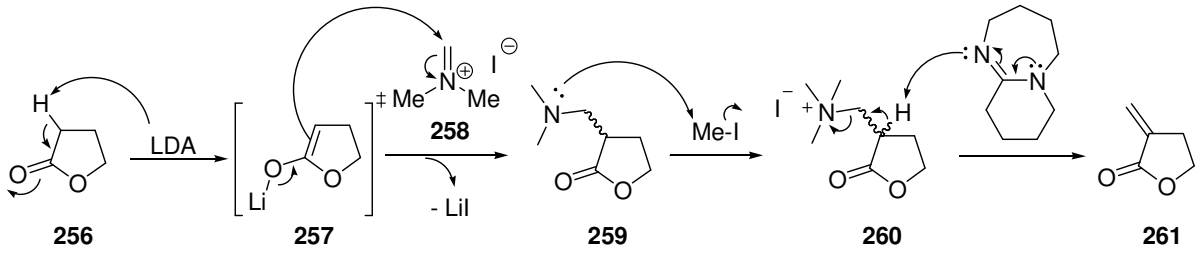
Scheme 68. Direct α-methylenation of GBL **253** using paraformaldehyde and NaH.

Although Arglabin (**96**) has good *anti*-tumor activities, its low solubility in polar solvents and low absorption rates are necessary to be modified by introduction polar functionalities within the molecules. Among the synthetic analogues of Arglabin (**96**), the dimethylamino-methylated Arglabin hydrochloride salt (*i.e.* Arglabin-DMA·HCl, **255**) showed most promising biological profiles (Scheme 69).[27] Therefore, *Mannich* type reaction using *Eschenmoser*'s salt was attempted to introduce α-aminoalkyl group directly into GBLs.



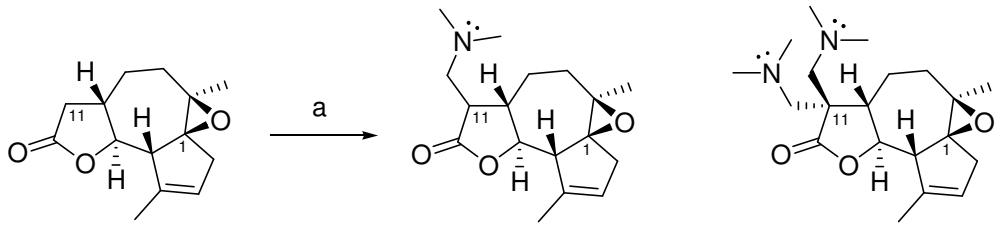
Scheme 69. Arglabin (**96**) and Arglabin-DMA·HCl (**255**)

Dimetylaminomethylation of GBL using *Eschenmoser*'s salt (**258**)[150] is advantageous because not only direct α-aminoalkylation can be affordable but also α-methylenation can be achieved by subsequent *Hoffmann* degradation using MeI and DBU (Scheme 70).[150a]



Scheme 70. Mechanism of *Mannich* reaction using *Eschenmoser*'s salt (**258**) and subsequent formation of α-methylene group *via Hoffmann* degradation.

With different amounts of LDA and *Eschenmoser*'s salt, α-dimethylaminomethylations of **251** were attempted (Scheme 71). No reaction was observed with 1.0-1.5 eq. of LDA. In contrast, with 5.0 eq. of LDA afforded *di*-aminoalkylated product **263** in 31 % yield instead of *mono*-aminoalkylated **262**.



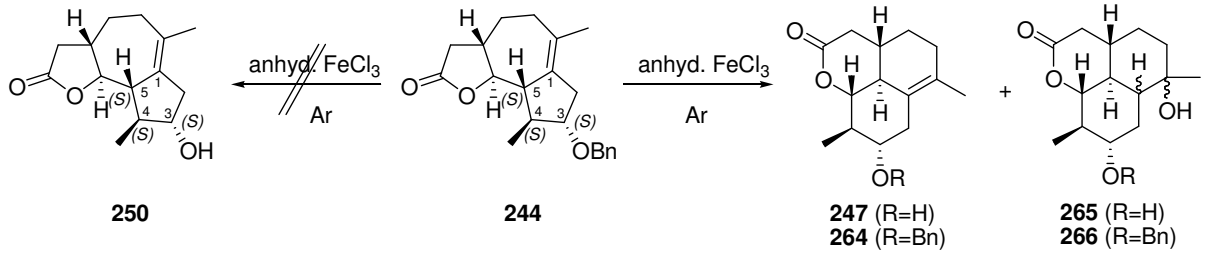
251 **262** **263**

Reagents and conditions: a) i) BuLi (5.0 eq.), DIPA (5.2 eq.), THF, at 0°C→-78°C, 15 min. ii) *Eschenmoser*'s salt (10 eq.) in THF, rt., 5 h, 31% (**263**).

Scheme 71. Direct α-dimethylaminomethylation of **251** using *Eschenmoser*'s salt.

2. Rearrangement of 5,7,5-tricyclic GBL to 6,6,6-tricyclic δ-valerolactone

2.1 Rearrangement of 5,7,5-tricyclic GBL to 6,6,6-tricyclic δ-valerolactone



250 **244** **247** (R=H) **264** (R=Bn) **265** (R=H) **266** (R=Bn)

Reagents and conditions: anhyd. $FeCl_3$, CH_2Cl_2, Ar atmosphere, 0°C.

Scheme 72. Debenzylation of **244** using anhyd. $FeCl_3$.

As stated in chapter 3.5, attempts for the debenzylation of **244** with anhyd. $FeCl_3$ led to the undesired 6,6,6-tricyclic δ-valerolactone **247** as major product and the hydroxylated **265** as a side product (Scheme 72). The results are shown in Table 17.

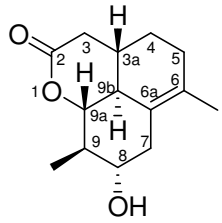
Table 17. The rearrangement of **244** using anhyd. $FeCl_3$.

Entry	Anhyd. $FeCl_3$ (eq.)	Rxn. Time (h)	Yield (%)	
			247	**265**
1	1+1+2.5 [a]	2.3	56	2
2	1+1+3 [b]	18.0	71	29

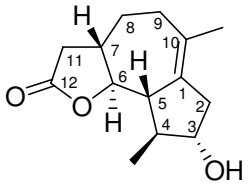
[a] Addition at 0 min, 50 min, 85 min, respectively. [b] Addition at 0 h, 14 h, 18 h, respectively.

Treatment of **244** with 1 eq. of anhyd. $FeCl_3$ showed two intermediate spots on the TLC, which were further transformed into much polar spots. In 40 min reaction time, the starting material was still present with 1 eq. of $FeCl_3$. In contrast, a longer reaction time (14 h) showed a complete conversion of **244** into two intermediates. Upon extra addition of $FeCl_3$, these intermediates were changed ultimately into **247** and **265**. A long reaction time caused a significant increase of **265** as side product (Entry 2, Table 17) compared with the short reaction time (Entry 1, Table 17). ^{13}C-NMR of **247** and **250** showed the same numbers and types of carbons, but some chemical shifts of them were significantly different (Table 18). The structural ambiguousness of **247** was made clear upon epoxidation of both **247** and **250** leading to X-ray crystal structures.

Table 18. Comparison of ^{13}C-NMR data in **247** and **250**.



247

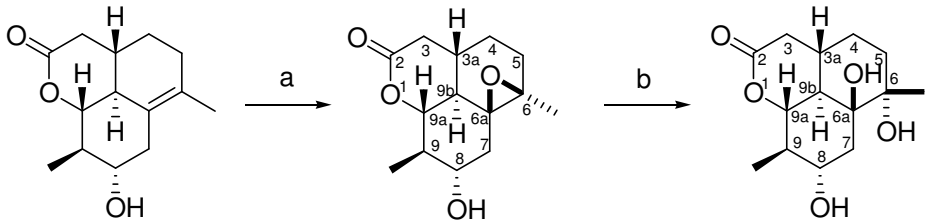


250

Peaks	δ (ppm)	Type [a]	Peaks	δ (ppm)	Type [a]
9-Me	13.5	CH_3	4-Me	18.6	CH_3
6-Me	19.2	CH_3	10-Me	23.9	CH_3
4 or 5	27.6	CH_2	8	28.3	CH_2
5 or 4	31.6	CH_2	9	34.7	CH_2
3a	34.9	CH	11	37.2	CH_2
7 or 3	36.9	CH_2	2	39.7	CH_2
3 or 7	37.8	CH_2	4	46.4	CH
9b	44.7	CH	7	49.4	CH
9	44.9	CH	5	53.2	CH
8	72.5	CH	3	78.0	CH
9a	86.6	CH	6	87.7	CH
6	122.0	quart.	10	132.7	quart.
6a	130.7	quart.	1	133.0	quart.
2	170.9	quart.	12	176.0	quart.

[a] quart.=quarternary carbon.

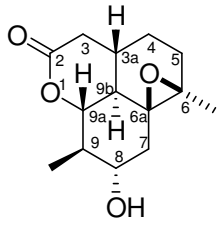
Treatment of **247** with *m*CPBA led to a mixture of **267** in 67% of yield white crystalline (Scheme 73), which was recrystallized using Et_2O to give X-ray structure shown in Figure 14.



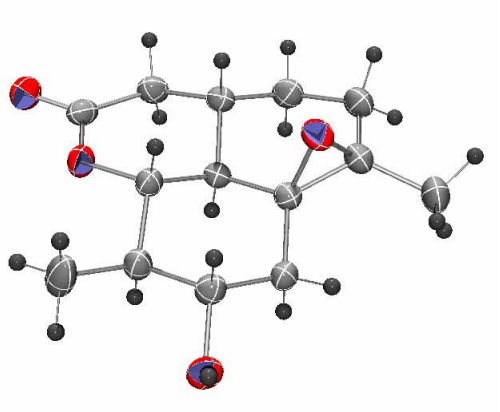
247 **267** **268**

Reagents and conditions: a) *m*CPBA (1.5 eq.), CH_2Cl_2, -10°C, 14.5 h, 67%; b) DEAD (1.2 eq.), PPh_3 (1.2 eq.), MeI (1.2 eq.), abs. THF, 0°C→rt., 92.5 h, 44%.

Scheme 73. Further transformations of **247** to **267** and **268** *via* epoxidation and *Mitsunobu* reaction.



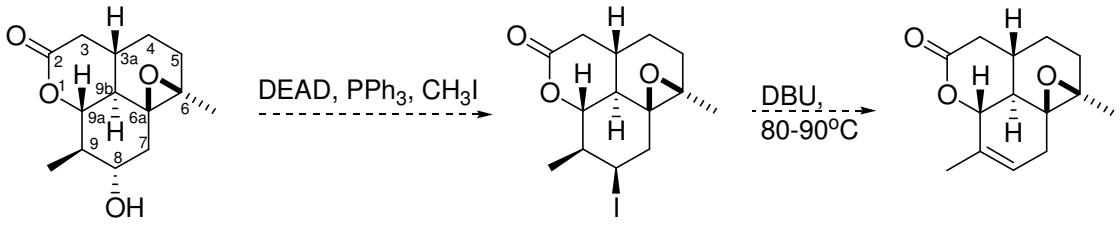
267



267

Figure 14. X-ray crystal structure of **267** (Thermal ellipsoid, 50% probability).

Indeed, the configuration of hydroxyl group at C-8 in **267** was attempted to be inverted to **269** *via* a *Mitsunobu* reaction[151] in order to try subsequently *anti*-elimination,[152] leading to the formation of **270** containing the double bond at C8-C9 (Scheme 74).



267 **269** **270**

Scheme 74. Desired transformation from **267** to **269** and **270** *via* a *Mitsunobu* inversion and a subsequent *anti*-elimination using DBU, respectively.

However, the *Mitsunobu* reaction did not afford **269**. Upon reaction of **267** with DEAD, PPh_3, and MeI, a new product **268** was obtained. NOE studies showed that the signal between $7H_A$/6-Me is stronger than $7H_B$/6-Me, and no signal between 9b-H/6-Me. Consequently, the hydroxyl group did not undergo *Mitsunobu* reaction. However these conditions effected epoxide opening to give rise to **268** (Scheme 73).

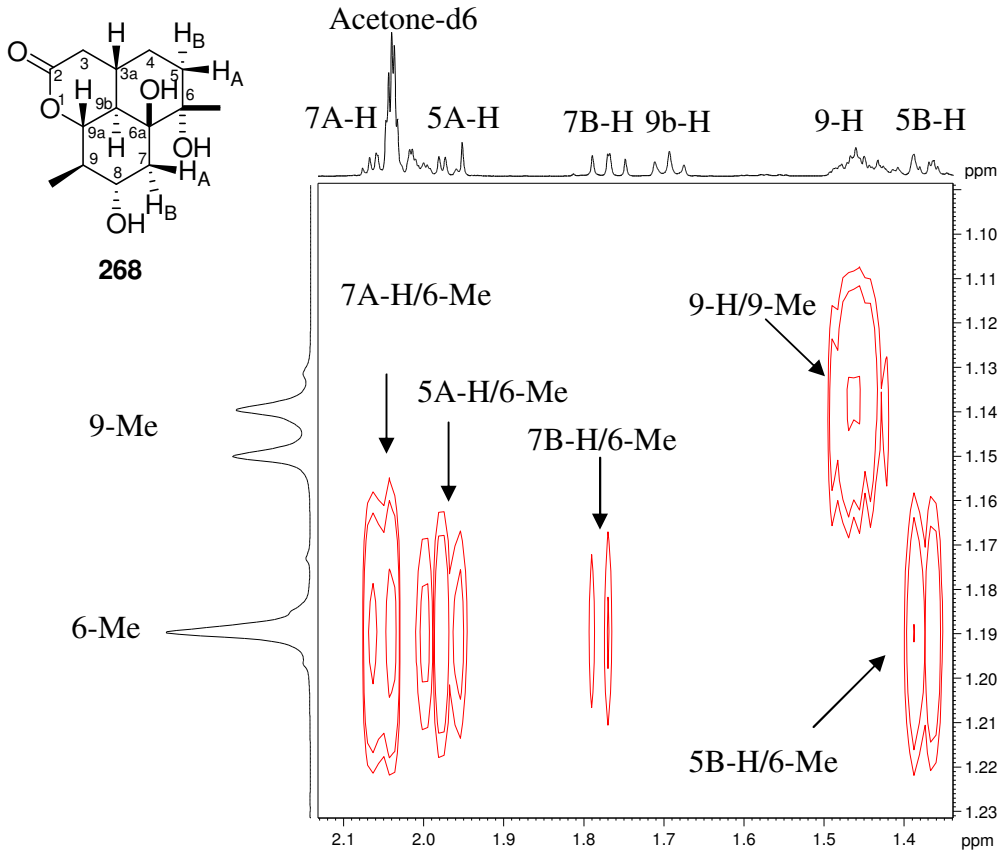
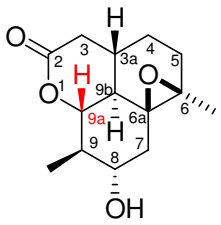
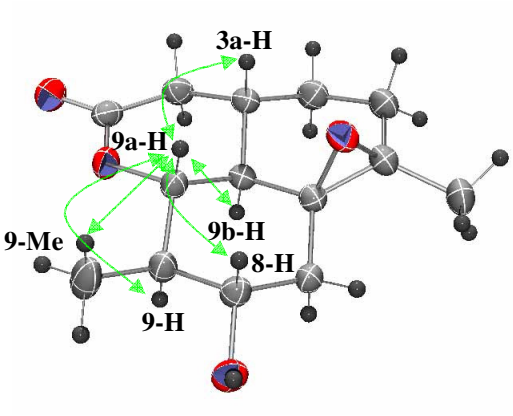


Figure 15. NOE signals of **268** in Acetone-d6.

Besides the X-ray structures of **267** and **249**, NOE spectra allowed to ascertain the skeletal change (Figure 16 and Figure 17). The 9a-H of **267** showed the five NOE signals, being correlated with 9-Me, 9b-H, 9-H, 3a-H, and 8-H, respectively (Figure 16).



267



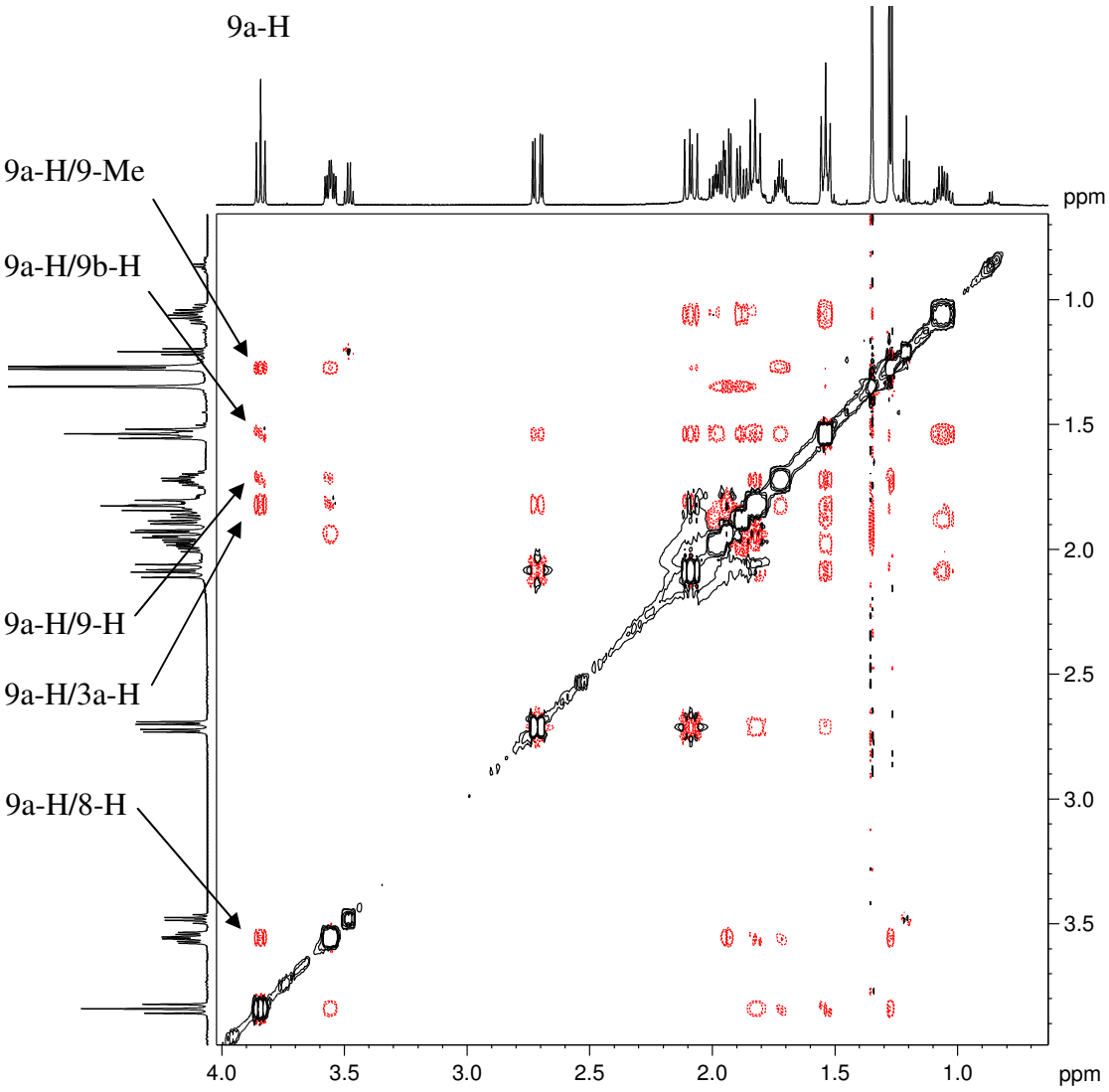


Figure16. NOE-Spectrum of **267** in $CDCl_3$.

On the other hand, the corresponding proton 6-H in **249** showed the seven NOE signals as shown in Figure 17. Different from **267**, NOE signals between 6-H/$2H_B$, 6-H/$8H_B$, and 6-H/$11H_B$ were observable in **249** (Figure 17). These differences of NOE signals between **267**

and **249** manifest a skeletal change of **267** as well.

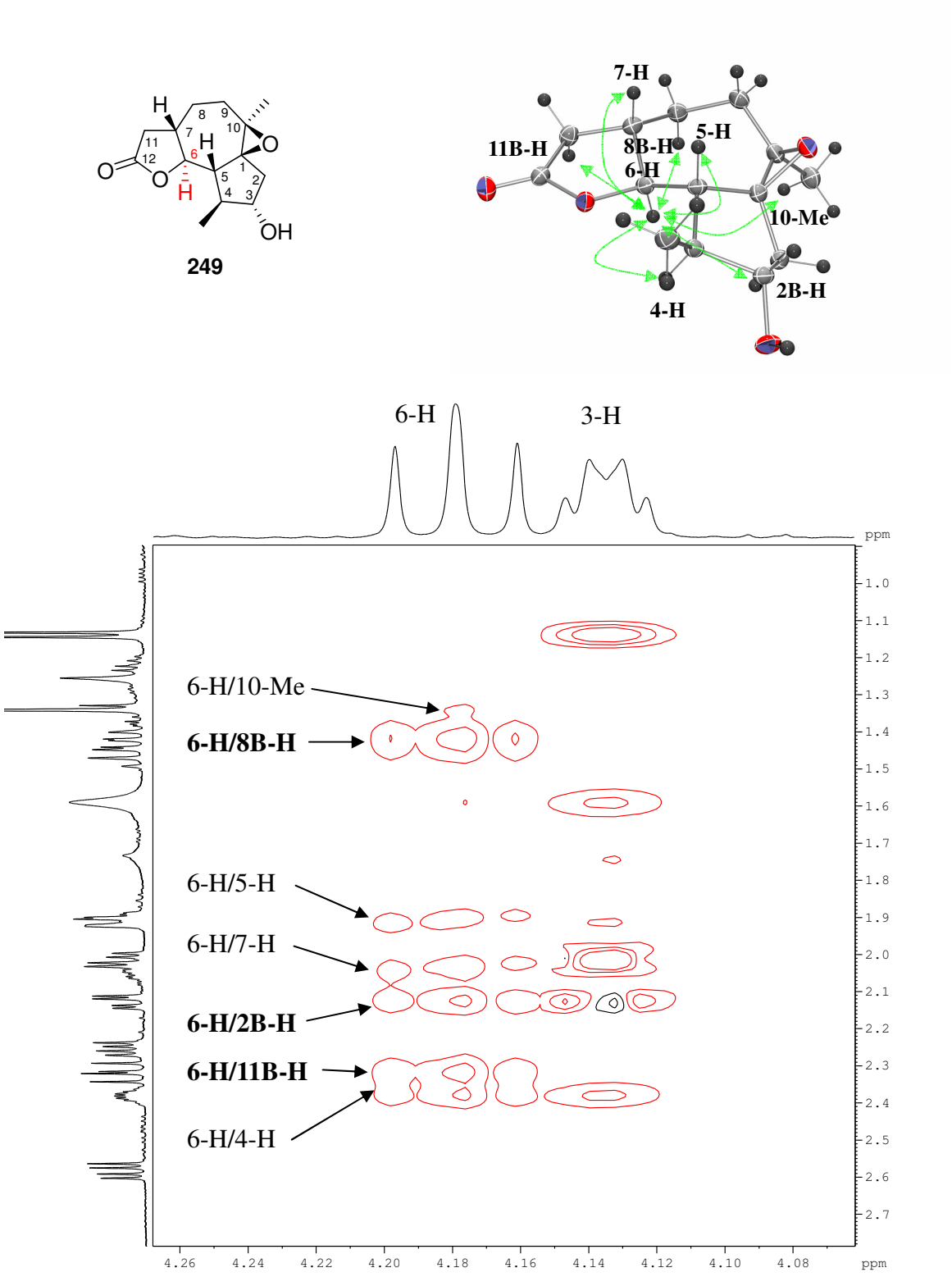


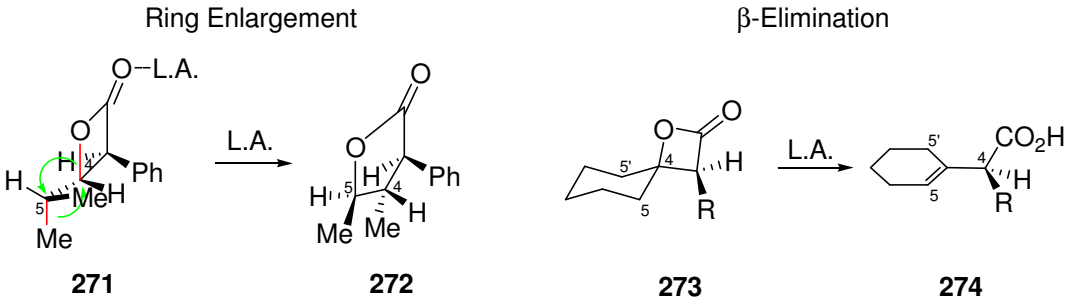
Figure 17. NOE-Spectrum of **249** in $CDCl_3$.

2.2 *Wagner-Meerwein* rearrangement

In general, molecular rearrangements are mediated by intermediates such as carbocations,[153] radicals,[154] and anions[155] through energetically favored transition states.[156] Furthermore, various sigmatropic rearrangements,[157] are not proceeding *via* intermediates but follow a concerted reaction mechanism, are also well known.

In 1899, the molecular rearrangement of isoborneol to camphene was discovered by *Wagner* and subsequently studied in detail by *Meerwein* later.[158] This rearrangement, so-called *Wagner-Meerwein* rearrangement[158] (*i.e.* W-M rearrangement), is a 1,2-shift from a less stable carbocations to a more stable ones. In bicycle terpenes, the W-M rearrangement is frequently observed due to the possibility of releasing ring strain. Usually, as a result of this rearrangement, an inversion of the final migration center is obtained.[158]

Mulzer et al. reported the ring enlargement of β-lactones such as **271** to γ-butyrolactones **272** *via* W-M rearrangement with different Lewis acid catalysts (Scheme 75).[159] Lewis acids and solvents are important for the migratory aptitude of a given group. For example, weak Lewis acids such as $MgBr_2$ and $TiCl_4$ lead to H-migration predominantly, whereas strong Lewis acids such as $AlBr_3$ and $FeBr_3$ increase the ratio of alkyl migration products significantly.[159] They proved experimentally that only if C-4 is tertiary and both C-5 positions are secondary, β-elimination occurs. Principally, the migrating substituents must be arranged in antiperiplanar configuration each others (Scheme 75).

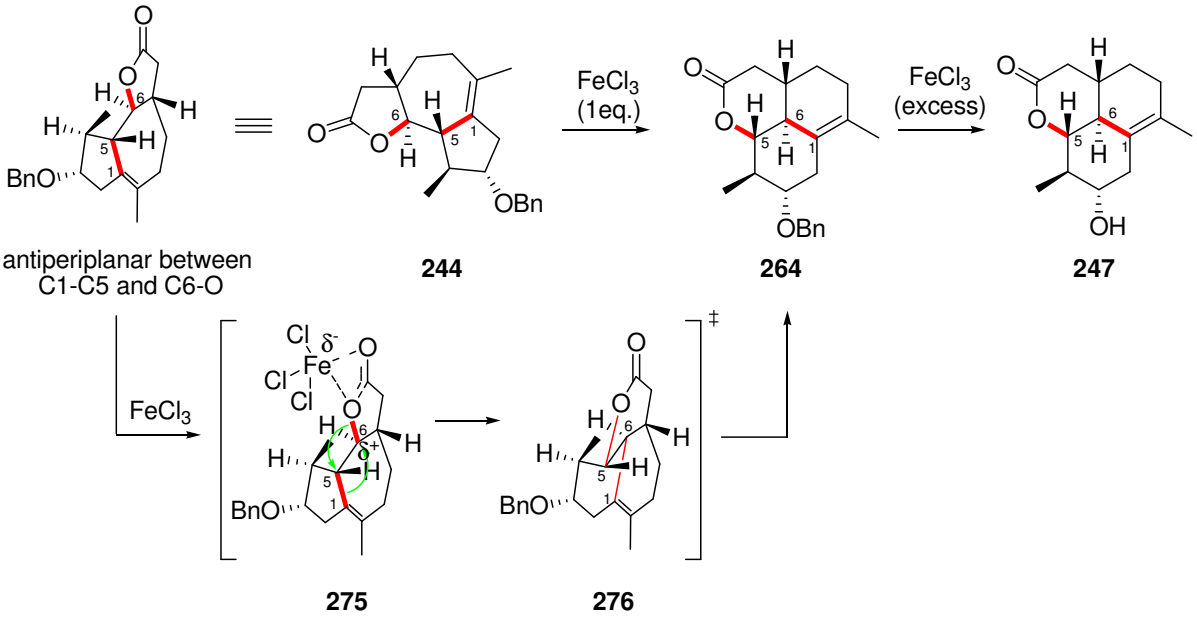


Scheme 75. Ring enlargement *Vs* β-elimination of β-lactones using Lewis acids.

Migratory aptitudes of substituents in monocyclic lactones are dependant on Lewis acids used. However, in case of conformationally constrained 5,7,5-tricyclic lactone like **244**, only the alkyl substituent, *i.e.* the σ-bond between C1-C5, can migrate because only the C1-C5 bond is antiperiplanar with the electron deficient C6-O bond (Scheme 76).

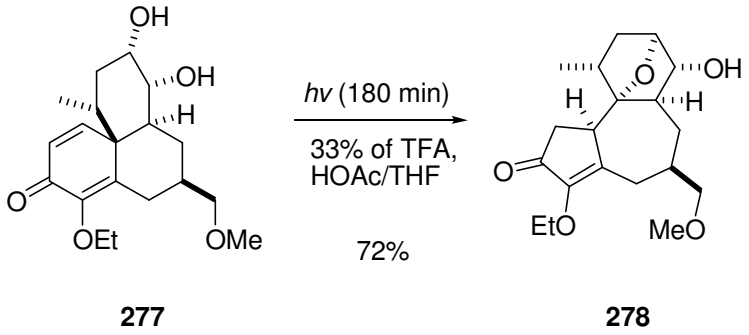
According to the X-ray structures, NOE studies, and TLC monitoring, we can explain the mechanism of the novel rearrangement from 5,7,5-tricyclic γ-butyrolactone to 6,6,6,-tricyclic δ-valerolactone as shown in Scheme 76; Upon the treatment of **244** with stoichiometric amounts of anhyd. $FeCl_3$, the Lewis acid coordinates to the ester moiety causing electron

deficient properties at C6. The C1-C5 bond is arranged antiperiplanar to C6-O, and consequently, **244** is rearranged to give **264** as an intermediate. Upon further addition of anhyd. $FeCl_3$, **264** undergoes debenzylation leading ultimately to **247**. The resulting 6,6,6-tricyclic **247** was formed with inversion of both C5 and C6 stereocenters (Scheme 76). Accordingly, this rearrangement occurs not in stepwise *via* a carbocations but concertedly *via* a partially electron deficient stand at C6 catalyzed by a Lewis acid. If carbocations would be present during the rearrangement, erosion of stereochemistry could happen at C5 or C6 in **247**.



Scheme 76. Postulation of mechanism upon the rearrangement of **244** and subsequent debenzylation with anhydrous $FeCl_3$.

Rearrangements being accompanied with simultaneous ring-enlargement and contraction are known. For examples, a photorearrangement of the 6,6,6-tricyclic system **277** afforded daphnane, **278**, containing the 5,7,6-tricyclic skeleton in good yield (Scheme 77).[160]

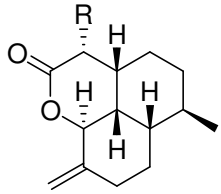


Scheme 77. Photorearrangement from 6,6,6-tricyclic **277** to 5,7,6-tricyclic **278** by *Carreira et al.*[160]

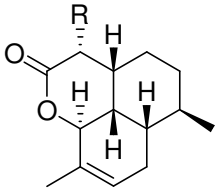
However, the rearrangement from 5,7,5-tricyclic systems to 6,6,6-tricyclic systems *via* ring enlargement and contraction at the same time is not known yet. It is known that γ-butyrolactones have a higher ring strain by 2.4 kcal/mol than δ-valerolactones, calculated by *Bach and Dmitrenko*.[161] According to *Khoury et al.*,[162] a cycloheptene has 4.4 kcal/mol of ring strain energy (*i.e.* RSE), while a cyclohexene has 0.3 kcal/mol. In addition, the *mono*-methylated cyclopentane has ca. 6.0 kcal/mol higher RSE than the *mono*-methylated cyclohexane.[162] Probably, the higher ring strains of the γ-butyrolactone, cycloheptene, and cyclopentane moieties in **244** might be driving forces for the rearrangement from 5,7,5-tricyclic γ-butyrolactones to 6,6,6-tricyclic δ-valerolactones.

2.3 Synthetic applications of 6,6,6-tricyclic δ-valerolactone analogues as building blocks for natural products syntheses

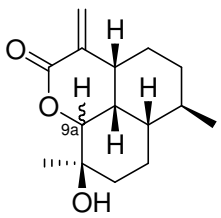
Indeed, **247** has structural similarities with naturally or semi-synthetically obtainable cadinane sesquiterpene lactones such as Arteannuin derivatives, Annulide, and isoannulide (Scheme 78).[163]



279 Arteannuin I (R=CH_3)
280 Annulide (R=CH_2)



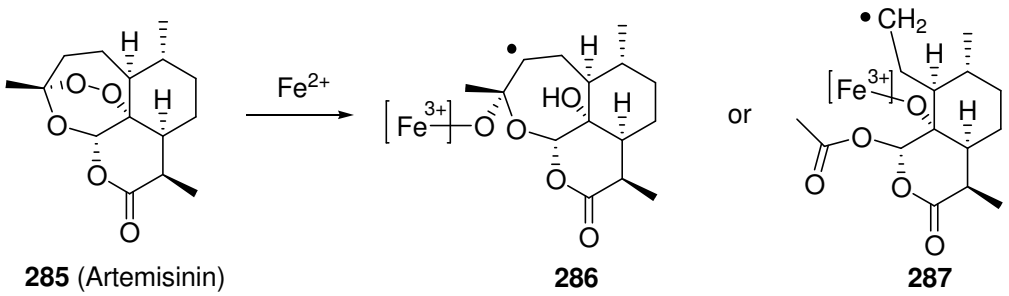
281 Arteannuin J (R=CH_3)
282 Isoannulide (R=CH_2)



283 Arteannuin E (β-9aH)
284 Arteannuin F (α-9aH)

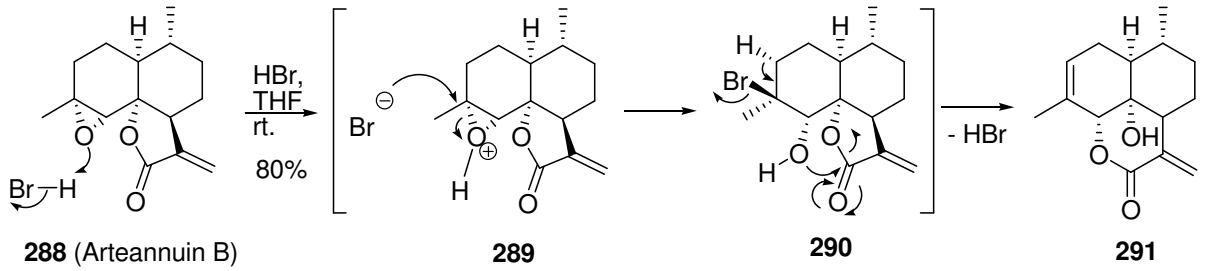
Scheme 78. Naturally obtained 6,6,6-tricyclic sesquiterpene lactones **279**-**284**.

Arteannuin E (**283**) shows 100% and 42% of the growth inhibitory activities against leukemia P388 cell at a 10 μg/ml and 1 μg/ml, respectively.[164] Besides, those Arteannuin derivatives are used as important building blocks for the synthesis of Artemisinin (**285**, Quinghaosu),[165] which is one of the most promising antimalarial drug even against multi-drug resistant parasites. In 1972, Artemisinin was first extracted from *Artemisia annua* L. in China, and its structure containing a peculiar endo-peroxide bridge was elucidated by X-ray analysis in 1979. This trioxane moiety is known as the origin of the antimalarial[166] and anticancer activity.[167] It is cleaved by Fe^{2+} and yields highly reactive carbon radical species which are able to damage biomolecules (Scheme 79).[168] Despite its promising biological activities, Artemisinin (**285**) is difficult to isolate from natural constituents due to its sensitivity towards acids, bases, and high temperature.[169]



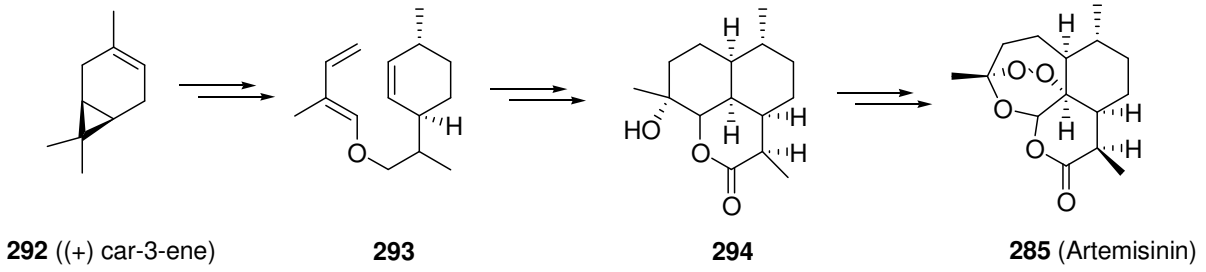
Scheme 79. The generation of highly reactive carbon radicals by Fe^{2+} from Artemisinin.

Some syntheses towards 6,6,6-tricyclic sesquiterpene lactones are known.[170] *Bhattacharya et al.* synthesized **291** from Arteannuin B (**288**) in 80% yield by treatment of HBr (Scheme 80).



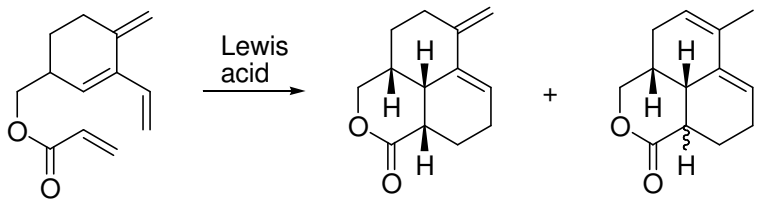
Scheme 80. Synthetic approaches by *Bhattacharya et al.* towards **291**.[170a]

Ravindranathan et al. sytnthesized Artemisinin (**285**) using **294** as the precursor which was prepared from **293** *via* intramolecular *Diels-Alder* reaction shown in Scheme 81.[170b]



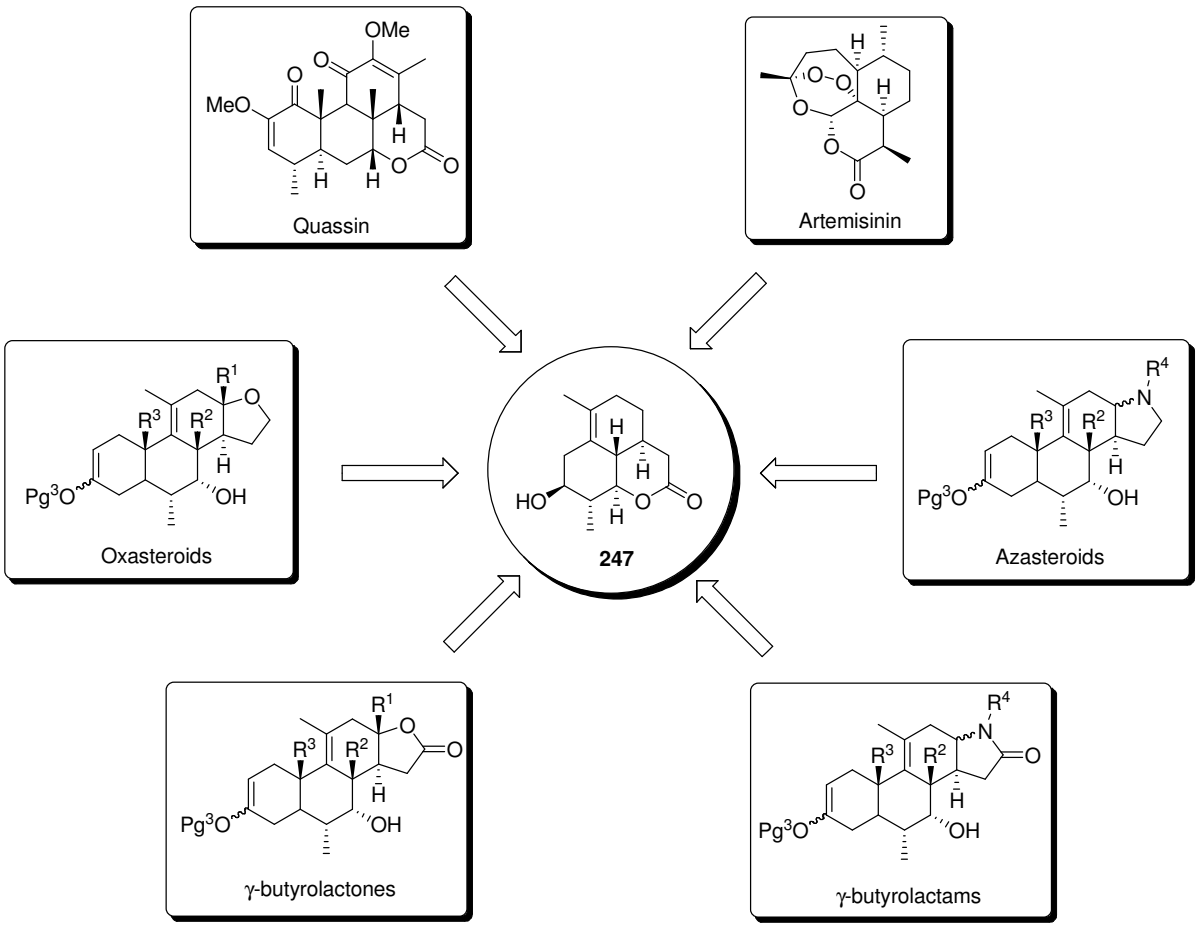
Scheme 81. Formation of **294** *via* intramolecular *Diels-Alder* reaction as the precursor towards Artemisinin (**285**) by *Ravindranathan et al.*[170b]

Another example for the formation of 6,6,6-tricyclic sesquiterpene lactones was reported by *Brummond et al.*[170c] In this synthetic approach, trienes **295** were transformed into **296** and **297** *via* intramolecular *Diels-Alder* reaction (Scheme 82).



Scheme 82. Synthesis of 6,6,6,-tricyclic lactones **296** and **297** by *Brummond et al.*[170c]

The 6,6,6-tricyclic δ-valerolactone **247** analogues could be potentially used as useful building blocks not only for the Artemissinin but also for Quassin,[171] oxa-/aza-steroids[172] compounds, and γ-butyro lactones and lactams (Scheme 83).



Scheme 83. Synthetic application of **247** for the natural product syntheses.

3. Conformational analysis of saturated γ-butyrolactone ester chromophores *via* Circular Dichroism

3.1 Circular Dichroism

Circular Dichroism (*i.e.* CD) is an important spectroscopic technique to determine the structural conformations of chiral biomolecules such as peptides and proteins. The advances of analytical techniques provide us with profits to isolate and identify rapidly unknown chiral mixtures. For example, HPLC-CD gives informations about the number of chiral compounds in the mixture and the chiralitiy at the same time.[173] In principle, such CD-coupled techniques are based on the CD technique to determine the chirality of isolated compounds. Upon a plane polarized light passing through a solution containing an optically active substance, the left and right circularly polarized components of the plane polarized light are absorbed by different amounts, which is dependent on the chirality of substances. The rest components of plane polarized light being not absorbed by chiral chromophores are recombined and the resulting elliptically polarized light are measured as an extent of molar ellipticity ([θ]).

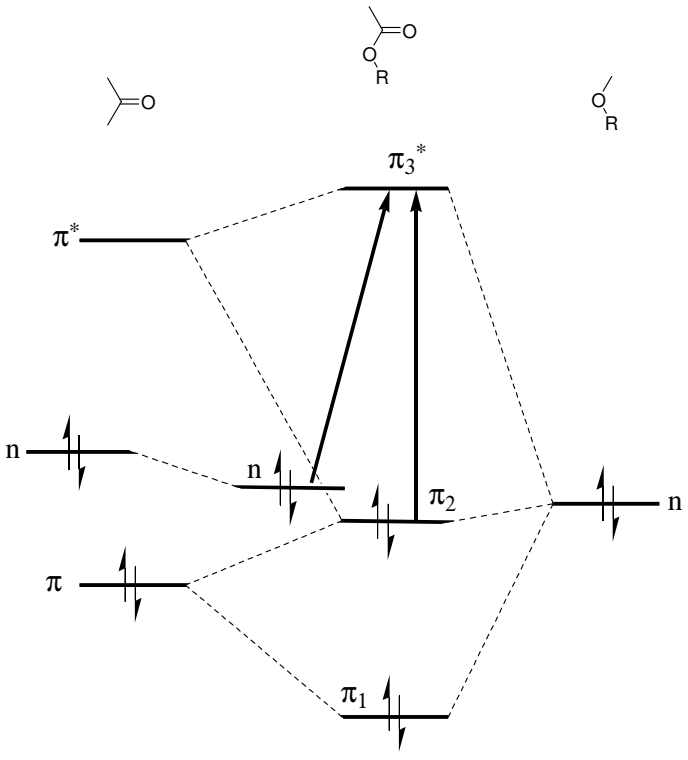


Figure 18. Approximate energy level diagram for the ester carbonyl system.[174]

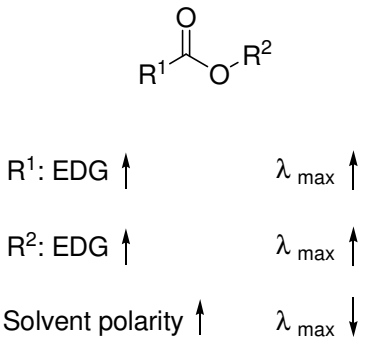
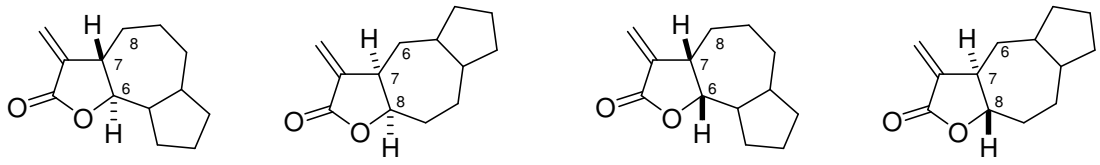


Figure 19. Trends of λ_{max} of n→π* transition in carboxylic esters depending on the substituents and solvents.[174]

The typical electronic transition state of carboxylic esters is shown in Figure 18.[174] The possible two transitions with low energy are the $n\rightarrow\pi_3^*$ and $\pi_2\rightarrow\pi_3^*$ transitions. *W. D. Closson and P. Haug* showed experimentally that a weak absorption band near 210 nm is the $n\rightarrow\pi^*$ transition of ester chromophores.[174] The absorption maximum (λ_{max}) of carboxylic esters corresponding to $n\rightarrow\pi^*$ transition follows trends depending on the substituents and solvents (Figure 19). When the substituents adjacent to carbonyl and to ester oxygen atom have higher electron donating effects, λ_{max} of $n\rightarrow\pi^*$ transition shows redshift (*i.e.* bathochromic shift) (Figure 19). The higher polarity of solvents leads the λ_{max} of $n\rightarrow\pi_3^*$ transition to shift at a shorter wavelength (*i.e.* hypsochromic shift), whereas a redshift occur in the case of $\pi_2\rightarrow\pi_3^*$ (Figure 19).[174] These trends are similar with cyclic esters such as γ-butyrolactones, whose $n\rightarrow\pi^*$ transition of γ-butyrolactones is centered 214 nm in isooctane.[174] Some other examples about λ_{max} of lactone ester chromophores were also investigated and used to determine the stereochemistry of lactones by other groups.[175]

A large number of sesquiterpene lactones (*i.e.* SLs) containing α-methylene-γ-lactone chromophore were investigated by means of CD [176] and ORD to determine their stereochemistry.[177] CD is often used by phytochemists as an useful analytical tool to investigate stereochemistry of 5,7,5-ring fused guaianolides (*i.e.* GLs) and pseudoguaianolides (*i.e.* PGLs) containing α-methylene-γ-lactone chromophore.[178] In 1969, *Geissmann et al.* reported an empirical rule about Cotton Effect (*i.e.* CE) in the CD spectra of SLs containing α-methylene-γ-lactone chromophores, especially GLs and PGLs (Scheme 84).[179] The $n\rightarrow\pi^*$ transitions of the α-methylene-γ-lactone chromophores appear in a range of 246-261 nm due to the bathochromic shift resulting from the delocalization of π-electrons on C=O *via* conjugation. Regardless of structural type, C7-C6 *trans*-closed GLs or PGLs (Type I) and *cis*-fused those at C7-C8 (Type II) show a negative CE, whereas C7-C6 *cis*-fused GLs or PGLs (Type III) and *trans*-closed those at C7-C8 (Type IV) show a positive CE (Scheme 84).[176a, 179a]

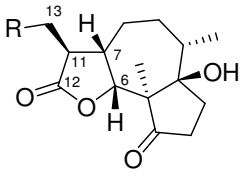


Type	**I**	**II**	**III**	**IV**
Sign of CE	(-)	(-)	(+)	(+)

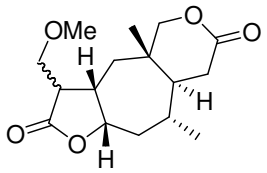
Scheme 84. Differences in Cotton Effects of GLs and PGLs according to the stereochemistry at C7.[179a]

Some SLs containing saturated γ-butyrolactone chromophores also were examined by *Geissmann et al.* (Scheme 85, Table 19).[176a] They explained that the sign of the CE usually cannot be predicted in this class of compounds because of the uncertainty of the

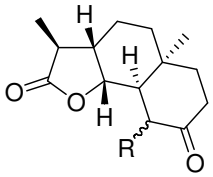
conformation of the γ-lactone ring. However, noteworthy, the *cis*-ring fused GLs **298**-**301** show positive CEs at λ_{max} between 215 nm and 236 nm, which is comparable with C7-C6 *cis*-ring fused GLs or PGLs in Type III (Scheme 84), although the n→π* transitions are hypsochromically shifted compared with conjugated α-methylene-γ-lactones. When H atom is replaced by an atom containing unshared electrons, λ_{max} is shifted bathochromically by 10-15 nm for oxygen and by 20 nm for nitrogen (Entries 1-3, Table 19). C7-C6 *cis*-fused 13-methoxydihydropsilotropin (**302**) shows a negative CE at λ_{max} = 231 nm (Entry 5, Table 19). An eudesmanolides derivative **303** shows a positive CE at λ_{max} = 217 nm (Entry 6, Table 19).



298, Dihydrocoronopilin (R=H)
299, 13-Methoxydihydrocoronopilin (R=OMe)
300, 13-Dimethylaminodihydrocoronopilin (R=N(CH$_3$)$_2$)
301, 13-Dimethylaminodihydrocoronopilin hydrochloride (R=N(CH$_3$)$_2$·HCl)



302, 13-Methoxydihydropsilotropin



303. Tetrahydrosantonin

Scheme 85. CD of saturated γ-lactones measured by *Geissmann et al.*[176a]

Table 19. CD of saturated γ-lactones.[176a]

Entry	Compound	λ_{max} (nm)	$[\theta]$	$\Delta\varepsilon_{max}$ [a]
1	**298**	215	+3540	+1.1
2	**299**	225	+1250	+0.4
3	**300**	236	+1305	+0.4
4	**301**	220	+2920	+0.9
5	**302**	231	-1328	-0.4
6	**303**	217	+4450	+1.3

[a] For better comparison the $[\theta]$ values have been transformed into $\Delta\varepsilon_{max}$ by the equation $[\theta]=3300\cdot\Delta\varepsilon_{max}$

Saturated γ-lactone chromophores have not been intensively investigated as like amide chromophores of peptides and proteins, probably, because of relatively low intensity of $[\theta]$ resulting from the forbidden n→π* transition. As shown in Table 19, however, the α,β-saturated GBLs **298**-**301**, whose rings are *cis*-fused at C6-C7, showed also positive CEs like the C6-C7 *cis*-ring fused GLs and PGLs (type III) containg α,β-unsaturated conjugated γ-lactone chromophore (Scheme 84). In addition, **302** exhibited a negative CE like type II that is the corresponding *cis*-fused α,β-unsaturated GLs and PGLs. Therefore, CD spectra of

Arglabin (**96**) and Arglabin-DMA·HCl (**255**), whose rings are *trans*-fused at C6-C7, were measured first in order to know the trends in the case of *trans*-fused GLs.

3.2 CD measurements of the C6-C7 *trans*-fused SLs containing GBL ester chromophore

Interestingly, CD patterns in *trans*-fused GLs showed different CE in the cases of containing an α,β-unsaturated γ-butyrolactone and a saturated γ-butyrolactone. The CD spectra in methanol of Arglabin (**96**)[180] and Arglabin-DMA·HCl (**255**)[180] are shown in Figure 20. In the case of Arglabin (**96**), a positive CE at λ_{max} = 208 nm ($\Delta\varepsilon_{max}$ = +5.4) were observed, which are the n→π* transition of α,β-unsaturated carbonyl chromophore and presumably the π→π* transition, respectively. UV absorption of solvent is dependent on the length of cells. Smaller pathlength of cell decrease the solvent absorbance significantly. For example, the cutoff of MeOH in the case of 0.1 mm of cell is 186 nm, while that in the case of 10 mm cell is 205 nm.[181] The negative CE at λ_{max} = 255 nm of Arglabin (**96**) corresponding to the C=C-C=O chromophore is in agreement with *Geissman*'s rule. In the case of α,β-saturated GL, the CD spectra of Arglabin-DMA·HCl (**255**) showed a positive CE at λ_{max} = 221 nm ($\Delta\varepsilon_{max}$ = +0.7) and a negative CE at λ_{max} = 201 nm ($\Delta\varepsilon_{max}$ = -4.3). With respect to the n→π* transition of **96** and **255**, they showed opposite signs of CE (Figure 20), which is comparable with the same CE in entries 1-4 of Table 19 and in type (III) of Scheme 84. Consequently, the *trans*-fused GLs showed different pattern with *cis*-fused GLs.

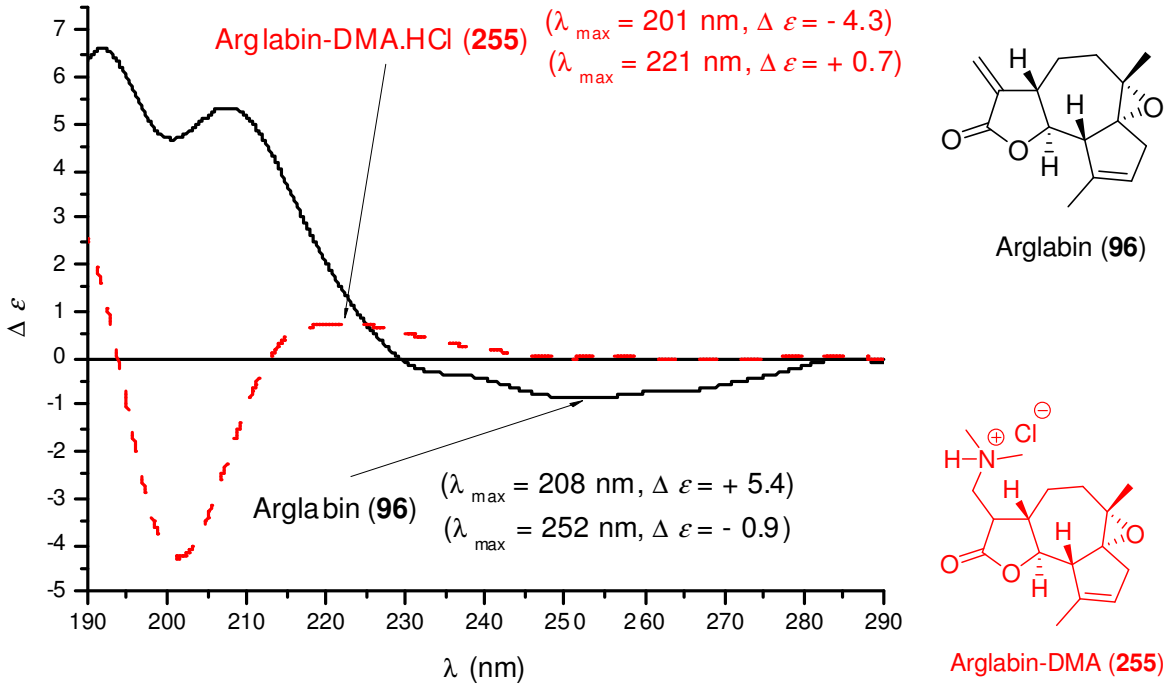
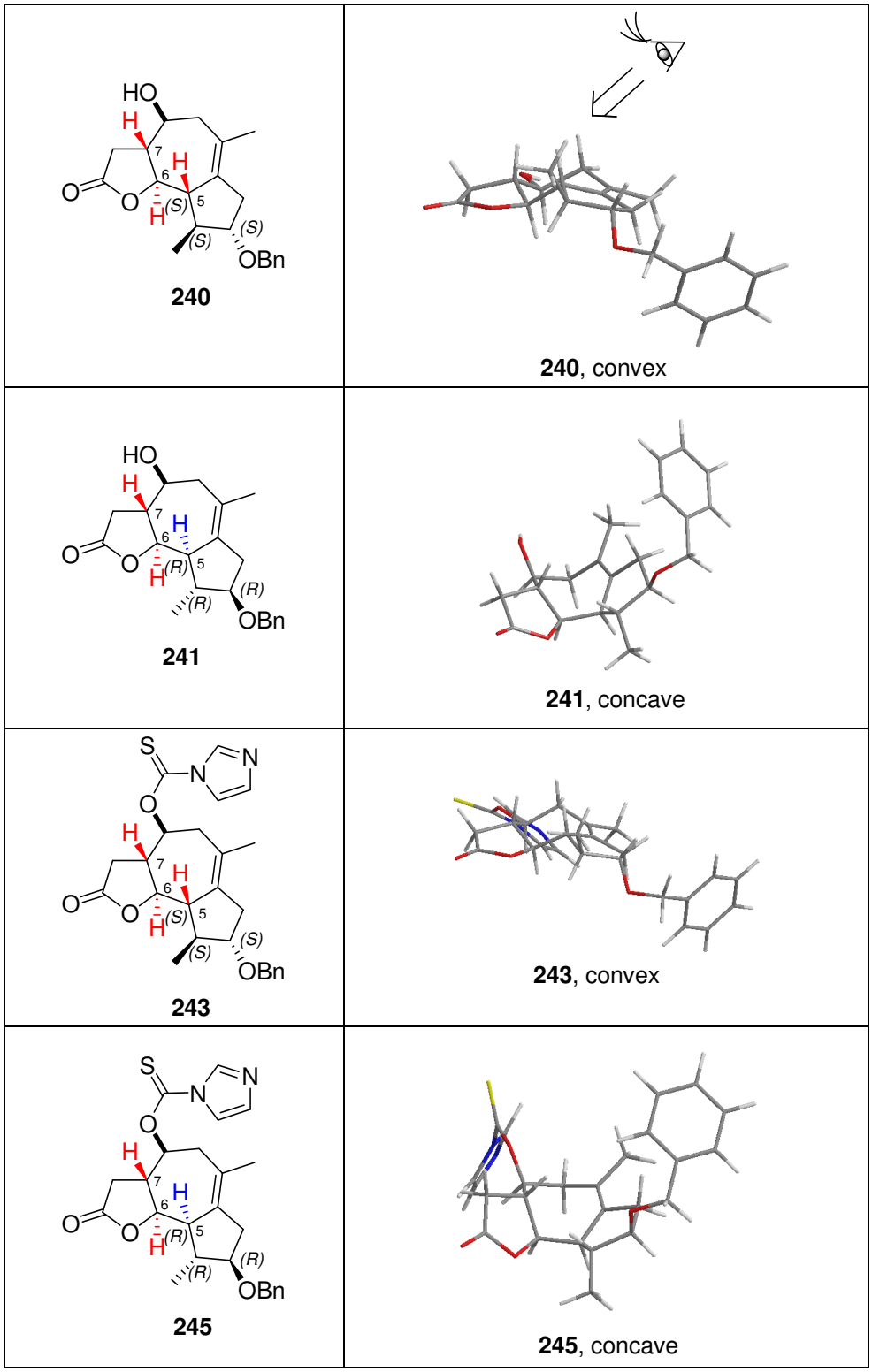


Figure 20. Comparison of CD spectra between Arglabin (**96**)[180] and Arglabin-DMA·HCl (**255**).[180]

It was known that the asymmetric surroundings of chromophores are responsible for the sign of the CE.[182] Not only the chiral centers C6 and C7 but also the third chiral center (C5) is supposed to be important to decide the chiral environment of GLs.



Scheme 86. Asymmetrically synthesized GLs **240-241**, **243** and **245**.

Therefore, the CD spectra of the asymmetrically synthesized GLs (**240-241**, **243** and **245**) were also measured. Molecular calculations using MOPAC envisioned the conformations of *trans*-fused GLs at C6-C7 (Scheme 86). According to the stereochemistry at C5, the whole conformation of 5,7,5-tricyclic compounds is determined (Scheme 86). The (S)-C5 in **240** and **243** leads a convex conformation, while the (R)-C5 in **241** and **245** leads a concave conformation from the top and front view of the 5,7,5-tricyclic skeleton.

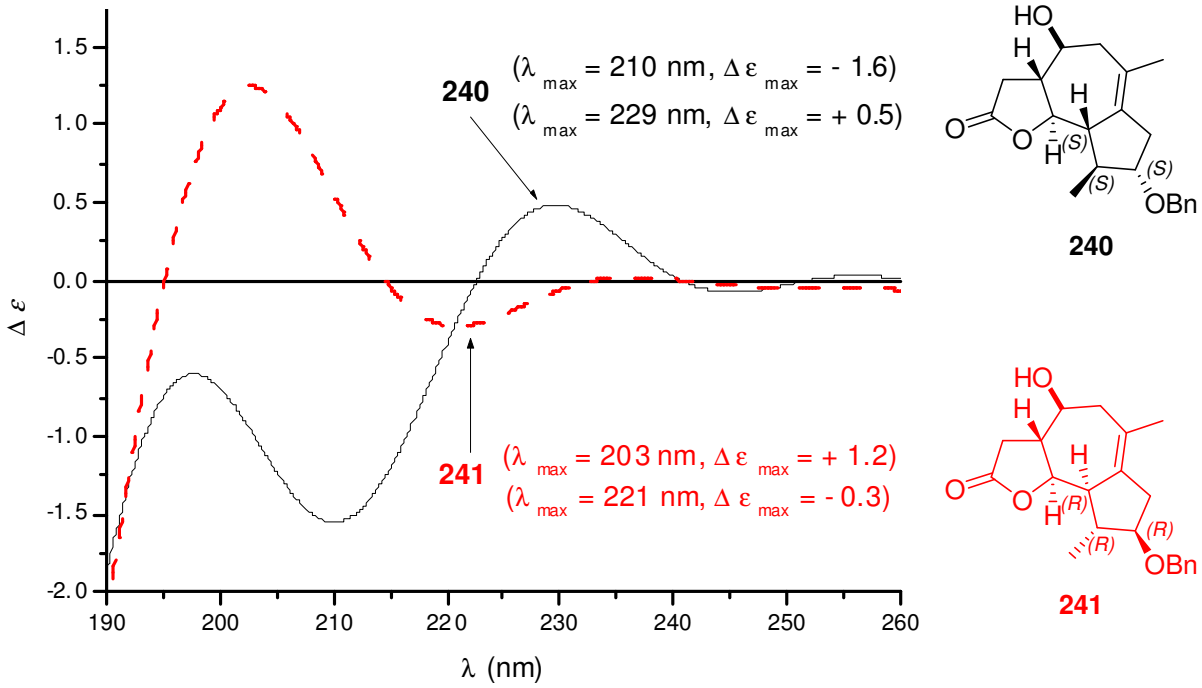


Figure 21. Comparison of CD spectra between **240** and **241**.

The comparison of the CD spectra between **240** and **241** show opposite signs of CE each other (Figure 21). Indeed, the CE of **240**, presenting a convex conformation, showed a positive CE at λ_{max} = 229 nm ($\Delta\varepsilon_{max}$ = +0.5) and a negative CE at λ_{max} = 210 nm ($\Delta\varepsilon_{max}$ = -1.6), whereas **241**, presenting a concave conformation, showed a negative CE at λ_{max} = 221 nm ($\Delta\varepsilon_{max}$ = -0.3) and a positive CE at λ_{max} = 203 nm ($\Delta\varepsilon_{max}$ = +1.2) as shown in Figure 21. In order to see the trends of CE in the case containing the same stereochemistry at C5, the CD spectra of **241** and **245** were compared each other. **241** and **245**, showing a concave conformation resulting from (R)-C5, showed same pattern of signs of CE (Figure 22). A positive CE at λ_{max} = 205 nm ($\Delta\varepsilon_{max}$ = +2.7) and a negative CE at λ_{max} = 229 nm ($\Delta\varepsilon_{max}$ = -1.0) were observed in **245**.

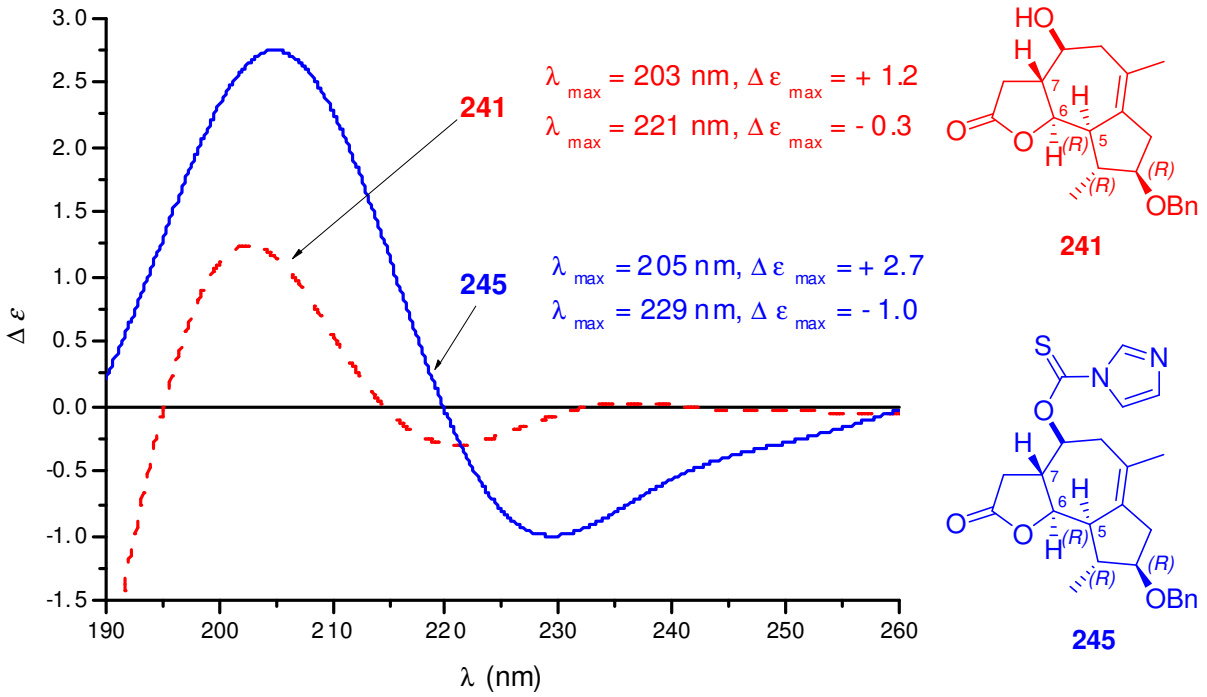


Figure 22. CD spectra of **241** and **245**.

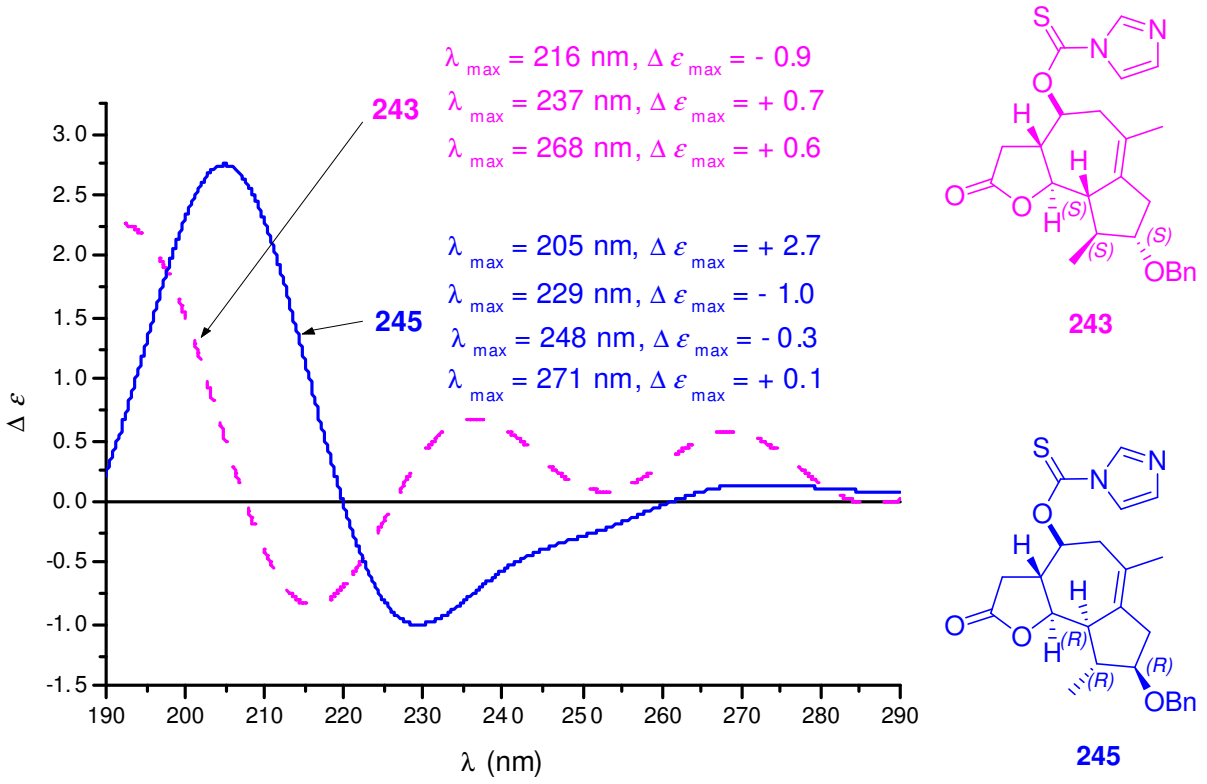
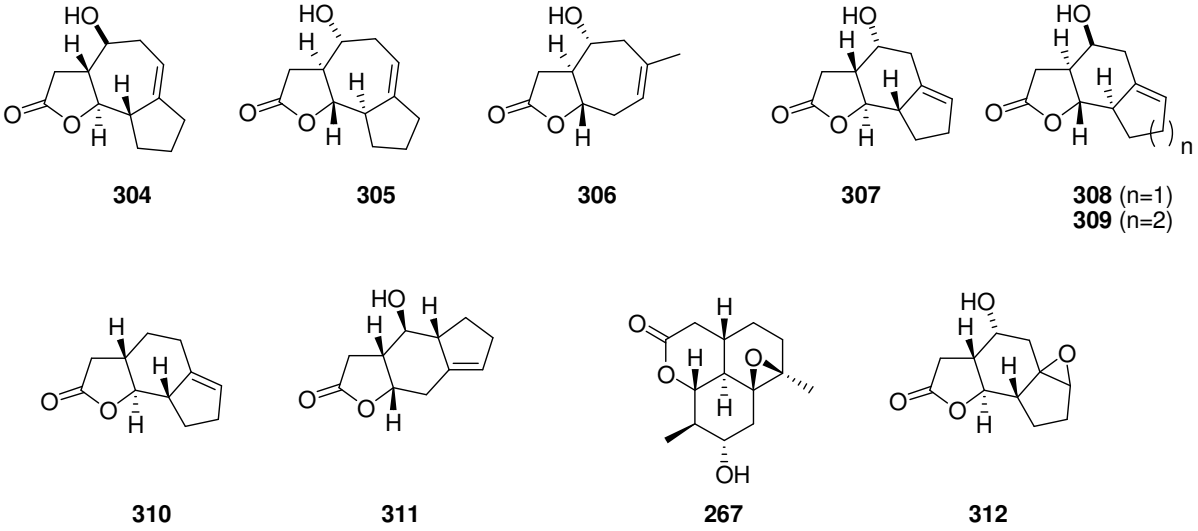


Figure 23. Comparison of CD spectra between **243** and **245**.

Another comparison between **243** and **245** was carried out. In both cases, 1st and 2nd CEs from short wavelength are opposite pattern of CEs. A negative CE at λ_{max} = 216 nm ($\Delta\varepsilon_{max}$

= -0.9) and a positive CE at λ_{max} = 237 nm ($\Delta\varepsilon_{max}$ = +0.7) were observed in **243** (Figure 23). An additional CE at λ_{max} = 268 nm in **243** and two CEs at λ_{max} = 248 nm and at λ_{max} =271 in **245** were observed. These λ_{max} might be absorptions of either imidazole (280 nm)[183] or the O-C-N and the O-C=S conjugation in the imidazolylthiocarbamate chromophore like the absorptions that two λ_{max} at 249.5 nm and at 290.0 nm in a monothiocarbamate $Me_2NC(S)OMe$[184] or the characteristic absorption peaks at 250 nm and 280 nm in a dithiocarbamate R^1-S-C(=S)-N-$(R^2)_2$, attributing to S-C-N and S-C=S conjugation, respectively.[185]



Scheme 87. C6-C7 *trans* fused SLs.

Table 20. Measurement of signs of CE in different types of SLs.

Entry	Substance	1st CE		2nd CE	
		λ_{max} (nm)	$\Delta\varepsilon_{max}$	λ_{max} (nm)	$\Delta\varepsilon_{max}$
1	**304**	204	- 11.1	233	+ 0.4
2	**305**	203	+ 7.4	225	- 0.5
3	**306**	206	+ 0.6	225	- 0.5
4	**307**	209	- 3.5	223 [a]	- 1.9
5	**308**	209	- 4.0	223 [a]	- 2.1
6	**309**	207	- 5.7	223 [a]	- 2.9
7	**310**	209	+ 6.0	229 [a]	+ 1.8
8	**311**	209	- 8.9	222	- 4.6
9	**267**	219	+ 0.9	231	+ 0.9
10	**312**	217	+ 0.8	229	+ 0.5

[a] Peaks appear as a shoulder.

An absorption at near 270 nm of **243** and **245** might be shifted hypsochromically due to the imidazolium moiety, a electron withdrawing group (*i.e.* EWG), compared with dimethylamino group as an electron donating group (*i.e.* EDG).

The patterns of CE in saturated GLs were further investigated. As shown in Scheme 87, CD spectra of 4 types of SLs are measured. **304** show the same patterns of CE with **240** having a negative CE at λ_{max} = 210 nm and a positive CE at λ_{max} = 229 (Entry 1, Table 20). In addition, a GL **305** and a xanthanolide **306** showed also same pattern of CE with **241** showing a positive CE at λ_{max} = 203 nm and a negative CE at λ_{max} = 221 nm (Entry 2, Table 20).

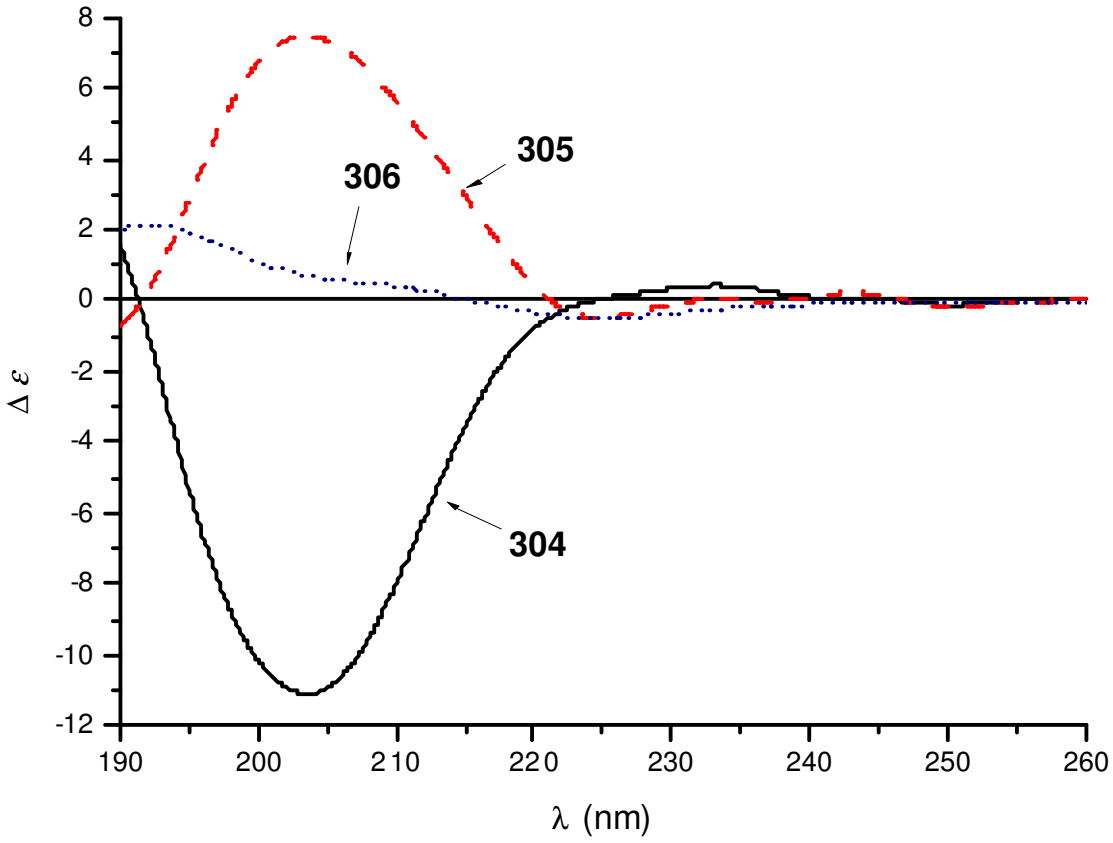
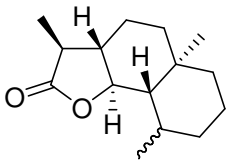


Figure 24. CD spectra of **304**-**306**.

Eudesmanolides derivatives **307**-**309** showed two negative CEs at λ_{max} = 207-209 nm and at λ_{max} = 223 nm as a shoulder (Entries 4-6, Table 20 and Figure 25). Whereas, **310** has two positive CEs at λ_{max} = 209 nm ($\Delta\varepsilon_{max}$ = +6.0) and at λ_{max} = 227 nm ($\Delta\varepsilon_{max}$ = +1.8) (Entry 7, Table 20 and Figure 25).

Eudesmanolides **307** and **310**, being just different from each other owing to existence of hydroxyl group at C4, showed an opposite signs of CE to each other. The CE of **307** is comparable with **313** having similar molecular skeleton (Scheme 88).[177] The *cis*-ring fused **311** showed two negative CEs as a shoulder at λ_{max} = 209 nm ($\Delta\varepsilon_{max}$ = -8.9) and λ_{max} = 222 nm ($\Delta\varepsilon_{max}$ = -4.6) as like **307**-**309** (Entry 8, Table 20 and Figure 25).



313, (+) CE at λ_{max} = 230 nm

Scheme 88. Reference of CE in eudesmanolides derivatives.[177]

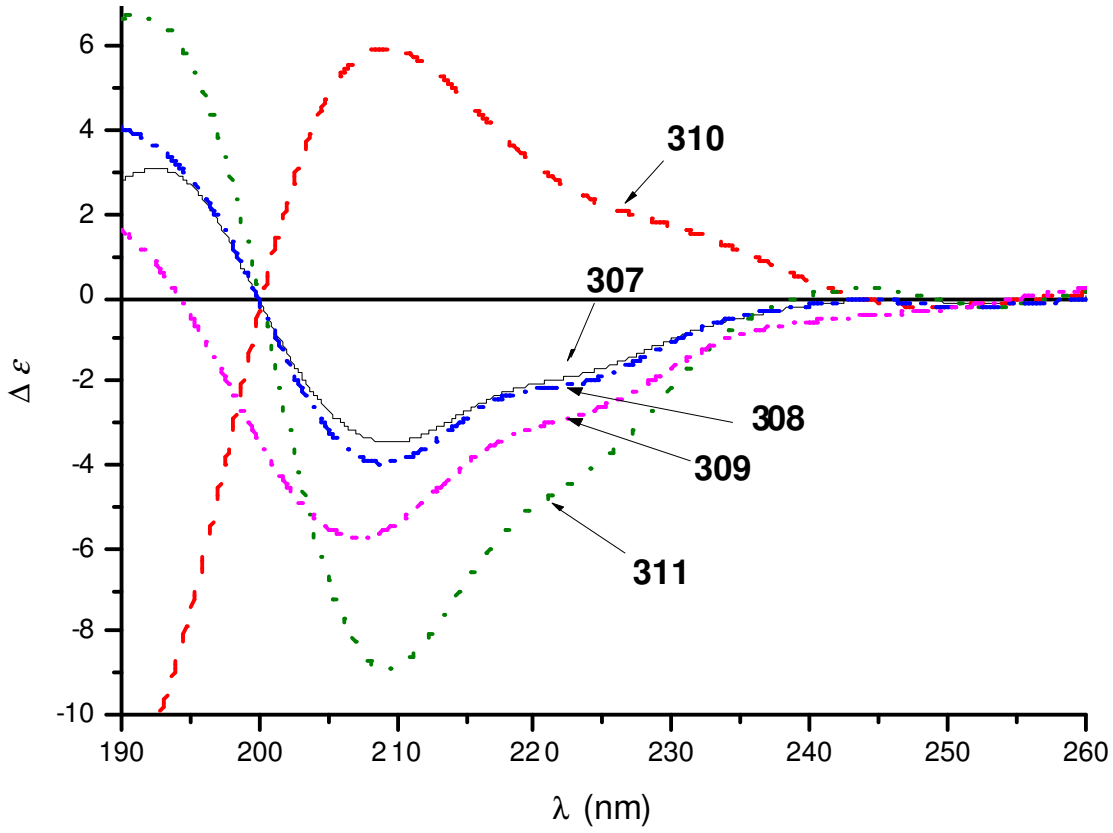


Figure 25. CDs of **307**-**311**.

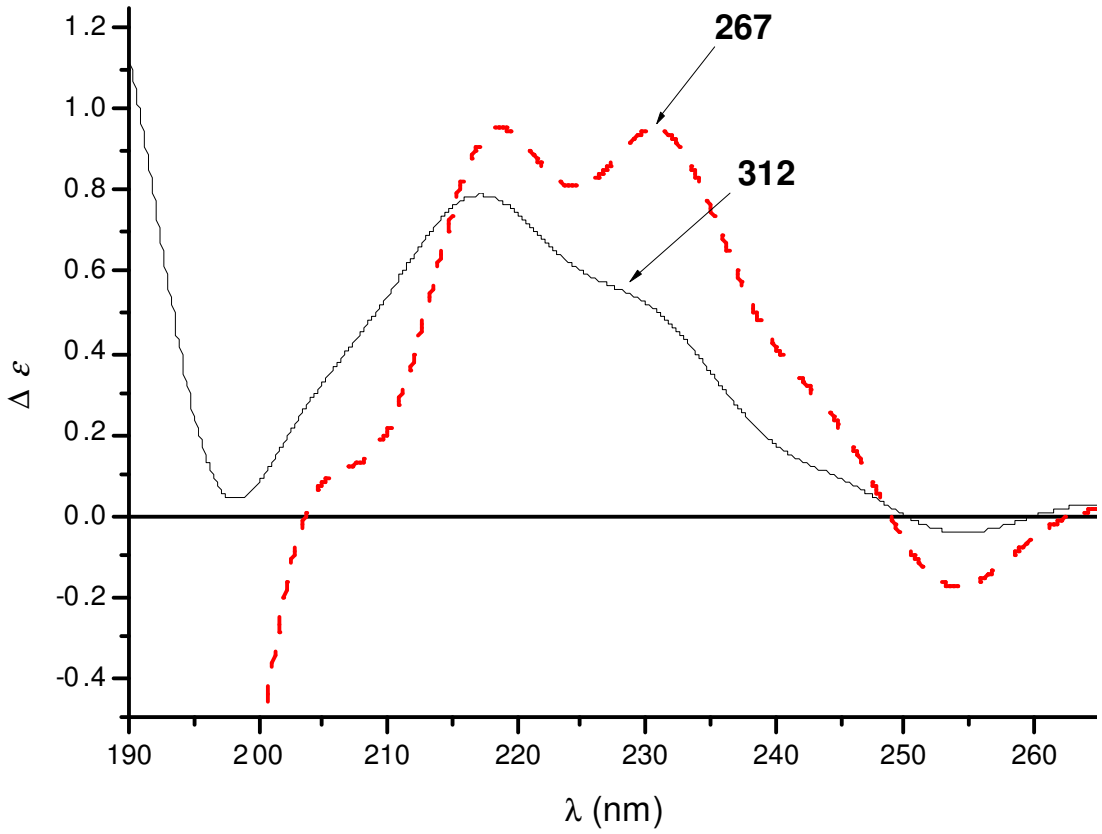


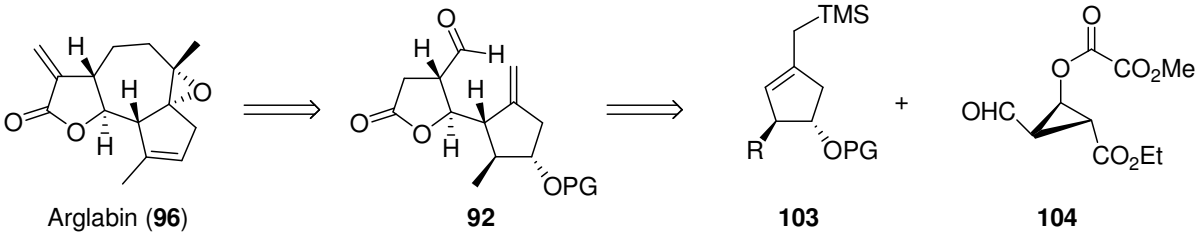
Figure 26. CDs of **267** and **312**.

The lactone compounds containing epoxide showed two positive signs of CE at λ_{max} = 219 nm and 231 nm in the case of **267**, whilst two positive signs of CE at λ_{max} = 217 nm and 229 nm in the case of **312** (Entries 9-10, Table 20 and Figure 26).

C. Summary

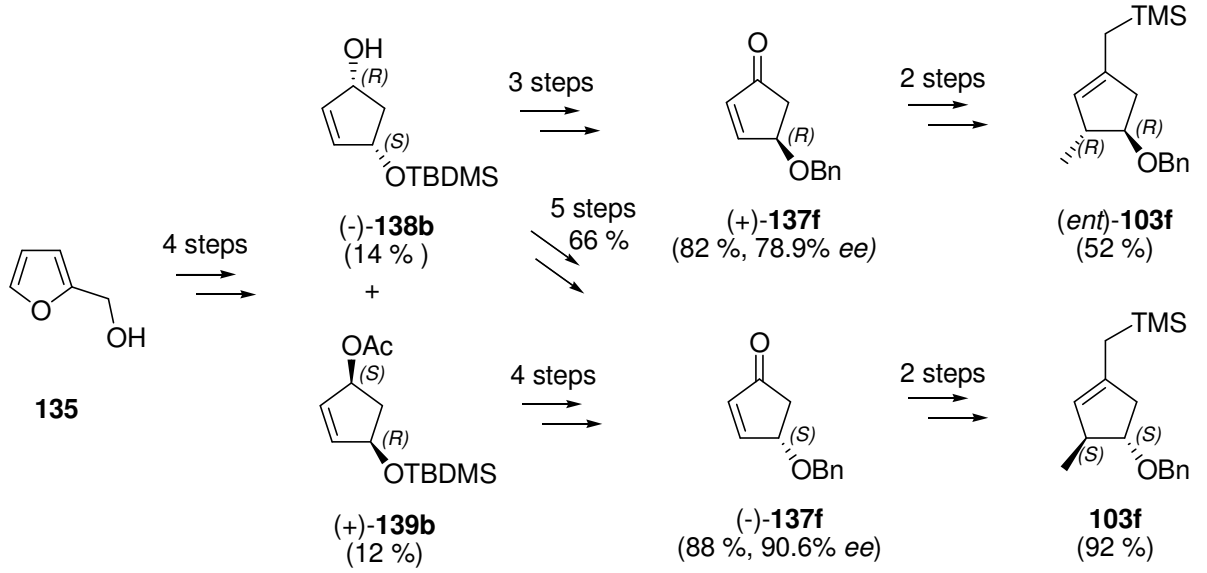
1. Asymmetric synthesis towards Arglabin (96)

Many naturally-occurring guaianolides (*i.e.* GLs) and pseudoguaianolides (*i.e.* PGLs) are based on a 5,7,5-fused ring skeleton and show a broad biological profile.[30,31] Among them, Arglabin (**96**) has attracted special attention due to its promising antitumor and cytotoxic activity.[58] In the present work the asymmetric synthesis towards Arglabin (**96**) were investigated (Scheme 88).



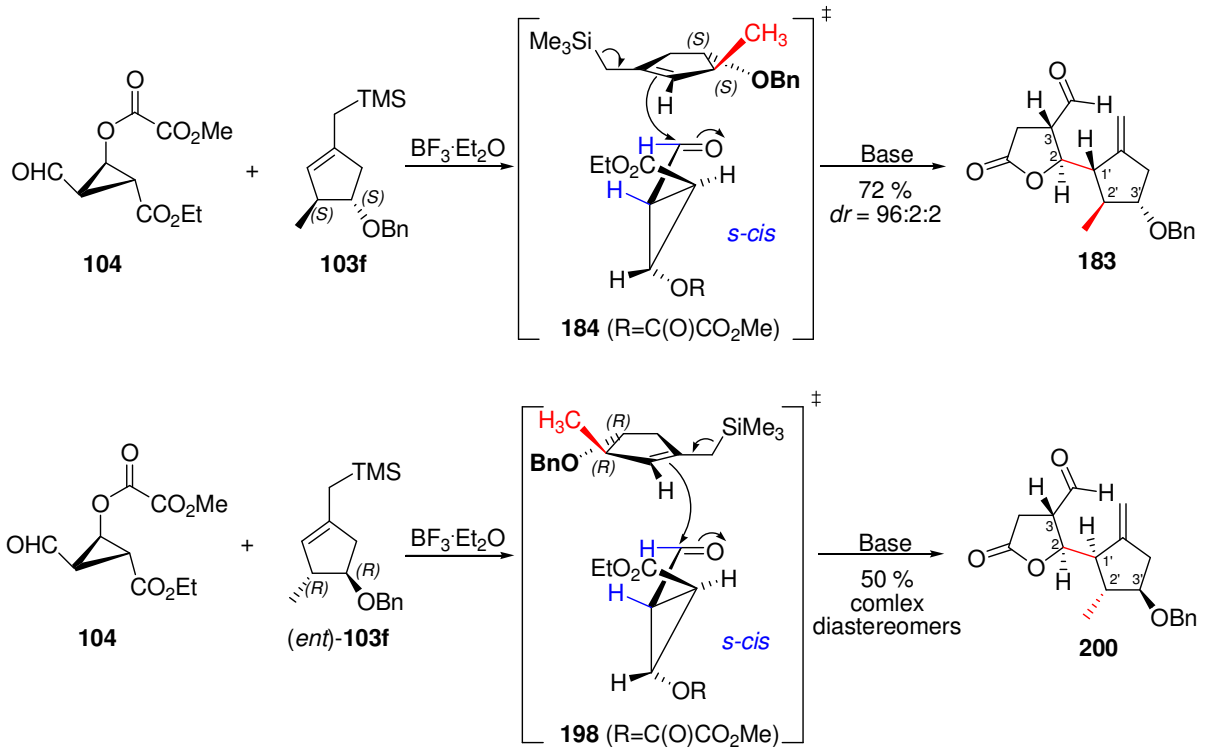
Scheme 88. Retrosynthetic analysis towards Arglabin (**96**).

For the synthesis of **92**, the key intermediate for envisioned the synthesis of Arglabin (**96**), optically active cyclic allylsilanes **103** were synthesized. **103f** and (*ent*)-**103f** were synthesized from fufuryl alcohol (**135**) in 10 % overall yield in ten steps and 6 % overall yield in nine steps respectively, *via* (-)-**137f** and (+)-**137f** as the intermediates (Scheme 89). Alternatively, (-)-**138b** was also transformed into (-)-**137f** in 66 % yield in five steps, which was used as the precursor for the synthesis of **103f**.



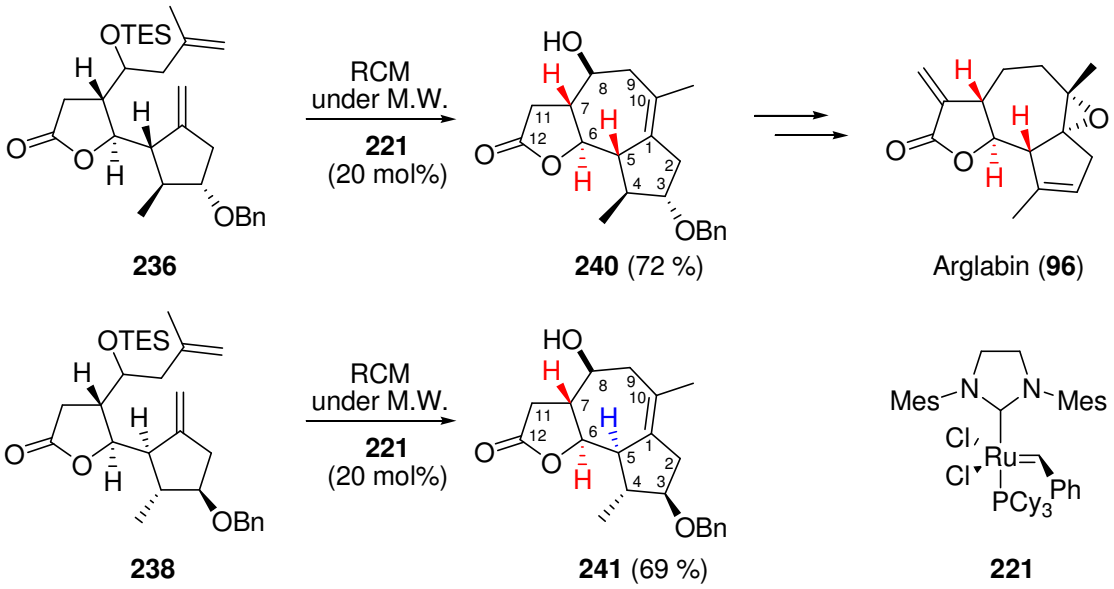
Scheme 89. Synthesis of optically active cyclic allylsilanes.

The 2,3-*anti* substituted γ-butyrolactones (*i.e.* GBLs) **183** and **200** were synthesized as the key intermediates for the synthesis of Arglabin (**96**). **183** was synthesized in 72 % yield as the major diastereomer from *Sakurai* allylation of **103f** with **104** and subsequent retroaldol lactonization. The same protocol with (*ent*)-**103f** and **104** afforded **200** in 50 % yield as the major diastereomer. In both cases, the stereochemistry was controlled predominantly by *Felkin-Anh* rule and *anti*-addition *via* the corresponding transition states **184** and **198**, respectively (Scheme 90).



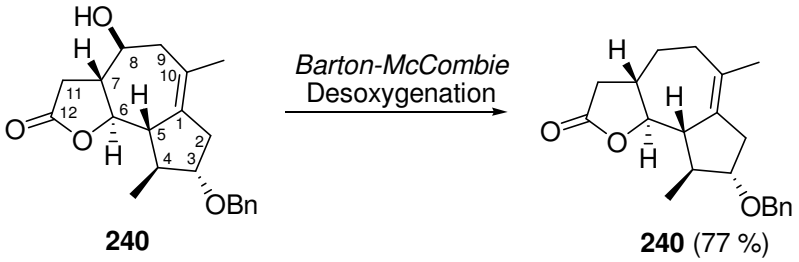
Scheme 90. The major diastereomers obtained from *Sakurai* allylation and subsequent retroaldol lactonization of **103f** and (*ent*)-**103f** with **104**.

Microwave assisted RCM reaction using Grubbs (II) catalyst (**221**, 20 mol%) afforded **240** (72 %) and **241** (69 %) from the corresponding precursor **236** and **238**, respectively (Scheme 91). The chiral centers of **240** at C-5, C-6, and C-7 coincide with those of Arglabin (**96**), while those in **241** were different (Scheme 91). Consequently, allylsilane **103f** was disclosed to be suitable for the synthesis of Arglabin (**96**) (Scheme 91).



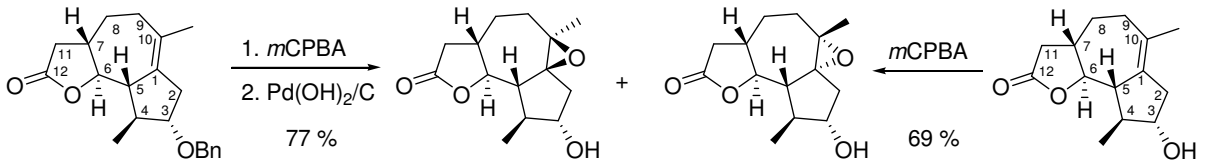
Scheme 91. RCM of **236** and **238** using Grubbs (II) under microwave irradiation.

The oxygen at C-8 could be removed successfully *via Barton-McCombie* desoxygenation of **240** in 77 % yield (Scheme 92).



Scheme 92. *Barton-McCombie* desoxygenation of **240**.

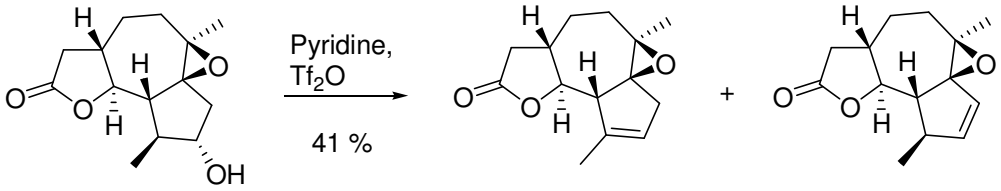
As another key step, diastereoselective epoxidation at the double bond C1-C10 is necessary. In order to know the effect of homoallyl alcohol at C-3 on the diastereoselectivity, epoxidations of **244** and **250** were carried out using *m*CPBA. First, epoxidation of **244** led mainly to the undesired diastereomers (**249**:(*epi*)-**249=**3:1). **250**, being hoped to have some neighboring participation effect of homoallyl alcohol *via* complexation with *m*CPBA, led again mainly to the epoxide with the unnatural configuration of Arglabin (**249**:(*epi*)-**249=**2:1). (Scheme 93).



244		**249**	(3	:	1)	(*epi*)-**249**
		249	(2	:	1)	(*epi*)-**249** **250**

Scheme 93. Attempts for the diastereoselective epoxidation using *m*CPBA.

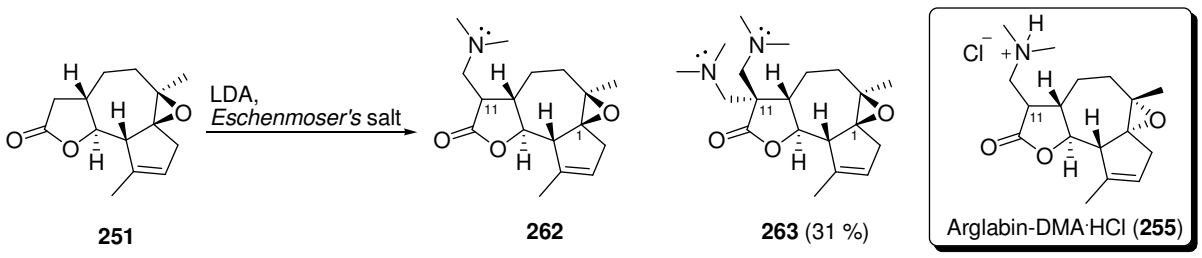
Dehydration of **249** using Tf_2O showed a dependance on the reaction temperature. At 0°C, only the *Zaitsev* product **251** was obtained, while *Hofmann* product **252** was also observed in the same reaction at rt. (Scheme 94).



249		**251**	**252**
	at 0 °C ⟶ rt.	100	0
	at rt.	64	36

Scheme 94. Regioselective dehydration of **249** dependent on reaction temperature.

For the direct synthesis of Arglabin-DMA·HCl (**255**), the most biologically promising analogue of Arglabin, α-aminoalkylation was performed using *Eschenmoser'*s salt. Upon usage of 1.0-2.0 eq. of LDA, the desired **262** could not be obtained. However, 5.0 eq. of LDA led to the double aminoalkylated **263** in 31 % of yield (Scheme 95).

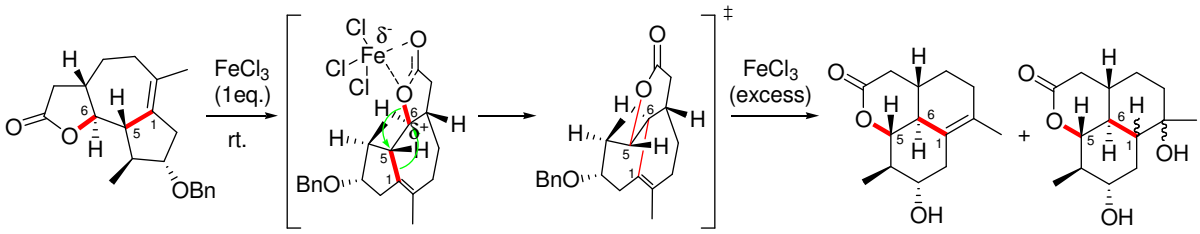


251 **262** **263** (31 %)

Scheme 95. α-aminoalkylation of **251** using *Eschenmoser*'s salt.

2. Rearrangement from 5,7,5-tricyclic γ-butyrolactone to 6,6,6-tricyclic δ-valerolactone system

In the course of debenzylation of **244** using excess of anhyd. $FeCl_3$, the rearranged product **247** was obtained, which was indirectly proved by the X-ray crystal structure and NOE study of **249**. This rearrangement is a kind of *Wagner-Meerwein* rearrangement mediated carbocation with Lewis acids catalyst. Upon addition of 1 eq. of anhyd. $FeCl_3$, the C-6 became electon deficient. At the same time C6-O and C1-C5 bonds in **244**, being oriented antiperiplanarly each other, were rearranged to give **276** as intermediate. Extra addition of anhyd. $FeCl_3$ afforded the debenzylated **247** in 56 % of yield. Upon longer reaction times, addition of water to give rise to **265** was observed in addition (Scheme 96).

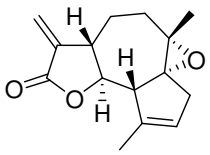


	247	265
2.3 h	56 %	2 %
18 h	71 %	29 %

Scheme 96. *Wagner-Meerwein* rearrangement of **244** to **247** under anhyd. $FeCl_3$.

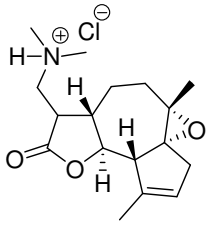
3. Conformational analysis of saturated GLs using Circular Dichroism

Natural GLs contain usually a α,β-unsaturated γ-butyrolactone chromophore which have a characteristic Cotton Effect (*i.e.* CE) at near 250 nm. Among them, *cis*-annulated GLs at C6-C7 showed a positive CE and their α,β-saturated synthetic analogues showed a positive CE at near 220 nm.[176a] Different with *cis*-annulated GLs at C6-C7, Arglabin (**96**)[180] and Arglabin-DMA·HCl (**255**),[180] the *trans*-fused GLs, showed opposite CE signs of the γ-butyrolactone ester chromophore corresponding to the n→π and π→π* transition, respectively (Scheme 97).



Arglabin (**96**)

a positive CE for π-->π* and a negative CE for n-->π*

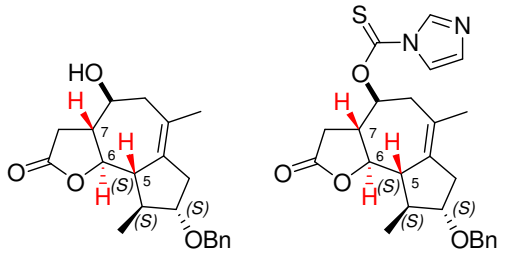


Arglabin-DMA (**255**)

a negative CE for π-->π* and a positive CE for n-->π*

Scheme 97. Pattern of CE signs in CD spectra of Arglabin (**96**) and Arglabin-DMA·HCl (**255**).

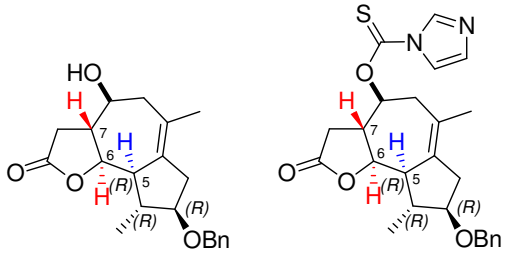
GLs, being synthesized asymmetrically during the synthesis towards Arglabin (**96**), were measured the signs of CE mainly in the 190-260 nm region with MeOH. As far as CEs show, not only stereochemistry of C6-C7 but also C5 was important to decide the signs of CE, which means the conformation of GLs are dependent on the stereochemistry of C-5. As results, (*S*)-C5 led to a convex conformation of GL and this conformation showed a negative CE at near 210 nm and a positive CE at near 230 nm in the cases of **240** and **243**. In contrast, (*R*)-C5 led to a concave conformation in **241** and **245**, which showed a positive CE at near 205 nm and a negative CE at near 230 nm (Scheme 98, and see detail in Chapter D).



240 **243**

convex coformation

a negative CE for π-->π* and a positive CE for n-->π*



241 **245**

concave coformation

a positive CE for π-->π* and a negative CE for n-->π*

Scheme 97. The signs of CE in CD spectra of GLs depending on the stereochemistry of C-5.

D. Experimental part

General Remarks:

Reactions with air and moisture-sensitive reagents were conducted under N_2 or Ar atmosphere, so called *Schlenk*-technicque, in completely dried glassware by heating.

Column Chromatography: Silica gel Geduran 60 (0.063-0.20 mm) or Flash silica gel 60 (0.040-0.063 mm) of Merck Co. Ltd., were used as stationary phase and mixed solvents of petroleum ether / ethyl acetate, being simply distilled with $CaCl_2$, were used as eluent. The each experimental procedure gives more detailed information about the eluents.

Thin Layer Chromatography (TLC): Silica gel 60 F_{254} on aluminum plates of Merck Co. Ltd., (layer thickness: 0.2 mm) was used. The UV-light (λ = 254 nm) was adopted for the detection. Mostain, Vanillin sulfuric acid, Molybdato phosphoric acid (5% in EtOH), and Iodine were used as developper.

Most of **diastereomeric ratio (*dr*)** was measured by comparison with the integrations of the related diastereomeric signals in ^{13}C-NMR and ^{1}H-NMR.

Nomenclature: The nomenclature of compounds in experimental part was followed by IUPAC rule using IUPAC name pro (*ver*. 3.50) of ACD.

^{1}H-NMR was measured by the following instruments: Bruker AC 250 (250 MHz), Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) and Bruker Avance 600 (600 MHz). The chemical shift (δ) was referred in ppm, which was calibrated on $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.49 ppm), CD_3OD (3.34 ppm), Acetone-d_6 (2.05 ppm), Tetrahydrofuran-d_8 (1.85, 3.76 ppm) or Tetramethylsilane (0.00 ppm) as internal standard. The coupling constant *J* was noted in Hz. The following abbreviations represent spin-spin splitting patterns: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet of doublet, ddddd = doublet of doublet of doublet of doublet of doublet, dt = doublet of triplet. The notation A and B means following definition; A is the proton which is projected out of the plane of molecule, whereas B is the one which is sunk backward from the plane.

^{13}C-NMR was measured by the following instruments: Bruker AC 250 (62.9 MHz), Bruker Avance 300 (75.5 MHz), Bruker Avance 400 (100.6 MHz), Bruker ARX 400 (100.6 MHz), and Bruker Avance 600 (150.9 MHz). The chemical shift (δ) were calibrated on $CDCl_3$ (77.16 ppm), DMSO-d_6 (39.52 ppm), CD_3OD (49.00 ppm), Acetone-d_6 (29.84 ppm), Tetrahydrofuran-d_8 (25.62, 67.97 ppm) or Tetramethylsilane (0.00 ppm) as internal standard. The multiplicities of signals were assigned by DEPT 90 and 135 (DEPT; distortionless enhancement by polarization transfer), and the notations were allotted as follow: + = primary and tertiary C-atoms (positive DEPT 135 signal; tertiary C-atoms: DEPT 90 signal), - = secondary C-atoms (negative DEPT signal), quart. = quarternary C-atoms (DEPT signal intensity zero).

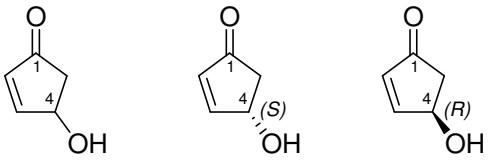
In some cases the COSY, HSQC, HMBC, and NOESY signals were investigated for the exact assignment of the stereochemistry as needed.

Melting point was measured with Büchi 510K and is uncorrected. **IR (Infrared) spectra** were measured Bio-Rad Excalibur FT-IR series and Tensor 27 Brucker. **Mass spectra** were measured in the mass spectroscopy department of the University of Regensburg using Finnigan MAT 95, MAT SSQ 710A and Thermoquest Finnigan TSQ 7000. **Optical Rotation** was measured by Perkin-Elmer 241 MC polarimeter using 1.0 dm or 0.1 dm measuring celll with 589 nm wavelength of Na-D-Line as light source. The concentration was noted in [g/100ml] unit. The specific optical rotation was calculated with the following formular:

$$[\alpha]^{\theta}_{D} = ([\alpha]_{exp} \times 100)/(c \times d)$$

θ = temperature (°C)
$[\alpha]_{exp}$ = measured optical ortation value
c = concentration (g/100ml)
d = length of the cuvette

CD spectra were measured with JASCO model JA710/720 at the institute of Bioanalytic and Sensoric of the University of Regensburg (Research group of Prof. Dr. O. Wolfbeis) at 21 °C between 190 nm-300 nm in the MeOH solvent. The number of scans ranged between 10-18. The length of the cylindrical cuvette was 0.1 mm, the resolution was 0.1 nm, 1.0 nm of the band width, 50 mdeg of the sensitivity, the response was 1-2 sec, and the speed was 50 nm/min. The background (MeOH) was subtracted to each spectrum. The absorption value was measured as Molar Circular Dichroism ($\Delta\varepsilon$). **Monocrystal X-ray analysis** was measured at the central X-ray analysis department of University of Regensburg. **Chiral HPLC** was measured at the central HPLC analysis department of University of Regensburg. **Gas chromatography** was measured at the central GC analysis department of University of Regensburg. **Microwave syntheses** were conducted by Synthewave™ S 402 (monocavity) of Prolabo, France, which has 2.45 GHz frequency and 300 W maximal power, under Ar sparging.



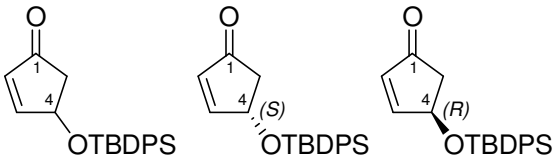
136 (-)-**136** (+)-**136**

4-hydroxy-2-cyclopenten-1-one (136); (4*S*)-4-hydroxy-2-cyclopenten-1-one ((-)-136); (4*R*)-4-hydroxy-2-cyclopenten-1-one ((+)-136)

A solution of fufuryl alcohol (11 ml, 0.13 mmol) in H_2O (370 ml) was treated with KH_2PO_4 (0.63g, 4.63 mmol). pH = 4.1 was adjusted with H_3PO_4 (some droplets), then refluxed at 99°C for 40 h. (When the reaction was carried out under N_2 purging, much clear reaction mixture was obtained and it was easy to handle). The cooled reaction mixture was separated the solution from the caramel sludge. The water phase was washed with PE and concentrated under reduced pressure carefully. Red oil was dissolved in CH_2Cl_2 (100 ml), dried over $MgSO_4$, filtrated and concentrated. Column chromatography afforded **136** (5.18 g, 41 %) as pale red oil.

TLC $\mathbf{R}_f$ = 0.21 (PE:EA = 1:1, Mostain). **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e.

Synthesis of (+)-**136**: (+)-**137b** (640 mg, 3.0 mmol) was dissolved in 10 ml of mixed solvent (AcOH:THF:H_2O=3:1:1) and it was stirred for 44 h at rt. AcOH was added additionally (2×0.2 ml). The reaction mixture was concentrated under reduced pressure. Column chromatography (PE:EA = 2:1 & EA) afforded (+)-**136** (259 mg, 88 %) as colorless oil. $[\alpha]_D^{20}$ + 98.5 ((+)-**136**, c 0.80, $CHCl_3$). Same reaction condition with (-)-**137b** yielded (-)-**136** (74 %) as colorless oil.

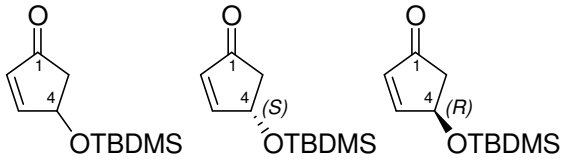


137a (+)-**137a** (-)-**137a**

4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-cyclopenten-1-one (137a)

Into a solution of **136** (2.0 g, 20.4 mmol) in THF (20 ml), abs. Et_3N (4.6 ml, 32.6 mmol) and DMAP (49.8 mg, 0.41 mmol) were added subsequently. It was cooled down to 0°C and treated with TBDPSCl (5.2 ml, 20.4 mmol) *via* syringe. It was stirred for 12 h at rt. to develop ivory colored emulsion. It was poured into aqueous 0.5*N* HCl (20 ml). The separated org. phase was washed with 0.5*N* HCl, 5% $NaHCO_3$, and brine. It was dried over Na_2SO_4 and

concentrated to give **137a** (6.63 g, 97 %) as colorless oil.
TLC $\mathbf{R}_f$ = 0.35 (PE:EA = 9:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.08 (s, C(CH_3)$_3$, 9H), 2.43 (dd, *J* = 18.2 Hz, 2.3 Hz, 1H, 5), 2.50 (dd, *J* = 18.2 Hz, 5.9 Hz, 1H, 5), 4.95 (m, 1H, 4), 6.11 (dd, *J* = 5.7 Hz, 1.2 Hz, 1H), 7.34 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 7.42 (m, 6H, aromatic), 7.69 (m, 4H, aromatic). **^{13}C-NMR** (75.5 Hz, $CDCl_3$): δ 19.3 (quart., $C(CH_3)_3$), 27.0 (+, C(CH_3)$_3$), 45.0 (-, 5-C), 72.0 (+, 4-C), 128.1 (+, aromatic), 130.3 (+, aromatic), 134.7 (quart. *ipso*), 135.9 (+, aromatic), 163.8 (+, 3-C), 206.5 (quart., *C*=O).
Synthesis of (-)-**137a**: (+)-**136** (240 mg, 2.44 mmol) was dissolved in DMF (3 ml). DMAP (596.2 mg, 4.88 mmol) was added at rt. In 15 min, TBDPSCl (750 µl, 2.93 mmol) was added drop by drop *via* syringe. The reaction mixture was stirred for 12 h at rt. H_2O (10 ml) was added and it was extracted with E_2O (2×20 ml). The combined org. phase was dried over Na_2SO_4 and concentrated. Column chromatography (PE:EA = 3:2) afforded (-)-**137a** (quant. yield). $[\alpha]_D^{22}$ - 3.0 (c 1.02, $CHCl_3$). Same reaction with (-)-**136** afforded (+)-**137a** (quant. yield).

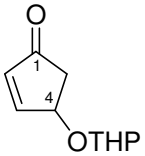


137b (-)-**137b** (+)-**137b**

4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-cyclopenten-1-one (137b)

137a (23 g, 234.5 mmol) was dissolved in THF (60 ml). DMAP (574 mg, 4.7 mmol) and Et_3N (39 ml, 281.4 mmol) were added subsequently at 0°C. In 15 min, a solution of freshly distilled TBDMSCl (45.9 g, 304.8 mmol) in THF (60 ml) was added dropwise via dropping funnel over 1 h. The reaction mixture was stirred for 1 h further and Et_2O (200 ml) was added. Work-up with 0.5*N* HCl was carried out carefully under ice bath. It was stirred for 30 min and extracted with (2×100 ml). The combined org. phase was washed with 0.5*N* HCl, 5% $NaHCO_3$, and brine. It was dried over Na_2SO_4, concentrated and subjected to column chromatography (PE:EA = 9:1) to yield **137b** (73 g, 82 % till 3rd column chromatography) as colorless oil.
TLC $\mathbf{R}_f$= 0.22 (PE:EA = 19:1, Vanillin sulfuric acid). **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e.
Synthesis of (-)-**137b**: (-)-**138b** (1.9 g, 8.86 mmol) was dissolved in CH_2Cl_2 (31 ml) and 3Å M.S. was put into the solution. PCC (2.8 g, 12.99 mmol) was added and the reaction mixture was stirred for 19 h at rt. Simple filtration and concentration was performed. Column chromatography (PE:EA = 9:1) afforded (-)-**137b** (1.56 g, 83 %) as colorless oil. $[\alpha]_D^{21}$ -

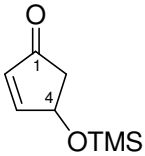
40.8 ((-)-**137b**, c 1.07, $CHCl_3$). Same reaction condition with (+)-**138b** yielded (+)-**137b** (88 %) as colorless oil. $[\alpha]_D^{21}$ + 53.1 ((+)-**137b**, c 1.03, $CHCl_3$).



137c

4-(tetrahydro-2*H*-pyran-2-yloxy)-2-cyclopenten-1-one (137c)

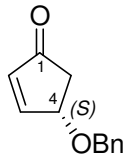
To a solution of **136** (1.0 g, 10.2 mmol) in 20 ml of CH_2Cl_2, 3,4-dihydro-2H-pyran (1.2 ml, 12.75 mmol) and PTSA (10 mg, 0.05 mmol) were added subsequently at 20°C. The reaction mixture was stirred for 14 h to develop a dark green colored mixture. Et_2O (25 ml) was added and it was washed with sat. $NaHCO_3$ and brine subsequently. Column chromatography afforded **137c** (1.6 g, 82 %). The NMR is authenticated by ref. 78e.



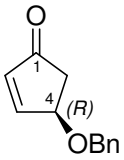
137d

4-[(trimethylsilyl)oxy]-2-cyclopenten-1-one (137d)

To a solution of **136** (1.0 g, 1.02 mmol) in CH_2Cl_2 (30 ml), Et_3N (2.9 ml, 2.07 mmol) and TMSCl (1.6 ml, 12.6 mmol) were added subsequently at 0°C. It was stirred for 2 h at rt. to develop pale brown colored mixture. The reaction was quenched with sat. $NaHCO_3$ (40 ml). The mixture was extracted with CH_2Cl_2 (6×50 ml), dried over Na_2SO_4, and concentrated. Column chromatography (PE:EA = 5:1) afforded **137d** (781 mg, 45 %) as colorless oil.
TLC $\mathbf{R}_f$ = 0.43 (PE:EA=5:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.16 (s, Si(C*H*$_3$)$_3$, 9H), 2.23 (dd, *J* = 18.2 Hz, 2.1 Hz, 1H, 5), 2.69 (dd, *J* = 18.2 Hz, 5.9 Hz, 1H, 5), 4.95 (m, 1H, 4), 6.18 (dd, *J* = 5.5 Hz, 2.2 Hz, 1H), 7.45 (dd, *J* = 5.5 Hz, 2.2 Hz, 1H). **^{13}C-NMR** (75.5 Hz, $CDCl_3$): δ 0.1 (+, Si(*C*H$_3$)$_3$), 44.9 (-, 5-C), 70.5 (+, 4-C), 134.7 (+), 163.8 (+), 206.5 (quart., *C*=O).



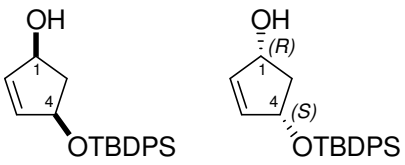
(-)-**137f**



(+)-**137f**

(4*S*)-4-(benzyloxy)-2-cyclopenten-1-one ((-)-137f); (4*R*)-4-(benzyloxy)-2-cyclopenten-1-one ((+)-137f)

The synthesis of (-)-**137f** from the (+)-**140**: (+)-**140** (4.3 g, 22.60 mmol) was dissolved in CH_2Cl_2 (50 ml) and 3Å M.S. was added. PCC (4.9 g, 22.60 mmol) was added as two portions and the reaction mixture was stirred for 23 h at rt. It was filtrated through celite cake and concentrated. Column chromatography (PE:EA = 5:1) afforded (-)-**137f** (4.0 g, 94 %, 90.6%*ee*) as colorless oil. TLC $\mathbf{R}_f$ = 0.61 ((-)-**137f**, PE:EA = 1:1, Vanillin sulfuric acid).
The synthesis of (-)-**137f** from the (+)-**142**: (+)-**142** (120 mg, 0.52 mmol) was dissolved in 2 ml of mixed solvent (THF:MeOH:H_2O=3:1:1) and LiOH (15 mg, 0.62 mmol) was added. Et_2O (5 ml) and H_2O (1 ml) were added and org. phase was separated. The combined org. phase was washed with 5% $NaHCO_3$ (3 ml) and brine (3 ml), which was dried over Na_2SO_4 and concentrated. This crude mixture was dissolved in CH_2Cl_2 (3 ml), and then PCC (13.4 mg, 0.62 mmol) and 3Å M.S. were added, which was stirred for 13 h at rt. The reaction mixture was filtrated though celite cake and the filtrate was concentrated and subjected to column chromatography (PE:EA = 2:1) to give (-)-**137f** (69 mg, 71 %, 84 %*ee*).
^{1}H-NMR of (-)-**137f** (300 MHz, $CDCl_3$): δ 2.27 (dd, *J* = 18.1 Hz, 2.2 Hz, 1H, 5), 2.59 (ddd, *J* = 18.1 Hz, 6.0 Hz, 1H, 5), 4.53 (dd, *J* = 18.9 Hz, 11.5 Hz, 2H, OC*H*$_2$Ph), 4.67 (dddd, *J* = 6.0 Hz, 2.5 Hz, 1.9 Hz, 1.4 Hz, 1H, 4), 6.16 (dd, *J* = 5.8 Hz, 1.4 Hz, 1H, 2), 7.27-7.42 (m, 5H, aromatic), 7.50 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H, 3). **^{13}C-NMR** of (-)-**137f** (75.5 Hz, $CDCl_3$): δ 41.8 (-, 5-C), 72.0 (-, O*C*H$_2$Ph), 76.9 (+, 4-C), 128.0 (+, aromatic), 128.2 (+, aromatic), 128.7 (+, aromatic), 135.8 (+), 137.5 (quart., *ipso*), 206.0 (quart., *C*=O). $[\alpha]_D^{22}$ -38.8 ((-)-**137f**, c 0.95, $CHCl_3$).
The synthesis of (+)-**137f** from (-)-**138b**: (+)-**137f** (82 %, 78.9 %*ee*) was obtained in three steps from (-)-**138b**. $[\alpha]_D^{22}$ + 32.4 ((+)-**137f**, c 1.02, $CHCl_3$).

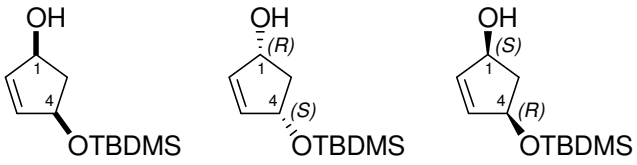


138a (+)-**138a**

4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-cyclopenten-1-ol (138a)

A solution of **137a** (3.1 g, 9.21 mmol) in TBME (10 ml) was added dropwise into the solution of $LiAlH_4$ (228 mg, 5.99 mmol), LiI (616 mg, 4.60 mmol) in toluene (19 ml) at -13°C over 30 min. It was stirred for 1.5 h and quenched with sat. NH_4Cl (40 ml). In 1 h stirring of the reaction mixture, it was filtrated and washed with toluene (2×20 ml). The combined org. phase was dried over Na_2SO_4, concentrated, and subjected to column chromatography (PE:EA = 5:1) to give **138a** (890 mg, 46 %, *dr* = 82:18) as colorless oil.
Kinetic resolution of **138a**: To a solution of **138a** (1.4 g, 4.14 mmol) in 5 ml of TBME, Et_3N (3.9 ml, 2.82 mmol), PPL (0.5 g, 0.12 g/mmol), and vinyl acetate (18 ml, 195.3 mmol) were added subsequently at rt. It was stirred for 84 h at the same temperature. The solvent was removed under reduced pressure and the mixture was carried out column chromatography (PE:EA = 5:1) to give (+)-**138a** (1.1 g, 80 %, recovered S.M.) and (-)-**139a** (224 mg, 14 %) as colorless oil. $[\alpha]_D^{20}$ - 1.4 ((+)-**138a**, c 1.1, $CHCl_3$).

TLC $\mathbf{R}_f$ = 0.21 ((+)-**138a**, PE:EA = 5:1, Vanillin sulfuric acid). **^{1}H-NMR** of (+)-**138a** (300 MHz, $CDCl_3$): δ 1.07 (s, C(C*H*$_3$)$_3$, 9H), 1.65 (ddd, *J* = 13.7 Hz, 4.7 Hz, 4.7 Hz, 1H, 5), 2.55 (ddd, *J* = 13.7 Hz, 7.3 Hz, 6.7 Hz, 1H, 5), 4.44-4.57 (m, 1H), 4.60-4.70 (m, 1H), 5.84 (ddd, *J* = 5.8 Hz, 1.6 Hz, 1.4 Hz, 1H), 5.90 (ddd, *J* = 5.5 Hz, 1.9 Hz, 1.4 Hz, 1H), 7.34-7.50 (m, 6H, aromatic), 7.63-7.74 (m, 4H, aromatic). **^{13}C-NMR** of (+)-**138a** (75.5 Hz, $CDCl_3$): δ 19.2 (quart., *C*(CH$_3$)$_3$), 27.0 (+, C(*C*H$_3$)$_3$), 44.6 (-, 5-C), 75.1 (+), 76.1 (+), 127.8 (+, aromatic), 129.8 (+, aromatic), 134.0 (quart., *ipso*), 134.2 (quart., *ipso*), 135.7 (+), 135.9 (+, aromatic), 137.0 (+).



138b (-)-**138b** (+)-**138b**

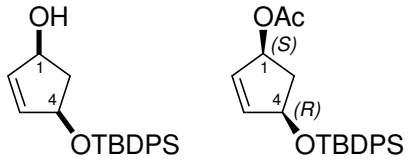
4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-cyclopenten-1-ol (138b)

To a heterogeneous solution of $LiAlH_4$ (734 mg, 18.36 mmol) in toluene (20 ml), a solution of **137b** (6.0 g, 28.25 mmol) dissolved in 15 ml of TBME was added over 3 h at -20°C. In

finishing of addition of **137b**, the reaction was completed. Sat. NH_4Cl (20 ml) was added carefully at 0°C and it was stirred for 1 h. The reaction mixture was filtrated through the celite cake (3 cm) under water vacuum suction, and then the cake was washed with EA (200 ml). Org. phase was separated from the aqueous phase *via* separating funnel. Aqueous phase was extracted with EA (3×50 ml). The combined org. phase was dried over $MgSO_4$, concentrated, and subjected to column chromatography (PE:EA = 9:1) to give **138b** (5.2 g, 86 %) as colorless oil.

TLC $\mathbf{R}_f$= 0.32 (PE:EA = 5:1, Vanillin sulfuric acid). **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e.

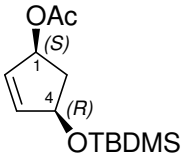
Kinetic resolution of **138b**: To a solution of **138b** (3.0 g, 13.99 mmol) in 20 ml of TBME, Et_3N (1.3 ml, 9.52 mmol), PPL (1.7 g, 0.12 g/mmol), and vinyl acetate (6.5 ml, 69.95 mmol) were added subsequently at rt. It was stirred for 14 h at the same temperature. The solvent was removed under reduced pressure and the mixture was carried out column chromatography (PE:EA = 9:1 & 5:1) to give (-)-**138b** (1.4 g, 47 %, 87.7 %*ee*) and (+)-**139b** (1.4 g, 39 %, 98.4 %*ee*) as colorless oil. TLC $\mathbf{R}_f$ = 0.15 ((-)-**138b**, PE:EA = 9:1, Vanillin sulfuric acid). $[\alpha]_D^{20}$ - 18.4 ((-)-**138b**, c 1.10, $CHCl_3$).



138a (-)-**139a**

(1*S*,4*R*)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-cyclopenten-1-yl acetate (139a)

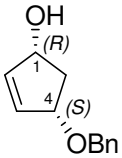
From the kinetic resolution of **138a**, (-)-**139a** (224 mg, 14 %) was obtained as colorless oil. TLC $\mathbf{R}_f$ = 0.21 ((-)-**139a**, PE:EA = 5:1, Vanillin sulfuric acid). **^{1}H-NMR** of (-)-**139a** (300 MHz, $CDCl_3$): δ 1.07 (s, C(C*H*$_3$)$_3$, 9H), 1.75 (ddd, *J* = 13.9 Hz, 5.1 Hz, 5.1 Hz, 1H, 5), 2.07 (s, C(O)C*H*$_3$, 3H), 2.65 (ddd, *J* = 13.9 Hz, 7.3 Hz, 7.4 Hz, 1H, 5), 4.65-4.73 (m, 1H), 5.33-5.42 (m, 1H), 5.85 (ddd, *J* = 5.5 Hz, 1.6 Hz, 1.4 Hz, 1H), 5.92 (ddd, *J* = 5.5 Hz, 1.6 Hz, 1.4 Hz, 1H), 7.32-7.50 (m, 6H, aromatic), 7.62-7.75 (m, 4H, aromatic). **^{13}C-NMR** of (-)-**139a** (75.5 Hz, $CDCl_3$): δ 19.2 (quart., *C*(CH_3)$_3$), 21.4 (+, C(O)*C*H_3), 27.0 (+, C(*C*H_3)$_3$), 41.1 (-, 5-C), 75.8 (+), 76.9 (+), 127.8 (-, aromatic), 129.9 (+, aromatic), 131.4 (+), 134.0 (quart., *ipso*), 134.1 (quart., *ipso*), 135.8 (+, aromatic), 138.9 (+), 171.0 (quart., *C*=O). $[\alpha]_D^{20}$ + 0.4 ((-)-**139a**, c 1.0, $CHCl_3$).



(+)-**139b**

(1*S*,4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-cyclopenten-1-yl acetate ((+)-139b)

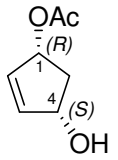
From the kinetic resolution of **138b**, (+)-**139b** (1.4 g, 39 %, 98.4 %*ee*) was obtained as colorless oil. TLC $\mathbf{R}_f$ = 0.55 ((+)-**139b**, PE:EA = 9:1, Vanillin sulfuric acid). $[\alpha]_D^{20}$ + 0.6 ((+)-**139b**, c 1.10, $CHCl_3$).



(+)-**140**

(1*R*,4*S*)-4-(benzyloxy)-2-cyclopenten-1-ol ((+)-140)

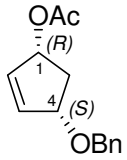
(+)-**139b** (1.9 g, 7.41 mmol) was dissolved in 15 ml of mixed solvent (THF:MeOH:H_2O=3:3:1). LiOH (213 mg, 8.89 mmol) was added at rt. and it was stirred for 1 h. H_2O (20 ml) was added and it was extracted with TBME (2×50 ml). The reaction mixture was dried over Na_2SO_4 and subjected to column chromatography (PE:EA = 9:1) to give (+)-**138b** (1.7 g, quant. yield). TLC $\mathbf{R}_f$= 0.28 ((+)-**138b**, PE:EA = 9:1, Vanillin sulfuric acid). Subsequently, NaH (380 mg, 15.84 mmol) was added into the solution of (+)-**138b** (1.7 g, 7.92 mmol) in THF (25 ml) at rt. In 20 min, BnBr (1.4 ml, 11.88 mmol) and Bu_4NI (307 mg, 0.83 mmol) were added. It was stirred for 12 h. Brine (5 ml) was put into the reaction mixture and most of THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (4×50 ml). The combined org. phase was dried over Na_2SO_4, concentrated, and subjected to column chromatography (PE:EA = 19:1) to yield benzylated intermediate (2.3 g, 96 %) as pale yellow oil. This intermediate ($C_{18}H_{28}O_2Si$, 2.3 g, 7.5 mmol) was dissolved in 36 ml of mixed solvent (AcOH(5*N*):THF=1:1) and stirred for 20 h at 65°C. The reaction mixture was cooled down to rt. and TBME (100 ml) was added. The separated org. phase was washed with 50 % of $NaHCO_3$ (150 ml) to give almost neutral pH. It was dried over Na_2SO_4 and concentrated. Column chromatography (PE:EA = 3:1) afforded (+)-**140** (1.4 g, 98%) as colorless oil. TLC $\mathbf{R}_f$= 0.46 ((+)-**140**, PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e.



(+)-**141**

(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate ((+)-141)

(-)-**138b** (6.5 g, 30.32 mmol) was dissolved in pyridine (22 ml, 300.3 mmol), and Ac_2O (13 ml, 136.4 mmol) was treated and it was stirred for 3h at rt. E_2O (150 ml) was added and the separated org. phase was washed carefully with 1*N* HCl (25 ml), sat. $NaHCO_3$ (4×50 ml), and brine (50 ml). The concentrated mixture was subjected to column chromatography (PE:EA = 9:1) afforded acetylated intermediate ($C_{13}H_{24}O_3Si$, 7.4 g, 95 %). TLC $\mathbf{R}_f$ = 0.70 (intermediate, PE:EA = 9:1, Vanillin sulfuric acid). This intermediate (948 mg, 3.69 mmol) was dissolved in THF (3 ml) and Et_3N (51 µl, 0.37 mmol) was added. A solution of TBAF (984 mg, 3.69 mmol) in THF was added into reaction mixture and it was stirred for 2 h. Et_2O (100 ml) and H_2O (5 ml) was added. The separated org. phase was concentrated and subjected to column chromatography (PE:EA = 1:1) afforded (+)-**141** (468 mg, 89 %) as colorless oil. **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e. TLC $\mathbf{R}_f$ = 0.34 ((+)-**141**, PE:EA = 1:1, Vanillin sulfuric acid).



(+)-**142**

(1*R*,4*S*)-4-(benzyloxy)-2-cyclopenten-1-yl acetate ((+)-142)

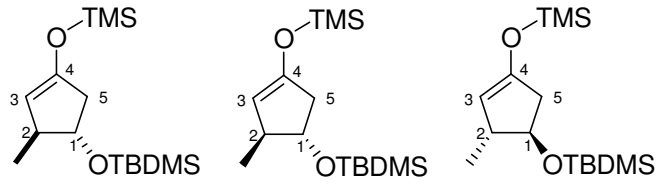
Synthesis of (+)-**142** using $Cl_3C(=NH)OBn$:[186] (+)-**141** (840 mg, 5.91 mmol) was added into the solution of $Cl_3C(=NH)OBn$ (2.1 g, 8.31 mmol) in CH_2Cl_2 (20 ml) and $Cu(OTf)_2$ (105 mg, 0.29 mmol) was added subsequently. It was stirred for 25 h at rt. Org. phase was dried, concentrated and conducted column chromatography (PE:EA = 5:1) to yield (+)-**142** (984 mg, 83 % containing small impurity). **^{1}H-NMR** and **^{13}C-NMR** were authenticated by ref. 78e. TLC $\mathbf{R}_f$ = 0.25 (PE:EA = 5:1, Vanillin sulfuric acid). $[\alpha]_D^{21}$ + 8.5 (c 1.10, $CHCl_3$).

General Work Procedure to synthesize silyl enol ethers via 1,4-*Michael* addition reaction (GWP1).

LiCl (0.3-0.5 eq.) and CuI (0.15-0.25 eq.) was added into the solution of 4-hydroxy protected α,β-unsaturated 2-cyclopentenone dissolved in abs. THF (5.5 ml/mmol) under N_2 atmosphere. When the solution became colorless, it was cooled down to -78°C and stirred for 15 min. TMSCl (4.2-5.3 eq.) was injected by syringe all at once to become clear solution. In 10 min stirring, CH_3MgCl (4.5 eq., 3M in THF) was injected *via* syringe little by little over 20-30 min. During the injection of CH_3MgCl, the color of solution was changed deep yellow to white emulsion. In finishing the injection of CH_3MgCl, it was stirred for 2 h further at -55°C. Anhyd. Et_3N (12 eq.) and the pre-cooled *n*-pentane were poured subsequently into the solution all at once with an interval of 20 min. Deep yellow emulsion was developed, then it was warmed up to 0°C. The emulsion was filtrated through the Celite® 535 cake (3 cm), by Fluka, and washed with *n*-pentane. The milky filtrate was washed with the pre-cooled sat. $NaHCO_3$ *via* separating funnel until being neutral or weak basic (ca. pH=8-9) solution. The resulting colorless solution was dried over Na_2SO_4, filtrated and the solvent was evaporated under reduced pressure and dried completely *in vacuo*. The resulting product was obtained as transparent light brown colored oil.

General Work Procedure to synthesize allylsilanes via $Ni(acac)_2$ catalyzed cross coupling of silyl enol ether with Grignard reagents (GWP2).

Before doing the coupling reaction the $TMSCH_2MgCl$ was freshly prepared using Mg (3.5 eq.), $TMSCH_2Cl$ (3.5 eq.) and cat. I_2 in dried Et_2O (3.8-4.2 ml/mmol). In finishing the dropping of $TMSCH_2Cl$ it was stirred for 1h further. $Ni(acac)_2$ was put into another 3-neck round bottom flask which is fixed to a reflux condenser, then it was dried under vacuum pump pressure and N_2 was purged. The freshly pre-made $TMSCH_2MgCl$ was transferred slowly by using a syringe to develop a dark colored suspension. The related silyl enol ethers were added little by little *via* syringe as concentrated. It was refluxed at 35°C for 1-2 days. The reaction was checked by TLC (PE:EA = 30:1, vanillin sulfuric acid developer). In complete conversion of S.M, H_2O was added carefully under ice bath. After vigorous bubbling the solution was separated from the sludge by filtration and the filtrate was rinsed by Et_2O. The resulting dark brown colored solution was dried over Na_2SO_4, filtrated, concentrated under reduced pressure and the concentrate was subjected to SiO_2 column chromatography (PE:EA = 30:1). The desired allylsilane was obtained as light brown oil.



(*rac*)-**146b** , **146b** , (*ent*)-**146b**

***tert*-butyl(dimethyl)({2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)silane ((*rac*)-146b)**

LiCl (124 mg, 2.93 mmol) and CuI (278 mg, 1.46 mmol) were added into the solution of **137b** (625 mg, 2.94 mmol) in abs. THF (10 ml). When the solution became clear it was cooled down to -72°C. TMSCl (1.5 ml, 12.47 mmol) was added. In 15 min stirring, CH_3MgCl (1.5 ml, 3.53 mmol, 3M in THF solution) was added little by little over 20 min and GWP1 was followed. SiO_2 column chromatography (PE:EA = 19:1 + 2 % of Et_3N) afforded (*rac*)-**146b** (561 mg, 64 %) as pale brown oil.
TLC $\mathbf{R}_f$ = 0.82 (PE:EA = 19:1, Molybdatophosphoricacid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.05 (d, *J* = 2.5 Hz, 6H, Si(C*H*$_3$)$_2$), 0.20 (s, 9H, Si(C*H*$_3$)$_3$), 0.89 (s, 9H, C(C*H*$_3$)$_3$), 1.00 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$), 2.22-2.32 (m, 1H, 5), 2.43-2.60 (m, 2H, 2, 5), 3.85 (ddd, *J* = 7.2 Hz, 5.4 Hz, 5.0 Hz, 1H, 1), 4.43-4.48 (m, 1H, 3). **^{13}C-NMR** (75.5MHz, $CDCl_3$): δ -4.6 (+, Si(*C*H$_3$)$_2$), -4.5 (+, Si(*C*H$_3$)$_2$), 0.2 (+, Si(*C*H$_3$)$_3$), 18.3 (quart., *C*(CH$_3$)$_3$), 19.6 (+, 2-*C*H$_3$), 26.0 (+, SiC(*C*H$_3$)$_3$), 43.5 (-, 5-C), 46.1 (+, 2-C), 78.6 (+, 1-C), 106.5 (+, 3-C), 150.8 (quart., 4-C). **IR (Film, cm^{-1})**: 2929, 2857, 1749, 1463, 1256, 1113, 836, 777. **MS (CI-MS, NH$_3$)**: *m/z* (%) = 376.3 (M_2+$NH_4^{+\cdot}$, 100), 348.3 (M_1+$NH_4^{+\cdot}$, 88).

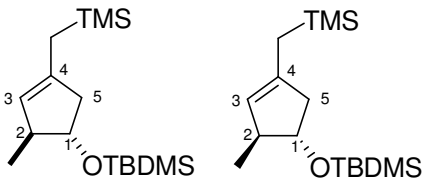
***tert*-butyl(dimethyl)({(1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)silane (146b)**

LiCl (898 mg, 21.19 mmol) and CuI (4.04 g, 21.19 mmol) were added into the solution of (-)-**137b** (1.5 g, 7.06 mmol) in abs. THF (40 ml). When the solution became clear it was cooled down to -72°C. TMSCl (3.7 ml, 29.65 mmol) was added. In 15 min stirring, CH_3MgCl (7.8 ml, 21.19 mmol, 3M in THF solution) was added little by little over 20 min and GWP1 was followed. SiO_2 column chromatography (PE:EA = 19:1 + 2% of Et_3N) afforded **146b** (853 mg, 40 %) as crude mixture.

***tert*-butyl(dimethyl)({(1*R*,2*R*)-2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)silane ((*ent*)-146b)**

LiCl (379 mg, 8.94 mmol) and CuI (851 mg, 4.47 mmol) were added into the solution of (+)-**137b** (1.6 g, 7.53 mmol) in abs. THF (50 ml). When the solution became clear it was cooled to -72°C. TMSCl (4.6 ml, 37.55 mmol) was added. In 20 min stirring, CH_3MgCl (4.5 ml,

13.41 mmol, 3M in THF solution) was added little by little over 20 min. Extra solution of LiCl (379 mg, 8.94 mmol), CuI (851 mg, 4.47 mmol), and CH_3MgCl (4.5 ml, 13.41 mmol) in 5 ml of THF was added in 3 h reaction time. After work-up following the GWP1, the mixture was subjected to column chromatography (ICN Alumina N-super I, PE:EA = 19:1 + 2% of Et_3N) to give **146b** (950 mg, 42 %).



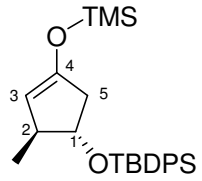
(*rac*)-**103b** , **103b**

***tert*-butyl(dimethyl)({2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl}oxy)silane ((*rac*)-103b); *tert*-butyl(dimethyl)({(1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl}oxy)silane (103b)**

$TMSCH_2MgCl$ (6.4 eq.) was freshly prepared in dried Et_2O (10 ml). (*rac*)-**146b** (500 mg, 1.66 mmol as crude mixture) in Et_2O (10 ml) was added into $Ni(acac)_2$ (796 mg, 3.10 mmol), then the freshly pre-made $TMSCH_2MgCl$ was transferred slowly *via* syringe. The reaction mixture was stirred for 16 h at rt. After work-up following the GWP2, the mixture was subjected to column chromatography (SiO_2, PE + 1 % of Et_3N) to give (*rac*)-**103b** (206 mg, 42 %) as pale brown oil.

TLC $\mathbf{R}_f$ = 0.39 (PE, Molybdatophosphoricacid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.01 (s, 9H, $Si(CH_3)_3$), 0.05 (d, *J* = 1.9 Hz, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 0.98 (d, *J* = 6.9 Hz, 3H, 3-CH_3), 1.49 (s, 2H, CH_2Si), 2.16 (m, 1H, 5), 2.42 (br dd, *J* = 15.9 Hz, 6.9 Hz, 1H, 5), 2.48-2.60 (m, 1H, 2), 3.88 (ddd, *J* = 6.9 Hz, 5.2 Hz, 4.7 Hz, 1H, 1), 4.96-5.01 (m, 1H, 3). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ -4.5 (+, $Si(CH_3)_2$), -4.4 (+, $Si(CH_3)_2$), -1.2 (+, $Si(CH_3)_3$), 18.4 (quart., $C(CH_3)_3$), 18.8 (+, 3-CH_3), 21.9 (-, CH_2Si), 26.1 (+, $C(CH_3)_3$), 46.7 (-, 5-C), 49.0 (+, 2-C), 81.1 (+, 1-C), 125.8 (+, 3-C), 138.1 (quart., 4-C). **IR (Film, cm^{-1})**: 2956, 2857, 1638, 1253, 1100, 840, 775.

Synthesis of **103b**: $TMSCH_2MgCl$ (5 eq.) was freshly prepared using Mg and $TMSCH_2Cl$ (5 eq.) and cat. I_2 in dried Et_2O (30 ml). **146b** (2.9 g, 9.65 mmol as crude mixture) in Et_2O (30 ml) was added into $Ni(acac)_2$ (769 mg, 2.99 mmol), then the freshly pre-made $TMSCH_2MgCl$ was transferred slowly *via* syringe. The reaction mixture was stirred for 18 h at rt. After conventional work-up, SiO_2 column chromatography (PE + 0.5 % of Et_3N) afforded **103b** (759 mg, 25 % in two steps from (-)-**137b**).

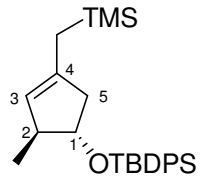


146a

***tert*-butyl({(1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)diphenylsilane (146a)**

LiCl (26 mg, 0.62 mmol), CuI (59 mg, 0.31 mmol) was added into the solution of (+)-**137a** (700 mg, 2.08 mmol) in THF (11 ml). When the solution became clear it was cooled to -72°C. TMSCl (1.3 ml, 10.40 mmol) was added. In 15 min stirring, CH_3MgCl (6.2 ml, 18.72 mmol) was added little by little over 30 min. The yellow emulsion was changed to white within 1.5 h stirring at the same temperature. Et_3N (3.5 ml, 24.96 mmol) was injected all at once and pre-cooled *n*-pentane (80 ml) was poured into. The yellow emulsion was developed and it was filtrated through the Celite® cake under the reduced pressure and washed with pre-cooled *n*-pentane (650 ml). The filterate was washed with pre-cooled sat. $NaHCO_3$ (3 ml) to give colorless solution. It was dried over Na_2SO_4, filtrated, concentrated *in vacuo*. The product (792 mg, 89.6 %) was obtained as clear pale brown oil.

TLC $\mathbf{R}_f$ = 0.85 (PE:EA = 9:1, Molybdatophosphoricacid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.19 (s, 9H, Si(C*H*$_3$)$_3$), 0.76 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$), 2.24-2.43 (m, 2H, 2, 5), 2.55-2.70 (m, 1H, 5), 3.91 (ddd, *J* = 6.4 Hz, 4.5 Hz, 4.0 Hz, 1H, 1), 4.44-4.49 (m, 1H, 3), 7.31-7.82 (m, 10H, aromatic). **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ 0.0 (+, Si(*C*H$_3$)$_3$), 19.0 (quart., *C*(CH$_3$)$_3$), 19.1 (+, 2-*C*H$_3$), 26.6 (+, SiC(*C*H$_3$)$_3$), 43.1 (-, 5-C), 46.1 (+, 2-C), 78.7 (+, 1-C), 100.5 (+, 3-C), 127.4 (+), 127.5 (+), 127.7 (+), 129.5 (+), 129.6 (+), 134.8 (+), 135.2 (quart., *ipso*), 135.8 (+), 150.8 (quart., 4-C). **IR (Film, cm^{-1})**: 2957, 2931, 2858, 1731, 1468, 1428, 1110, 822, 701. **MS (PI-CIMS, NH$_3$)**: *m/z* (%) = 425.3 ($MH^{+\cdot}$, 100), 347.1 ($[M\text{-}C_7H_7]^{+\cdot}$, 1), 274.2 ($[Ph_2Si(C_4H_9)OH+NH_4]^{+\cdot}$, 6), 169.1 ($[M\text{-}Ph_2Si(C_4H_9)O]^{+\cdot}$, 24), 90.1 ($HOSi(CH_3)_3$, 48).



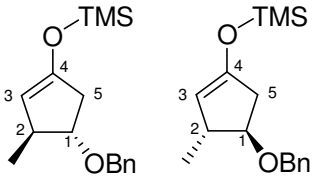
103a

***tert*-butyl({(1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl}oxy)diphenylsilane (103a)**

Grignard reagent, $TMSCH_2MgCl$ (3.58 mmol) in Et_2O (6 ml), was freshly prepared.

$Ni(acac)_2$ (46 mg, 0.18 mmol) was put into a 3-neck round flask then the pre-made $TMSCH_2MgCl$ was transferred using syringe at rt. to develop dark brown colored solution. Reflux condenser was equipped and it was warmed up to 35°C. The crude mixture of **146a** (760 mg, 1.79 mmol) was added bit by bit as concentrated over 30 min *via* syringe. The reaction mixture was refluxed for 53 h at 35°C. Another portion of $TMSCH_2MgCl$ (3.58 mmol) was added on the 45 h reaction time. When the **146a** was disappeared completely, Et_2O (20 ml) and H_2O (4 ml) were added under ice bath. The separated aqueous phase was extracted with Et_2O (3×50 ml). The combined org. phase was dried over Na_2SO_4, filtrated, concentrated under reduced pressure, and subjected to column chromatography (PE:EA = 30:1). **103a** (360 mg, 48 %) was obtained as clear and pale brown oil.

TLC $\mathbf{R_f}$= 0.92 (PE:EA = 19:1, Molybdatophosphoricacid), **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.00 (s, 9H, Si(CH_3)$_3$), 0.73 (d, *J* = 7.1 Hz, 3H, 2-CH_3), 1.08 (s, 9H, C(CH_3)$_3$), 1.39-1.55 (m, 2H, CH_2Si), 2.14-2.40 (m, 2H, 2, 5), 2.57-2.71 (m, 1H, 5), 3.95 (ddd, 1H, *J* = 6.0 Hz, 4.1 Hz, 4.1 Hz, 1), 4.96-5.00 (m, 1H, 3), 7.31-7.50 (m, 6H, aromatic), 7.60-7.79 (m, 4H, aromatic). **^{13}C-NMR** (75.5MHz, $CDCl_3$): δ 1.2 (+, 3×CH_3, Si(CH_3)$_3$), 18.6 (+, 2-CH_3), 19.3 (quart., $C(CH_3)_3$), 21.6 (-, CH_2Si), 27.1 (+, 3×CH_3, C(CH_3)$_3$), 46.5 (-, 5-C), 49.4 (+, 2-C), 81.4 (+, 1-C), 125.6 (+, 3-C), 127.6 (+, *ortho*), 129.6 (+, *para*), 134.8 (quart., *ipso*), 136.0 (+, *meta*), 138.2 (quart., 4-C). **IR (Film, cm^{-1}):** 2858, 1720, 1463, 1428, 1250, 1111, 1063, 844, 740, 702. **MS (PI-CIMS, NH_3)**: *m/z* (%) = 423.3 ([MH]$^{+\cdot}$, 3). 184.2 ([M-TBDPS] $^{+\cdot}$, 18), 90.1 (100).

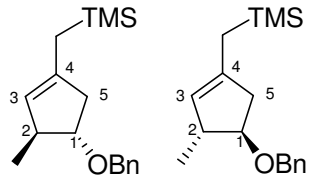


146f , (*ent*)-**146f**

benzyl (1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl ether (146f)

LiCl (103 mg, 2.42 mmol), CuI (231 mg, 1.21 mmol) was added into the solution of (-)-**137f** (1.52 g, 8.08 mmol) in THF (40 ml). When the solution became clear, it was cooled down to -72°C. TMSCl (5.0 ml, 40.4 mmol) was added. In 15 min stirring, CH_3MgCl (12.0 ml, 36.3 mmol) was added little by little over 30 min. The yellow emulsion was changed to white within 1.5 h stirring at the same temperature. Et_3N (13.4 ml, 96.9 mmol) was injected all at once and pre-cooled *n*-pentane (150 ml) was poured into. The yellow emulsion was developed and it was filtrated through the Celite pad under the reduced pressure and washed with pre-cooled n-pantane (500 ml). The filterate was washed with pre-cooled sat. $NaHCO_3$ (4×50 ml) to give colorless solution. It was dried over Na_2SO_4, filtrated, concentrated *in vacuo*. **146f** (2.11 g, 95 %) was obtained as clear pale brown oil.

TLC $\mathbf{R}_f$ = 0.45 (PE:EA = 19:1, Molybdatophosphoricacid). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 0.21 (s, 9H, Si(C*H*$_3$)$_3$), 1.06 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$), 2.30-2.44 (m, 1H, 5A), 2.53-2.67 (m, 1H, 5B), 2.68-2.82 (m, 1H, 2), 3.71 (ddd, *J* = 7.4 Hz, 4.9 Hz, 4.1 Hz, 1H, 1), 4.44-4.59 (m, 3H, 3, OC*H*$_2$), 7.23-7.38 (m, 5H, aromatic). **^{13}C-NMR** (150.1 MHz, $CDCl_3$): δ 0.2 (+, 3×CH_3, Si(*C*H$_3$)$_3$), 20.5 (+, 2-*C*H$_3$), 40.2 (-, 5-C), 43.4 (+, 2-C), 71.2 (-, O*C*H$_2$), 84.4 (+, 1-C), 106.5 (+, 3-C), 127.6 (+, *para*), 127.8 (+, *ortho*), 128.5 (+, *meta*), 138.8 (quart., *ipso*), 150.9 (quart., 4-C). **IR (Film, cm^{-1})**: 3365, 3064, 3031, 2926, 1714, 1618, 1454, 1016, 800, 777, 732, 696. **MS (PI-EIMS, 70 eV)**: *m/z* (%) 276.1 ($M^{+\cdot}$, 3), 261.1 ([M-CH_3]$^{+\cdot}$, 4), 185.1 ([M-C_7H_7]$^{+\cdot}$, 19), 170.1 (49), 155.1 (20), 118.0 (4), 91.0 ($C_7H_7^+$, 71), 69.0 (100). **HR-EIMS** Calcd. for $C_{16}H_{24}O_2Si$ [$M^{+\cdot}$]: 276.1546, Found: 276.1544. $[\alpha]_D^{21}$ - 11.1 (**146f**, c 0.38, $CHCl_3$). ($[\alpha]_D^{20}$ - 40.0 ((*ent*)-**146f**, c 0.13, $CHCl_3$).



103f , (*ent*)-**103f**

benzyl (1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl ether (103f)

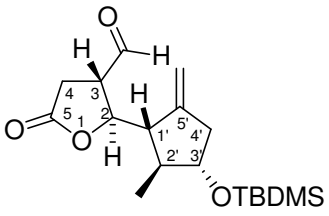
The Grignard reagent, $TMSCH_2MgCl$ (27.81mmol, 3.5 eq.) in Et_2O (20 ml), was freshly prepared. $Ni(acac)_2$ (356 mg, 1.39 mmol) was put into a 3-neck Schlenk flask. The pre-made $TMSCH_2MgCl$ was transferred using syringe at rt to develop dark brown colored solution. Reflux condenser was equipped and it was warmed up to 35°C. **146f** (2.05 g, 7.42 mmol) was added bit by bit as concentrated over 30 min *via* syringe. The reaction mixture was refluxed for 53 h at 35°C. When the S.M was disappeared completely, H_2O (6 ml) was poured into. The separated aqueous phase was extracted with Et_2O (3×50 ml). The combined org. phase was dried over Na_2SO_4, filtrated, concentrated under reduced pressure, and subjected to do column chromatography (PE:EA = 30:1). The desired allylsilane **103f** (1.99 g, 97 %) was obtained as clear and pale brown oil.

TLC $\mathbf{R}_f$ = 0.67 (PE:EA = 19:1, Molybdatophosphoricacid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.00 (s, 9H, Si(C*H*$_3$)$_3$), 1.01 (d, *J* = 6.9 Hz, 3H, 2-C*H*$_3$), 1.47-1.53 (br s, 2H, C*H*$_2$Si), 2.28 (ddddd, *J* = 16.5 Hz, 4.4 Hz, 2.7 Hz, 1.4 Hz, 1.1 Hz, 1H, 5), 2.52 (ddddd, *J* = 16.5 Hz, 6.9 Hz, 2.2 Hz, 1.4 Hz, 0.8 Hz, 1H, 5), 2.68-2.84 (m, 1H, 2), 3.72 (ddd, *J* = 6.9 Hz, 4.4 Hz, 4.1 Hz, 1H, 1), 4.45-4.56 (m, 2H, OC*H*$_2$), 4.99-5.04 (m, 1H, 3), 7.19-7.39 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ -1.2 (+, 3×CH_3, Si(*C*H$_3$)$_3$), 19.7 (+, 2-*C*H$_3$), 21.7 (-, *C*H$_2$Si), 43.5 (-, 5-C), 46.4 (+, 2-C), 71.1 (-, O*C*H$_2$), 87.2 (+, 1-C), 126.0 (+, 3-C), 127.5 (+, para), 127.7 (+, *ortho*), 128.4 (+, *meta*), 138.2 (quart., *ipso*), 139.0 (quart., 4-C). **IR (Film, cm^{-1})**:

3065 (w), 3032 (w), 2955 (w), 2928 (w), 2895 (w), 2874 (w), 1452 (m), 1371 (m), 1248 (m), 1096 (w), 837 (s), 778 (m), 733 (m), 696 (m). **MS (PI-DCIMS, CH_4)**: *m/z* (%) = 274.2 ($M^{+\cdot}$, 1), 259.1 ($[M\text{-}CH_3]^{+\cdot}$, 1), 183.1 ($[M\text{-}C_7H_7]^{+\cdot}$, 24), 93.1 ($[M\text{-}C_7H_7\text{-}HOSi(CH_3)_3]^{+\cdot}$, 9), 91.0 ($C_7H_7^{+\cdot}$, 44), 73.0 ($(CH_3)_3Si^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{17}H_{26}OSi$ [M^+]: 274.1753, Found: 274.1747. $[\alpha]_D^{21}$ + 49.4 (**103f**, c 3.16, $CHCl_3$). ($[\alpha]_D^{20}$ - 5.9 ((*ent*)-**103f**, c 0.29, $CHCl_3$).

General Work Procedure for *Sakurai* allylation of cyclopropanealdehydes under $BF_3{\cdot}Et_2O$ catalyst and subsequent intramolecular rearrangement to γ-butyrolactone carbaldehyde using $Ba(OH)_2{\cdot}8H_2O$ (GWP3).

Solution of cyclopropanealdehyde **104** (1.0-1.3 eq.) dissolved in abs. CH_2Cl_2 was cooled down to -78°C. In 20 min, the $BF_3{\cdot}Et_2O$ (0.5-1.9 eq.) was added and stirred for 15 min. The corresponding cyclopentenyl allylsilane **103** (1.0 eq.) was added then the mixture was stirred for 17 h (overnight) at -78°C. The reaction was checked by TLC (PE:EA = 1:1). Reaction was quenched by sat. $NaHCO_3$ (1.0-2.2 ml / ml of $BF_3{\cdot}Et_2O$) solution and it was slowly warmed up to rt. The separated org. phase was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. This intermediate was dissolved in MeOH (40 ml/mmol), and then $Ba(OH)_2{\cdot}8H_2O$ (0.5-1.0 eq.) was added bit by bit at 0°C. As a result, the fluorescent yellow colored solution was developed. The most of MeOH (80-90 *vol %*) was removed under reduced pressure. CH_2Cl_2 and H_2O were poured into the mixture and phases were separated by separating funnel. The aqueous phase was extracted with CH_2Cl_2 further. The combined org. phase was dried over Na_2SO_4, filtrated, concentrated and the concentrated was subjected to SiO_2 column chromatography (PE:EA = 3:1). The resulting product was obtained as pale yellow oil.



182

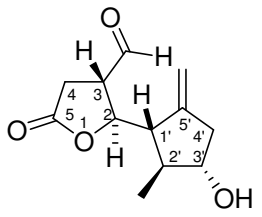
(2*R*,3*S*)-2-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-5-oxotetrahydro-3-furancarbaldehyde (182)

A solution of **104** (328 mg, 1.34 mmol) in 5 ml of CH_2Cl_2 was cooled down to -78°C under N_2 atmosphere. $BF_3{\cdot}Et_2O$ (170 µl, 1.34 mmol) and **103b** (400 mg, 1.34 mmol) in CH_2Cl_2 (5

ml) were added subsequently *via* syringe with 30 min and 20 min interval, respectively. The reaction mixture was stirred for 15 h, then it was quenched with sat. $NaHCO_3$ (0.4 ml) and allowed to warm up to rt. gradually. The dried and concentrated crude intermediate was dissolved in MeOH (10 ml) and cooled down to 0°C. A solution of $Ba(OH)_2 \cdot 8H_2O$ (634 mg, 2.01 mmol) in MeOH (20 ml) was added slowly *via* dropping funnel at 0°C. After conventional work-up, the mixture was subjected to column chromatography (PE:EA = 5:1 & 2:1). **182** (54 mg, 12 %) and the desilylated byproduct **182-1** (48 mg, 16 %) were obtained as oil.

TLC $\mathbf{R}_f$ = 0.64 (PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$) of **182**: δ 0.05 (d, J = 4.4 Hz, 6H, Si(CH_3)$_2$), 0.87 (s, 9H, C(CH_3)$_3$), 1.05 (d, $J_{2'\text{-}Me/2'}$ = 6.9 Hz, 3H, 2'-CH_3), 1.77-1.92 (m, 1H, 2'), 2.21-2.34 (m, 1H, 4'), 2.43-2.52 (m, 1H, 1'), 2.64 (dddd, $J_{4'/4'}$ = 15.9 Hz, $J_{4'/3'}$ = 6.0 Hz, $J_{4'/=CH2}$ = 1.6 Hz, $J_{4'/=CH2}$ = 1.1 Hz, 1H, 4'), 2.72 (dd, $J_{4/4}$ = 18.1 Hz, $J_{4/3}$ = 10.7 Hz, 1H, 4), 2.90 (dd, $J_{4/4}$ = 18.1 Hz, $J_{4/3}$ = 6.9 Hz, 1H, 4), 3.35 (dddd, $J_{3/4}$ = 10.7 Hz, $J_{3/4}$ = 6.9 Hz, $J_{3/2}$ = 5.8 Hz, $J_{3/CHO}$ = 1.1 Hz, 1H, 3), 3.71 (ddd, $J_{3'/4'}$ = 7.4 Hz, $J_{3'/2'}$ = 6.3 Hz, $J_{3'/2'}$ = 6.0 Hz, 1H, 3'), 4.94 (dd, 1H, $J_{2/1'}$ = 6.0 Hz, $J_{2/3}$ = 5.8 Hz, 1H, 2), 5.01 (br s, 1H, =CH_2), 5.10 (br s, 1H, =CH_2), 9.71 (d, $J_{CHO/3}$ = 1.1 Hz, 1H, CHO). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ -4.7 (+, Si(CH$_3$)$_2$), -4.5 (+, Si(CH$_3$)$_2$), 17.5 (+, 2'-CH$_3$), 18.1 (quart., C(CH$_3$)$_3$), 25.9 (+, C(CH$_3$)$_3$), 29.5 (-, 4-C), 43.4 (-, 4'-C), 44.6 (+, 2'-C), 49.4 (+, 3-C), 53.0 (+, 1'-C), 78.1 (+, 2-C), 80.6 (+, 3'-C), 112.3 (-, =CH$_2$), 146.6 (quart., 5'-C), 174.5 (quart., 5-C), 197.8 (quart., CHO). **IR (Film, cm^{-1})**: 2927, 2856, 1770, 1463, 1375, 1252, 1112, 836, 881. **MS (CI-MS, NH$_3$)**: *m/z* (%) = 356.2 ([M+NH$_4$]$^+$, 100), 339.2 ([MH]$^+$, 35), 298.2 (9).

$[\alpha]_D^{21}$ + 31.2 (c 1.11, $CHCl_3$).

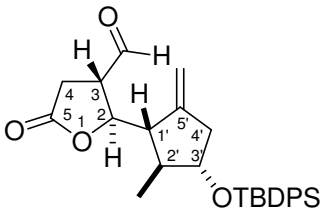


182-1

(2*R*,3*S*)-2-[(1*S*,2*S*,3*S*)-3-hydroxy-2-methyl-5-methylenecyclopentyl]-5-oxotetrahydro-3-furancarbaldehyde (182-1)

^{1}H-NMR (300 MHz, $CDCl_3$) of **182-1**: δ 1.11 (d, J = 6.9 Hz, 3H, 2'-CH_3), 1.80-3.02 (m, 7H), 3.29-3.54 (m, 1H), 4.90-5.00 (m, 1H), 5.00-5.09 (m, 1H), 5.09-5.17 (m, 1H), 9.72 (d, J = 1.1 Hz, 1H, CHO). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 17.9 (+), 29.7 (-), 42.6 (-), 44.4 (+), 49.7 (+), 53.6 (+), 77.8 (+), 80.7 (+), 112.4 (+), 146.5 (quart., 5'-C), 174.4 (quart., C=O), 198.0 (quart., CHO). **IR (Film, cm^{-1})**: 3411, 3019, 2960, 1761, 1213, 1111, 1021, 756, 665. MS (CI-MS,

NH_3): *m/z* (%) = 242.1 ($[M+NH_4]^{+\cdot}$, 100).



222

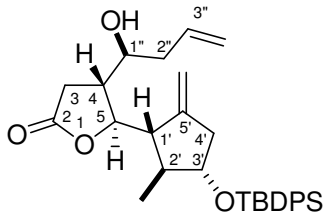
(2*R*,3*S*)-2-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-5-oxotetrahydro-3-furancarbaldehyde (222)

A solution of **104** (866 mg, 3.55 mmol) in 15 ml of CH_2Cl_2 was cooled down to -78°C under N_2 atmosphere. $BF_3{\cdot}Et_2O$ (495 ml, 3.90 mmol) and **103a** (1.5 g, 3.55 mmol) in CH_2Cl_2 (10 ml) were added subsequently via syringe. The reaction mixture was stirred for 39 h, then it was quenched with sat. $NaHCO_3$ (1.2 ml) and warmed up to rt. gradually over 3 h. The dried and concentrated crude intermediate was dissolved in MeOH (100 ml) and cooled down to 0°C. $Ba(OH)_2{\cdot}8H_2O$ (1.7 g, 5.32 mmol) was slowly added *via* dropping funnel at 0°C. After conventional work-up, the mixture was subjected to column chromatography (PE:EA = 3:1). **222** (394 mg, 24 %, *dr* = 60:40) was obtained as oil.

TLC $\mathbf{R}_f$ = 0.31 and 0.39 (PE:EA = 2:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.90 (d, $J_{2'/2'\text{-Me}}$ = 6.9 Hz, 3H, 2'-CH_3), 1.07 (s, 9H, C(CH_3)$_3$), 2.09 (ddd, $J_{2'/2'\text{-}Me}$ = 6.9 Hz, $J_{2'/1'}$ = 5.8 Hz, $J_{2'/3'}$ = 5.2 Hz, 1H, 2'), 2.26-2.40 (m, 2H, 1', 4'), 2.46 (dddd, $J_{4'/4'}$ = 16.2 Hz, $J_{4'/3'}$ = 6.3 Hz, $J_{4'/=CH2}$ = 1.6 Hz, $J_{4'/=CH2}$ = 1.1 Hz, 1H, 1H, 4'), 2.74 (dd, $J_{4A/4B}$ = 18.1 Hz, $J_{4A/3}$ = 10.4 Hz, 1H, 4A), 2.93 (dd, $J_{4B/4A}$ = 18.1 Hz, $J_{4B/3}$ = 6.9 Hz, 1H, 4B), 3.36 (dddd, $J_{3/4A}$ = 10.4 Hz, $J_{3/4B}$ = 6.9 Hz, $J_{3/2}$ = 6.0 Hz, $J_{3/CHO}$ = 1.1 Hz, 1H, 3), 3.80 (ddd, $J_{3'/4'}$ = 6.6 Hz, $J_{3'/4'}$ = 6.3 Hz, $J_{3'/2'}$ = 5.2 Hz, 1H, 3'), 4.82-5.01 (m, 2H, =CH_2), 5.03 (d, $J_{2/1'}$ = 6.9 Hz, $J_{2/3}$ = 6.0 Hz, 1H, 2), 7.32-7.48 (m, 6H, aromatic), 7.59-7.72 (m, 4H, aromatic), 9.72 (d, $J_{CHO/3}$ = 1.1 Hz, 1H, C*H*O). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 17.7 (+, 2'-*C*H_3), 19.2 (quart., *C*$(CH_3)_3$), 27.1 (+, C(*C*H_3)$_3$), 29.5 (-, 4-C), 42.8 (-, 4'-C), 44.8 (+, 2'-C), 49.9 (+, 3-C), 54.1 (+, 1'-C), 79.1 (+, 2-C), 80.7 (+, 3'-C), 112.3 (-, =*C*H_2), 127.7-127.8 (+, *ortho*), 129.8-129.9 (+, *para*), 133.6-134.1 (quart., *ipso*), 135.9-136.0 (+, *meta*), 146.9 (quart., 5'-C), 174.4 (quart., 5-C), 197.8 (quart., *C*HO). **IR (Film, cm^{-1})**: 3019, 2959, 1775, 1215, 1109, 755, 703, 665. **MS (PI-CIMS, NH_3)**: *m/z* (%) = 480.3 ($[M+NH_4]^{+\cdot}$, 100), 452.3 (5), 385.2 (6), 180.1 (5).

General Work Procedure for *Sakurai* allylation of lactonecarbaldehyde under $BF_3 \cdot Et_2O$ catalyst (GWP 4).

Solution of γ-butyrolactone carbaldehyde (1 eq.) dissolved in abs. CH_2Cl_2 (5.6 ml / mmol) was cooled down to -78°C. Corresponding allylsilane (1.0-2.0 eq.) was injected all at once. $BF_3 \cdot Et_2O$ (1.0 eq.) was added by syringe over 10 min, and then the mixture was stirred overnight. Reaction was monitored by TLC (PE:EA=1:1, vanillin sulfuric acid developer). Reaction was quenched by sat. $NaHCO_3$ (2.2 ml/ ml of $BF_3 \cdot Et_2O$) solution and it was slowly warmed up to ambient temperature. Org. phase was separated, and the combined org. phase was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The concentrate was subjected to SiO_2 column chromatography (PE:EA = 3:1) to give product as colorless oil.

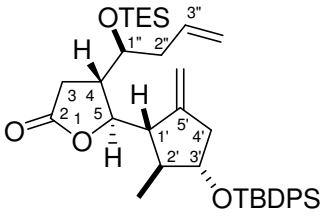


223

(4*R*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-[1''-hydroxy-3''-butenyl]dihydro-2(3*H*)-furanone (223)

222 (278 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (8 ml), then it was cooled down to -78°C. **173** (285 µl, 1.80 mmol) was added and stirred for 10 min. $BF_3 \cdot Et_2O$ (153 µl, 1.20 mmol) was added over 10 min by using a syringe. The reaction mixture was stirred for 26 h further at -78°C. After conventional work-up, the concentrate was subjected to column chromatography (PE:EA = 3:1). Crude **223** (289 mg, 95 %, *dr* = 54:26:12:8) was obtained as pale yellow oil.

TLC $\mathbf{R_f}$ = 0.62 (PE:EA = 2:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.82-0.98 (d, *J* = 6.9 Hz, 3H, 2'), 1.04-1.09 (s, 9H, C(C*H*$_3$)$_3$), 2.02-2.80 (m, 9H, 3, 4, 1', 2', 4', 2''), 3.59-3.78 (m, 2H, 3', 1''), 4.72-4.85 (m, 1H, 5), 4.86-4.90 (br d, 1H, =C*H*$_2$), 4.90-4.94 (br d, 1H, =C*H*$_2$), 5.11-5.27 (m, 2H, =C*H*$_2$), 5.68-5.88 (m, 1H, C*H*=CH$_2$), 7.32-7.48 (m, 6H, aromatic), 7.61-7.73 (m, 4H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 17.9 (+, 2'-*C*H$_3$), 19.3 (quart., *C*(CH$_3$)$_3$), 27.1 (+, C(*C*H$_3$)$_3$), 29.2 (-, 3-C), 40.2 (-, 4'-C), 42.3 (+, 2'-C), 43.2 (-, 2''-C), 44.2 (+, 4-C), 53.5 (+, 1'-C), 70.2 (+, 1''-C), 79.1 (+, 5-C), 83.9 (+, 3'-C), 111.2 (-, 5' =*C*H$_2$), 119.6 (-, 3'' =*C*H$_2$), 127.7 (+, *ortho*), 129.8 (+, *para*), 133.8 (quart., *ipso*), 135.9 (+, *meta*), 147.4 (quart., 5'-C), 177.0 (quart., *C*=O). **IR (Film, cm^{-1})**: 3419, 3018, 1765, 1216, 1109, 757. **MS (CI-MS, NH$_3$)**: *m/z* (%) = 522.4 (M+NH$_4^+$, 93), 505.4 (MH$^{+\cdot}$, 12), 427.3 (MH$^{+\cdot}$-C$_6$H$_6$, 100).

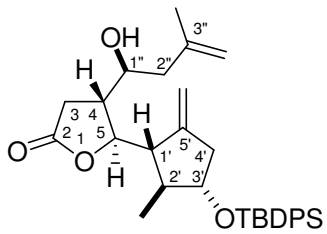


224

(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (224)

223 (289 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (5 ml) and then Et_3N (159 µl, 1.15 mmol) and TESCl (292 µl, 1.72 mmol) were added subsequently. It was stirred for 72 h at rt. Normal work-up in GWP 4 and subsequent column chromatography (PE:EA = 19:1) afforded **224** (230 mg, 65 %) as colorless oil.

TLC $\mathbf{R}_f$ = 0.32 & 0.35 (PE:EA = 9:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.63 (quart., *J* = 7.7 Hz, 6H, $Si(CH_2CH_3)_2$, diast.: 0.61, 0.60), 0.97 (t, *J* = 7.7 Hz, 9H, $Si(CH_2CH_3)_3$), diast.: 0.97, 0.96), 1.07 (s, 9H, $C(CH_3)_3$, diast.: 1.05, 1.06), 2.05-2.60 (m, 8H), 2.60-2.77 (m, 1H), 3.55-3.74 (m, 1H, SiOC*H*), 3.74-3.85 (m, 1H, SiOC*H*), 3.74-3.85 (m, 1H), 4.48-4.55 (m, 1H), 4.73-4.83 (m, 1H, $=CH_2$), 4.84-4.93 (m, 1H, $=CH_2$), 5.03-5.16 (m, 2H, $=CH_2$), 5.58-5.88 (m, 1H, $-CH=CH_2$), 7.32-7.48 (m, 6H, aromatic), 7.59-7.72 (m, 4H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 5.3 (-, $Si(CH_2CH_3)_3$, diast.: 5.4), 7.0 (+, $Si(CH_2CH_3)_3$, diast.: 7.0), 14.3 (+, CH_3, diast.: 14.5), 19.3 (quart., $C(CH_3)_3$, 19.3), 27.1 (+, $C(CH_3)_3$, diast.: 27.1), 28.7 (-, diast.: 29.0), 40.9 (-, diast.: 40.7), 41.2 (+, diast.: 41.6), 43.8 (+, diast.: 44.5), 43.8 (-, diast.: 43.9), 51.6 (+, diast.: 51.3), 72.2 (+, O*C*H, diast.: 72.5), 78.8 (+, O*C*H, diast.: 78.9), 84.3 (+, O*C*H, diast.: 84.6), 110.4 (-, $=CH_2$, diast.: 110.8), 118.4 (-, $=CH_2$, diast.: 118.4), 127.7 (+, aromatic, diast.: 127.7), 129.8 (+, aromatic, 129.8), 133.7 (+, $-CH=CH_2$, diast.: 133.7), 133.9 (quart., *ipso*, diast.: 133.9), 134.4 (quart., *ipso*, diast.: 134.3), 136.0 (+, aromatic, diast.: 136.0), 147.1 (quart., 5'-C, diast.: 146.6), 177.2 (quart., *C*=O, diast.: 177.0). **MS (PI-DCIMS, NH_3)**: *m/z* (%) = 636.3 ($[M+NH_4]^{+\cdot}$, 100), 619.2 ($MH^{+\cdot}$, 2).

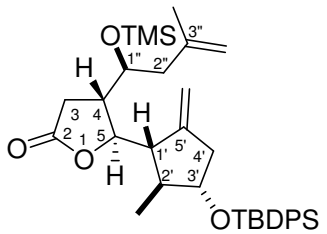


225

(4*R*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-[1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (225)

222 (94 mg, 0.20 mmol) was dissolved in abs. CH_2Cl_2 (3 ml), then it was cooled down to -78°C. **174** (73 µl, 0.41 mmol) was injected and stirred for 15 min. $BF_3{\cdot}Et_2O$ (28 µl, 0.22 mmol) was added over 10 min by using a syringe. The reaction mixture was stirred for 60 h further at -78°C. Work-up with sat. $NaHCO_3$ (500 µl) and column chromatography (PE:EA = 3:1) were carried out. The product **225** (65 mg, 62 %, *dr* = 40:36:14:10) was obtained as pale yellow oil.

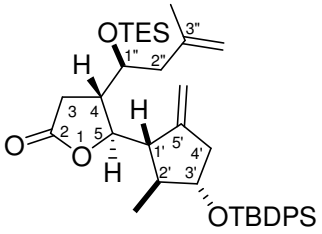
TLC $\mathbf{R}_f$ = 0.66 (PE:EA = 1:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.82-1.00 (d, *J* = 6.9 Hz, 3H, 2'-C*H*$_3$), 1.06 (s, 9H, C(C*H*$_3$)$_3$), 1.69-1.79 (s, 3H, 3"-C*H*$_3$), 1.94-2.79 (m, 9H, 3, 4, 1', 2', 4', 2"), 3.55-3.76 (m, 1H, 3'), 3.76-3.85 (m, 1H, 1"), 4.67-5.00 (m, 5H, 5, 5' =C*H*$_2$, 3" =C*H*$_2$), 7.31-7.49 (m, 6H, aromatic), 7.58-7.72 (m, 4H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 18.0 (+, 2'-*C*H$_3$, diast.: 17.9, 18.5), 19.3 (quart., *C*(CH$_3$)$_3$), 22.3 (+, 3"-*C*H$_3$, diast.: 22.4), 27.1 (+, C(*C*H$_3$)$_3$), 29.3 (-, 3-C, diast.: 29.1, 29.2), 42.5 (+, 2'-C, diast.: 42.1, 42.4), 43.2 (-, 4'-C, diast.: 43.4, 43.6), 43.4 (-), 44.2 (+, 2"-C), 44.5 (+, 4-C, diast.: 44.2), 53.6 (+, diast.: 53.3, 52.3), 68.5 (+, diast.: 68.3, 70.1), 79.1 (+, diast.: 79.0, 79,1), 83.8 (+, diast.: 83.5, 84.1), 111.2 (-, =*C*H$_2$, diast.: 110.5), 114.7 (-, =*C*H$_2$, diast.: 114.8, 115.0), 127.7 (+, *ortho*, diast.: 127.8), 129.9 (+, *para*, diast.: 129.8), 133.8 (quart., *ipso*, diast.: 134.3), 136.0 (+, *meta*, diast.: 135.9), 141.4 (quart., 3", diast.: 141.5), 147.5 (quart., 5', diast.: 147.0, 147.8), 177.1 (quart., *C*=O, diast.: 176.6, 176.8). **MS (PI-CIMS, NH$_3$)**: *m/z* (%) = 536.2 ([M+NH$_4$]$^{+\cdot}$, 100), 519.2 (M$^{+\cdot}$, 1).



226

(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{3"-methyl-1"-[(trimethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (226)

224 (65 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (2 ml) under N_2 then cooled to 0°C. Et_3N (52 µl, 0.38 mmol) and TMSCl (80 µl, 0.63 mmol) were added subsequently with a 10 min interval. It was stirred for 66 h at rt. Conventional work-up in GWP4 and column chromatography (PE:EA = 2:1) afforded **226** (40 mg, 54 %, *dr* = 42:37:14:7) as colorless oil.
TLC $\mathbf{R}_f$ = 0.73 (PE:EA = 2:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.06-0.15 (s, 9H, Si(C*H*$_3$)$_3$, diast.: 0.07, 0.11, 0.14), 0.81-1.01 (d, *J* = 6.6 Hz, diast.: 0.90, 0.93, 0.98), 1.06 (s, 9H, C(C*H*$_3$)$_3$), 1.62-1.79 (s, 3H, 3''-C*H*$_3$, diast.: 1.69, 1.75, 1.77), 1.86-2.00 (m, 1H), 2.01-2.13 (m, 1H), 2.14-2.37 (m, 4H), 2.38-2.58 (m, 2H), 2.59-2.79 (m, 1H), 3.55-3.75 (m, 1H), 3.79-3.95 (m, 1H), 4.41-4.54 (m, 1H), 4.57-5.04 (m, 4H), 7.30-7.49 (m, 6H, aromatic), 7.58-7.75 (m, 4H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 0.6 (+, Si(*C*H$_3$)$_3$, diast.: 1.2), 17.8 (+, 2'-*C*H$_3$, diast.: 18.1), 19.3 (quart., *C*(CH$_3$)$_3$, diast.: 19.4), 22.8 (+, 3''-*C*H$_3$, diast.: 22.9), 27.1 (+, C(*C*H$_3$)$_3$), 28.5 (-, 3-C, diast.: 28.9), 40.9 (+, diast.: 41.3), 43.8 (-, 4'-C, diast.: 43.9), 44.5 (+, *C*H), 44.6 (-, 2''-C, diast.: 44.8), 51.5 (+, *C*H, diast.: 52.3), 71.0 (+, *C*H, diast.: 77.4), 78.7 (+, *C*H, diast.: 78.8), 84.2 (+, *C*H, diast.: 84.6), 110.3 (-, =*C*H$_2$, diast.: 110.9), 114.1 (-, =*C*H$_2$, diast.: 114.3), 127.7 (+, *ortho*, diast.: 127.8), 129.8 (+, *para*, diast.: 129.9), 133.8 (quart., *ipso*, diast.: 133.9), 136.0 (+, *meta*, diast.: 136.1), 141.4 (quart., 3''-C), 146.7 (quart., 5'-C, diast.: 147.1), 177.1 (quart., 2, diast.: 177.3). **MS (PI-CIMS, NH_3)**: *m/z* (%) = 608.3 ([M+NH_4]$^+$, 100), 335.1 ([M-OTBDPS]$^+$, 1).

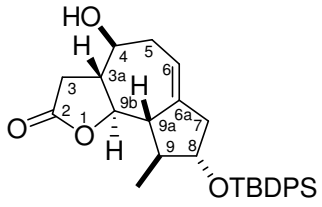


227

(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{3''-methyl-1''-[(triethylsilyl)oxy]-3''-butenyl}dihydro-2(3*H*)-furanone (227)

224 (110 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (7 ml) and then Et_3N (146 µl, 1.06 mmol) and TESCl (116 µl, 0.68 mmol) were added into sequentially. It was stirred for 44.5 h at rt. Conventional work-up in GWP4 and column chromatography (PE:EA = 9:1) afforded **227** (87 mg, 65 %, *dr* = 38:36:13:13) was obtained as pale brown oil.
TLC $\mathbf{R}_f$ = 0.46, 0.54 and 0.66 (PE:EA=9:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.62 (t, *J* = 7.5 Hz, 9H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.92-1.02 (m, 6H), 1.07 (s, 9H), 1.67-1.80 (m, 3H), 1.85-2.16 (m, 2H), 2.17-2.47 (m, 5H), 2.48-2.60 (m, 1H), 2.61-2.78 (m, 1H), 3.55-3.74 (m, 1H), 3.84-4.00 (m, 1H), 4.45-4.93 (m, 5H), 7.31-7.49 (m, 6H, aromatic), 7.59-7.73 (m, 4H, aromatic). **^{13}C-NMR** (75.5MHz, $CDCl_3$): δ 5.4 (-, diast.: 4.6, 5.3), 7.0 (+, diast.: 6.9, 7.0),

17.8 (+, CH_3, diast.: 17.9, 18.1, 18.8), 19.3 (quart., $C(CH_3)_3$, diast.: 19.6), 22.8 (+, CH_3, diast.: 22.7, 23.5), 27.1 (+, $C(CH_3)_3$, diast.: 27.0), 28.5 (-, diast.: 28.2, 32.7, 33.0), 40.8 (+, diast.: 40.5, 41.1, 41.4), 43.9 (-, diast.: 42.5, 42.9, 43.6), 43.9 (+, diast.: 43.5, 44.5), 45.0 (-, diast.: 44.0), 52.2 (+, diast.: 51.5, 52.8, 53.2), 78.8 (+, diast.: 78.7, 78.8, 79.0), 84.3 (+, diast.: 82.4, 82.6, 84.7), 110.8 (-, $=CH_2$, diast.: 110.2, 110.7, 111.3), 114.2 (-, $=CH_2$, diast.: 113.7, 113.9, 114.0), 127.7 (+, aromatic, diast.: 127.6, 129.8, 129.9), 134.4 (quart., diast.: 133.9, 134.3), 136.0 (+, aromatic, diast.: 135.9, 141.4, 141.5), 141.5 (quart., diast.: 141.4, 141.6), 147.0 (quart., diast.: 146.6, 146.7, 147.3), 177.0 (quart., C=O, 177.2, 177.3). **MS (pESI-MS, NH_4ac)**: *m/z* (%) = 650.4 ($[M+NH_4]^+$, 100), 1284.0 ($2M+NH_4^+$, 12).



228

(3a*R*,9b*R*)-8-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxy-9-methyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (228)

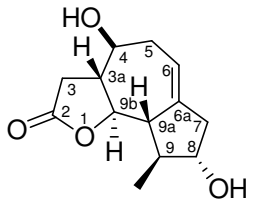
Grubbs (II) catalyst **221** (30.8 mg, 10.1 mol %) was added to the solution of **224** (230 mg, 0.37 mmol) in toluene and it was refluxed at 110°C for 288 h. Toluene was carefully evaporated under reduced pressure and CH_2Cl_2 (3 ml) was poured into reaction mixture. Anhydrous $ZnBr_2$ (419 mg, 1.86 mmol) and distilled H_2O (33.5 µl, 1.86 mmol) were subsequently added. The resulting heterogeneous mixture was refluxed at 45°C for 3 h. The reaction mixture was cooled down to rt., and work-up was carried out with H_2O and sat. $NaHCO_3$. SiO_2 column chromatography (PE:EA = 2:1) afforded **228** (85 mg, 48 %) as four diastereomers, which were separated into three portions. The 1st major diastereomer (43 mg, needle type crystal), 2nd and 3rd diastereomers (33 mg, crystal), and 4th diastereomer (9 mg, brown oil) were separated and analyzed by NMR and Mass spectrometry. Recrystallization was carried out with CH_2Cl_2 and *n*-pentane.

1st major diastereomer: TLC $\mathbf{R}_f$ = 0.17 (PE/EA = 1:1, Vanillin sulfuric acid). **m.p.** = 152°C, **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.8 Hz, 3H, 9-C*H*$_3$), 1.06 (s, 9H, C(C*H*$_3$)$_3$), 2.09 (ddq, *J* = 7.1 Hz, 6.8 Hz, 5.7 Hz, 1H, 9), 2.15 (ddd, *J* = 15.4 Hz, 8.3 Hz, 1.7 Hz, 1H, 5A), 2.22 (ddd, *J* = 15.2 Hz, 3.2 Hz, 1.2 Hz, 1H, 7B), 2.28-2.34 (m, 1H, 5B), 2.34-2.40 (m, 1H, 7A), 2.43 (dd, *J* = 17.5 Hz, 11.4 Hz, 1H, 3B), 2.64 (dddd, *J* = 11.0 Hz, 10.8 Hz, 9.0 Hz, 8.5 Hz, 1H, 3a), 2.67-2.73 (m, 1H, 9a), 2.87 (dd, *J* = 17.5 Hz, 8.8 Hz, 3A), 3.70-3.75 (m, 1H, 8), 3.85 (ddd, *J* = 7.9 Hz, 4.4 Hz, 1.3 Hz, 4), 4.59 (dd, *J* = 10.5 Hz, 8.6 Hz, 1H, 9b), 5.42-5.48 (m, 1H, 6), 7.33-7.48 (m, 6H, aromatic), 7.60-7.70 (m, 4H, aromatic). **^{13}C-NMR** (150.9 MHz,

$CDCl_3$): δ 19.3 (quart., *C*$(CH_3)_3$), 19.8 (+, 9-*C*H_3), 27.1 (+, C(*C*H_3)$_3$), 33.4 (-, 5-C), 35.3 (-, 3-C), 42.4 (-, 7-C), 44.1 (+, 3a-C), 44.7 (+, 9-C), 50.5 (+, 9a-C), 76.2 (+, 4-C), 78.1 (+, 8-C), 78.4 (+, 9b-C), 115.7 (+, 6-C), 127.7 (+, *meta*), 127.8 (+, *meta*), 129.8 (+, *para*), 129.9 (+, *para*), 134.0 (quart., *ipso*), 134.4 (quart., *ipso*), 135.9 (+, *ortho*), 136.0 (+, *ortho*), 145.2 (quart., 6a-C), 176.3 (quart., *C*=O). **IR (KBr, cm^{-1})**: 3429, 2957, 2928, 2856, 1761, 1425, 1109, 968, 701, 611. **MS (CI-MS, NH_3)**: *m/z* (%) = 494.6 ($[M+NH_4]^{+\cdot}$, 19), 274.4 (100), 256.4 (38) 238.3 (75). **HR-MS** Calcd. for $C_{29}H_{36}O_4{}^{28}Si$ [$MH^{+\cdot}$]: 477.2461, Found: 477.2458.

2nd and 3rd diastereomer as a mixture (*dr* = 55:45): TLC $\mathbf{R}_f$ = 0.23 (PE/EA = 1:1, Vanillin sulfuric acid). **m.p.** = 162-164°C, **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 0.98 (d, *J* = 7.0 Hz, 9-C*H*$_3$, diast.: 1.00), 1.04 (s, 9H, C(C*H*$_3$)$_3$, diast.: 1.05), 2.15-2.28 (m, 3H), 2.15-2.42 (m, 4H), 2.43-2.56 (m, 2H), 2.74-2.83 (m, 1H), 3.53 (ddd, *J* = 10.5 Hz, 10.1 Hz, 2.9 Hz, 1/2H), 3.99-4.04 (m, 1H), 4.30-4.37 (dd, *J* = 10.5 Hz, 10.5 Hz, 1/2H), 5.42-5.49 (m, 1/2H), 5.50-5.67 (m, 1/2H), 7.33-7.46 (m, 6H, aromatic), 7.60-7.70 (m, 4H, aromatic). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 18.9 (+, *C*$(CH_3)_3$), 19.3 (+, 9-*C*H_3), 27.1 (+, C(*C*H_3)$_3$), 29.8 (-), 33.7 (-), 34.9 (-), 35.5 (-), 38.0 (-), 42.8 (-), 42.9 (-), 46.8 (+), 46.9 (+), 52.3 (+), 52.7 (+), 53.5 (+), 55.2 (+), 66.0 (+), 70.8 (+), 78.9 (+), 79.0 (+), 80.5 (+), 84.2 (+), 117.5 (+), 118.2 (+), 127.7 (+, aromatic), 127.7 (+, aromatic), 127.8 (+, aromatic), 129.8 (+, aromatic), 129.9 (+, aromatic), 133.9 (quart., *ipso*), 134.5 (quart., *ipso*), 135.9 (+, aromatic), 136.0 (+, aromatic), 136.0 (+, aromatic), 144.1 (quart.), 145.8 (quart.), 175.5 (quart., *C*=O), 175.6 (quart., *C*=O). **MS (CI-MS, NH_3)**: *m/z* (%) = 494.6 ($[M+NH_4]^{+\cdot}$, 11), 274.4 (21), 256.4 (9), 238.3 (26), 180.2 (100). **HR-MS** Calcd. for $C_{29}H_{36}O_4{}^{28}Si$ [$MH^{+\cdot}$]: 477.2461, Found: 477.2462.

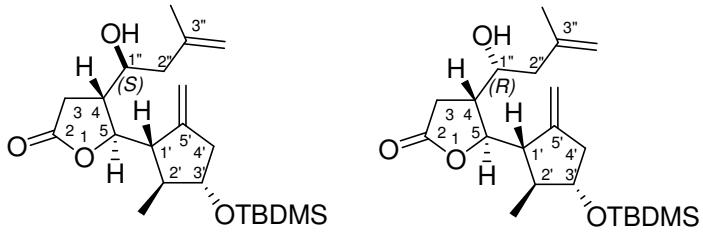
4th diastereomer: TLC $\mathbf{R}_f$ = 0.36 (PE/EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.9 Hz, 3H, 9-C*H*$_3$), 1.04 (s, 9H, C(C*H*$_3$)$_3$), 2.30-2.45 (m, 4H), 2.75 (ddt, 1H), 2.89 (1H), 3.70 (dt, *J* = 5.5 Hz, 4.7 Hz, 1H, 8), 4.06 (ddd, 1H, 4), 4.93 (dd, 1H), 5.36 (m, 1H), 7.40 (m, Ph, 6H), 7.77 (m, Ph, 4H). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 19.2 (quart., *C*$(CH_3)_3$), 19.7 (+, 9-C), 27.0 (+, C(*C*H_3)$_3$), 29.7 (-), 34.0 (-), 41.2 (+), 42.4 (-), 44.2 (+), 50.9 (+), 66.7 (+), 76.6 (+), 78.0 (+), 115.5 (+), 127.6 (+, aromatic), 127.7 (+, aromatic), 129.7 (+, aromatic), 129.8 (+, aromatic), 133.8 (quart.), 134.2 (quart.), 135.8 (+, aromatic), 145.7 (quart.), 176.8 (quart.). **MS (CI-MS, NH_3)**: *m/z* (%) = 494.6 ($[M+NH_4]^{+\cdot}$, 12), 399.5 (9), 274.4 (4), 256.4 (2), 238.3 (8), 203.2 (100), 180.3 (19). **HR-MS** Calcd. for $C_{29}H_{36}O_4{}^{28}Si$ [$MH^{+\cdot}$]: 477.2461, Found: 477.2456.



232

(3a*R*,4*S*,8*S*,9*S*,9a*S*,9b*R*)-4,8-dihydroxy-9-methyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (232)

TLC $\mathbf{R}_f$ = 0.36 (PE/EA = 1:1, Vanillin). **^{1}H-NMR** of major diastereomer (300 MHz, THF-d_8): δ 1.23 (d, *J* = 6.9 Hz, 3H, 9-C*H*$_3$), 2.15-2.57 (m, 6H), 2.59-2.75 (m, 3H), 3.35-3.55 (m, 1H), 3.56-3.76 (m, 1H), 3.95 (d, *J* = 10.0 Hz, 1H), 5.62-5.72 (m, 1H). **^{13}C-NMR** of major diastereomer (75.5 MHz, THF-d_8): δ 19.0 (+, 9-*C*H$_3$), 36.7 (-), 39.0 (-), 43.8 (-), 48.3 (+), 53.6 (+), 56.8 (+), 71.0 (+), 77.8 (+), 85.1 (+), 119.7 (+, 6-C), 144.5 (quart., 6a-C), 175.1 (quart., *C*=O): **^{1}H-NMR** of minor diastereomer (300 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.9 Hz, 3H, 9-C*H*$_3$), 2.12-2.63 (m, 6H), 2.64-2.89 (m, 2H), 2.90-3.10 (m, 1H), 3.71-3.89 (m, 1H), 3.95-4.07 (m, 1H), 4.26 (dd, *J* =10.4 Hz, 10.4 Hz, 1H), 5.48-5.75 (m, 1H). **^{13}C-NMR** of minor diastereomer (75.5 MHz, $CDCl_3$): δ 18.9 (+, 9-*C*H$_3$), 33.6 (-), 35.0 (-), 42.3 (-), 46.9 (+), 52.6 (+), 53.8 (+), 66.0 (+), 77.9 (+), 80.5 (+), 118.6 (+, 6-C), 144.4 (quart., 6a-C), 175.8 (quart., *C*=O).



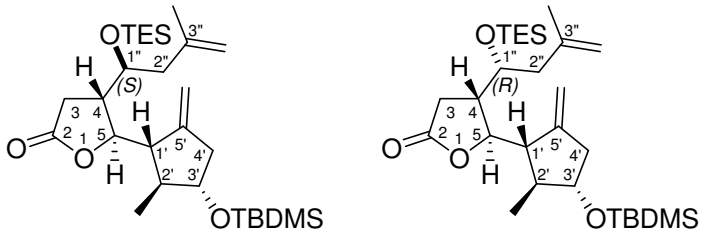
233

(4*R*,5*R*)-5-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-[(1"*S*)-1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (233)

182 (100 mg, 0.29 mmol) was dissolved in abs. CH_2Cl_2 (5 ml), then it was cooled down to -40°C. The allylsilane (105 µl, 0.58 mmol, 2.0 eq.) was added and stirred for 15 min. $BF_3{\cdot}Et_2O$ (37 µl, 0.29 mmol, 1.0 eq.) was injected over 10 min by using a syringe. The reaction mixture was stirred for 4 h further at -40°C. Sat. $NaHCO_3$ (200 µl) was injected then warmed to ambient temperature. Org. phase was separated and dried over Na_2SO_4, concentrated, and subjected to column chromatography (PE:EA = 5:1). **233** (47 mg, 40 %, *dr*

= 77:23) was obtained as pale yellow oil.

TLC $\mathbf{R}_f$ = 0.62 (PE:EA = 2:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.06 (s, 6H, Si(C*H*$_3$)$_2$, diast.: 0.05), 0.88 (s, 9H, C(C*H*$_3$)$_3$, diast.: 0.89), 1.05 (d, $J_{2'\text{-Me}/2'}$ = 6.6 Hz, 3H, 2'-C*H*$_3$, diast.: 1.06), 1.73-1.77 (br s, 3H, 3"-C*H*$_3$), 1.98-2.18 (m, 2H), 2.19-2.78 (m, 7H), 3.57-3.71 (m, 1H), 3.72-3.86 (m, 1H), 4.69 (dd, *J* = 5.2 Hz, 4.7 Hz, 1H, 5, diast.: 4.76), 4.82 (m, 1H, =C*H*$_2$, diast.: 4.85), 4.89-4.99 (m, 2H, =C*H*$_2$), 5.04 (m, 1H, =C*H*$_2$). **^{13}C-NMR** (75.5 MHz, $CDCl_3$) δ -4.6 (+, Si(*C*H$_3$)$_2$, diast.: -4.4), 17.8 (+, *C*H$_3$, diast.: 17.6), 18.1(quart., *C*(CH$_3$)$_3$, diast.: 18.2), 22.3 (+, *C*H$_3$, diast.: 22.8), 25.9 (+, C(*C*H$_3$)$_3$, diast.: 26.0), 29.5 (-, diast.: 31.7), 42.2 (+, diast.: 42.0), 43.8 (-, diast.: 43.4), 44.0 (+, diast.: 43.3), 44.1 (-, diast.: 43.9), 52.7 (+, diast.: 52.6), 68.4 (+, diast.: 70.2), 78.3 (+, diast.: 78.2), 84.0 (+, diast.: 83.7), 111.1 (-, =*CH*$_2$, diast.: 111.0), 114.8 (-, =*CH*$_2$, diast.: 115.0), 141.5 (quart., 3"-C, diast.: 141.4), 147.3 (quart., 5'-C, diast.: 147.6), 177.1 (quart., *C*=O, diast.: 177.0). **MS (PI-DCIMS, CH$_4$)**: *m/z* (%) = 395.5 ($MH^{+\cdot}$, 93), 331.5 (100) 263.3 ($[M\text{-OTBDMS}]^{+\cdot}$, 18).



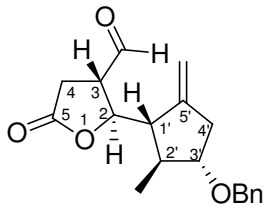
234

(4*S*,5*R*)-5-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{(1"*S*)-3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (234)

233 (47 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2 ml) and then Et_3N (28 µl, 0.20 mmol), DMAP (20 mg, 0.16 mmol) and TESCl (41 µl, 0.24 mmol) were added into sequentially. It was stirred for 12 h at rt. CH_2Cl_2 (5 ml) and 5% $NaHCO_3$ (200 µl) were poured into the mixture. The separated org. phase was dried over Na_2SO_4, filtrated, concentrated, and subjected to column chromatography (PE:EA = 9:1). The product **234** (30 mg, 49 %, *dr* = 73:27) was obtained as colorless oil.

TLC $\mathbf{R}_f$ = 0.81 (PE:EA = 2:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.04 (d, *J* = 4.7 Hz, 6H, Si(C*H*$_3$)$_2$, diast.: 0.06), 0.60 (quart., *J* = 7.8 Hz, 6H, SiC*H*$_2$, diast.: 0.61), 0.88 (s, 9H, C(C*H*$_3$)$_3$), 0.95 (t, 9H, *J* = 7.8 Hz, Si(CH$_2$C*H*$_3$)$_3$, diast.: 0.96), 1.06 (d, *J* = 6.7 Hz, 3H, 2'-C*H*$_3$, diast.: 1.07), 1.74 (br s, 3H, 3"-C*H*$_3$, diast.: 1.72), 2.01-2.59 (m, 7H), 2.29 (dd, *J* = 17.9 Hz, 3.1 Hz, 1H), 2.67 (dd, *J* = 17.9 Hz, 10.1 Hz, 1H), 3.62 (ddd, *J* = 8.9 Hz, 7.5 Hz, 6.4 Hz, 1H), 3.81-3.98 (m, 1H), 3.86 (ddd, *J* = 6.2 Hz, 6.0 Hz, 4.2 Hz, 1H, diast.: 3.92), 4.65 (dd, *J* = 4.9 Hz, 2.9 Hz, 1H, diast.: 4.48), 4.68-4.73 (m, 1H, =C*H*$_2$), 4.77-4.85 (m, 1H, =C*H*$_2$),

4.86-4.97 (m, 1H, =CH_2), 4.98-5.07 (m, 1H, =CH_2). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ -4.7 (+, Si(CH_3)$_2$, diast.: -4.6), -4.4 (+, Si(CH_3)$_2$, diast.: -4.3), 5.2 (-, SiCH_2, diast.: 5.3), 7.0 (+, $SiCH_2CH_3$), 17.7 (+, CH_3), 18.2 (quart., $C(CH_3)_3$), 23.4 (+, CH_3, diast.: 22.7), 25.9 (+, C(CH_3)$_3$), 33.1 (-, diast.: 28.5), 41.0 (+, diast.: 40.7), 42.5 (-, diast.: 44.3), 43.2 (+, diast.: 43.7), 44.0 (-, diast.: 44.9), 52.7 (+, diast.: 52.0), 70.0 (+, OCH, diast.: 70.9), 78.2 (+, OCH, diast.: 78.1), 82.8 (+, OCH, diast.: 84.4), 111.2 (-, =CH_2, diast.: 110.9), 113.8 (-, =CH_2, diast.: 114.2), 141.5 (quart., 3''-C, diast.: 141.4), 147.5 (quart., 5'-C, diast.: 147.2), 177.4 (quart., C=O, diast.: 177.3). **IR (Film, cm^{-1})**: 3076, 2956, 1781, 1462, 1375, 1250, 1179, 1108, 1007, 883, 836, 776, 737. **MS (CI-MS, NH_3)**: *m/z* (%) = 526.3 ([M+NH_4]$^{+\cdot}$, 100), 509.3 ([MH]$^{+\cdot}$, 79), 394.2 (MH$^{+\cdot}$-Si(CH_2CH_3)$_3$, 3), 377.2 ([M-OTBDMS]$^{+\cdot}$, 6).



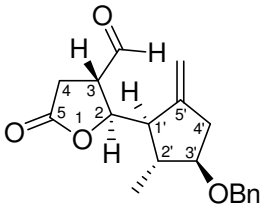
183

(2*S*,3*S*)-2-[(1'*S*,2'*S*,3'*S*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-5-oxotetrahydro-3-furancarbaldehyde (183)

$BF_3.Et_2O$ (276 µl, 2.18 mmol) was added into the solution of **104** (532 mg, 2.18 mmol) dissolved in CH_2Cl_2 (9 ml) at -78°C. In 15 min stirring, **103f** (495 mg, 1.80 mmol) dissolved in 2 ml of CH_2Cl_2 was added and it was stirred further for 2.5 h at -78°C. The reaction was quenched by sat. $NaHCO_3$ (200 µl) and the reaction mixture was warmed slowly up to ambient temperature. It was filtrated through Na_2SO_4 cake and the residue was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*. It was dissolved with MeOH (100 ml) then cooed down to 0°C. $Ba(OH)_2 \cdot 8H_2O$ (250 mg, 0.79 mmol) was added as several portions as solid. The reaction mixture was stirred for 17 h at 0°C. Approximately 80 % volume of MeOH was removed under reduced pressure at rt. $CHCl_3$ (50 ml) and H_2O (5 ml) were poured into and the org. phase was separated. The aqueous phase was extracted with $CHCl_3$ (2×50 ml). Combined org. phase was dried over Na_2SO_4, filtrated, concentrated. Column chromatography on SiO_2 (PE/EA = 1:1) afforded the desired product **183** (367 mg, 65 %, *dr* = 97:3) as colorless oil.

TLC $\mathbf{R}_f$ = 0.38 (PE/EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.07 (d, $J_{2'\text{-Me}/2'}$ = 7.0 Hz, 3H, 2'-CH_3), 2.20 (ddq, $J_{2'/2'\text{-Me}}$ = 7.0 Hz, $J_{2'/1'}$ = 5.5 Hz, $J_{2'/3'}$ = 5.0 Hz, 1H, 2'), 2.40 (m, 1H, 4'), 2.49 (m, 1H, 1'), 2.71 (dd, $J_{4A/4B}$ = 18.1 Hz, $J_{4A/3}$ = 10.4 Hz, 1H, 4A), 2.77 (m, 1H, 4'), 2.88 (dd, $J_{4B/4A}$ = 18.1 Hz, $J_{4B/3}$ = 7.1 Hz, 1H, 4B), 3.37 (dddd, $J_{3/4A}$ = 10.4 Hz, $J_{3/4B}$ = 7.1 Hz, $J_{3/2}$ = 6.0 Hz, $J_{3/CHO}$ = 1.0 Hz, 1H, 3), 3.58 (ddd, $J_{3'/4'A}$ = 6.2 Hz, $J_{3'/4'B}$ = 6.0 Hz, $J_{3'/2'}$ = 5.0 Hz, 1H, 3'), 4.49 (d, J = 11.8 Hz, 1H, -OCH_2Ph), 4.53 (d, J = 11.8

Hz, 1H, -OCH_2Ph), 4.94 (dd, $J_{2/1'}$ = 6.5 Hz, $J_{2/3}$ = 5.9 Hz, 1H, 2), 5.05 (m, 1H, =CH_2), 5.13 (m, 1H, =CH_2), 7.32 (m, 5H, aromatic), 9.64 (d, $J_{CHO/3}$ = 9.6 Hz, C*H*O). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 18.3 (+, 2'-*C*H_3), 29.4 (-, 4-C), 39.7 (-, 4'-C), 41.6 (+, 2'-C), 49.6 (+, 3-C), 54.1 (+, 1'-C), 71.5 (-, -O*C*H_2Ph), 80.5 (+, 2-C), 84.5 (+, 3'-C), 112.5 (-, =*C*H_2), 127.7 (+, *ortho*), 127.8 (+, *para*), 128.5 (+, *meta*), 138.1 (quart., *ipso*), 146.7 (quart., 5'-C), 174.2 (quart., 5-C), 197.7 (+, *C*HO). **IR (Film, cm^{-1})**: 3407, 3060, 3030, 2959, 2930, 2905, 2870, 2840, 1770, 1730, 1655, 1456, 1353, 1195, 1181, 1096, 1071, 1026, 1014, 958, 902, 774, 754, 738, 698, 666. **MS (PI-EIMS, 70 eV)**: *m/z* (%) = 314.1 ($M^{+\cdot}$, 15), 212.1 (2), 190.1 (3), 148.1 (3), 113.0 (5), 91.0 ($C_7H_7^{+\cdot}$, 100), 77.0 (10), 44.0 (7), 31.0 (7). **HR-EIMS** Calcd. for $C_{19}H_{22}O_4$ [$M^{+\cdot}$]: 314.1518, Found: 314.1518. $[\alpha]_D^{21}$ + 53.9 (c 0.98, $CHCl_3$)



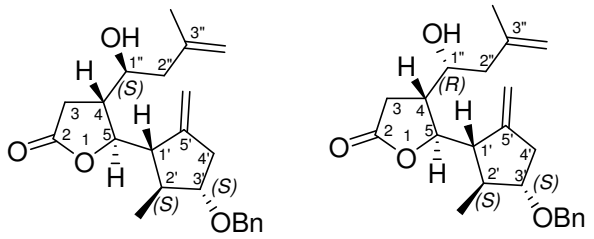
200

(2*S*,3*S*)-2-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-5-oxotetrahydro-3-furancarbaldehyde (200)

$BF_3.Et_2O$ (876 µl, 6.91 mmol) was added into the solution of **104** (978 mg, 4.00 mmol) dissolved in CH_2Cl_2 (15 ml) at -78°C. In 15 min stirring, (*ent*)-**103f** (1.0 g, 3.64 mmol) was added and it was stirred further for 2 h at -78°C. The reaction was quenched by sat. $NaHCO_3$ (400 µl) and the reaction mixture was warmed slowly up to an ambient temperature. It was filtrated through Na_2SO_4 cake and the residue was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo*. It was dissolved with MeOH (100 ml) then cooed down to 0°C. $Ba(OH)_2 \cdot 8H_2O$ (574 mg, 1.82 mmol) was added as several portions as a solid. The reaction mixture was stirred for 17 h at 0°C. With the same work-up procedure by **183, 200** (629 mg, 50 %, *dr* = 80:20) was obtained as pale yellow oil.

TLC $\mathbf{R}_f$ = 0.38 (PE/EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.90-1.17 (d, *J* = 7.1 Hz, 3H, 2'-C*H*$_3$, diast.: 1.07, 0.93), 1.94-2.20 (m, 1H), 2.20-2.55 (m, 2H), 2.56-2.82 (m, 2H), 2.83-3.03 (m, 1H), 3.27-3.95 (m, 2H), 4.34-4.64 (m, 2H), 4.84-5.01 (m, =CH_2, 1H), 5.01-5.20 (m, =CH_2, 1H), 7.20-7.40 (m, 5H, aromatic), 9.60 (d, *J* = 9.4 Hz, 1H, diast.: 9.64, *J* = 1.1 Hz). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 19.5 (+, 2'-*C*H_3, diast.: 18.5), 29.2 (-, diast.: 29.5), 31.1 (+, diast.: 31.0), 39.3 (-, diast.: 39.8), 41.5 (+, diast.: 41.7), 49.3 (+, diast.: 49.7), 52.8 (+, diast.: 54.1), 71.5 (-, diast.: 71.6), 77.4 (+), 80.8 (+, diast.: 80.6), 84.4 (+, diast.: 84.6), 112.2 (-, diast.: 112.7), 127.7 (+, aromatic, diast.: 127.9), 127.8 (+, aromatic, diast.: 127.9), 128.6 (+, aromatic, diast.: 128.6), 138.1 (quart., *ipso*), 147.2 (quart., diast.:

146.8), 174.5 (quart.), 197.8 (+, *C*HO). **IR (Film, cm^{-1})**: 3066, 2961, 1770, 1452, 1353, 1198, 1100, 1024, 752, 699. **MS (EI-MS, 70 eV)**: *m/z* (%) = 315.1 ($MH^{+\cdot}$, 14), 314.1 ($M^{+\cdot}$, 10), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{19}H_{22}O_4$ [$M^{+\cdot}$]: 314.1518, Found: 314.1511. $[\alpha]_D^{20}$ -25.0 (c 0.53, $CHCl_3$)



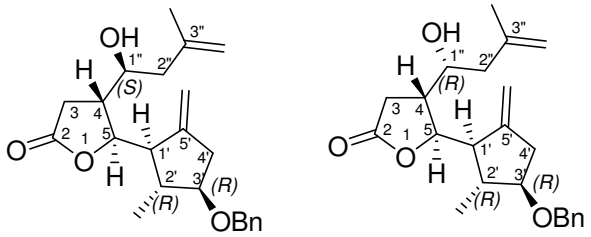
235

(4*R*,5*S*)-5-[(1'*S*,2'*S*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-(1"-hydroxy-3"-methyl-3"-butenyl)dihydro-2(3*H*)-furanone (235)

183 (560 mg, 1.78 mmol) was dissolved in CH_2Cl_2 (10 ml), then it was cooled down to -78°C. **174** (643 µl, 3.56 mmol) was added and stirred for 15 min. $BF_3{\cdot}Et_2O$ (226 µl, 1.78 mmol) was added over 10 min via a syringe. The reaction mixture was stirred for 50 h further at -78°C. Sat. $NaHCO_3$ (500 µl) was injected then warmed up to ambient temperature. Org. phase was separated and dried over Na_2SO_4, concentrated, and subjected to column chromatography (PE:EA = 3:1). **235** (529 mg, 80 %, *dr* = 75:22:3) was obtained as pale yellow oil.

TLC $\mathbf{R}_f$ = 0.63 (PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.09 (d, $J_{2'\text{-Me}/2'}$ = 6.9 Hz, 3H, 2'-CH_3, diast.: 1.11)**,** 1.72 (br s, 3H, 3"-CH_3, diast.: 1.73), 2.05 (dd, *J* = 13.4 Hz, $J_{2"/1"}$ = 9.6 Hz, 1H, 2", diast.: 2.12), 2.09 (dd, *J* = 13.4 Hz, $J_{2"/1"}$ = 4.0 Hz, 1H, 2"), 2.19 (ddq, $J_{2'/2'\text{-Me}}$ = 6.9 Hz, $J_{2'/3'}$ = 7.1 Hz, $J_{2'/1'}$ = 6.3 Hz, 1H, 2', diast.: 2.20), 2.31-2.40 (m, 2H, 1', diast.: 2.42, 4'A, diast.: 2.34), 2.45 (m, 1H, 4, diast.: 2.46), 2.52 (dd, *J* = 17.8 Hz, 9.7 Hz, 1H, 3A, diast.: 2.33), 2.67 (dd, *J* = 17.8 Hz, 5.4 Hz, 1H, 3B, diast.: 2.73), 2.75 (m, 1H, 4'B, diast.: 2.77), 3.53 (ddd, *J* = 7.1 Hz, 6.5 Hz, 6.1 Hz, 1H, 3', diast.: 3.50), 3.76 (ddd, *J* = 9.3 Hz, 3.8 Hz, 3.8 Hz, 1H, 1", diast.: 3.64), 4.53 (s, 2H, O*CH*$_2$Ph, diast.: 4.55), 4.69 (dd, *J* = 5.7 Hz, 5.0 Hz, 1H, 5, diast.: 4.73), 4.80 (m, 1H, =*CH*$_2$ at 4", diast.: 4.79), 4.92 (m, 1H, =*CH*$_2$ at 4", diast.: 4.94), 4.99 (br s, 1H, =*CH*$_2$ at 5', diast.: 4.97), 5.06 (br s, 1H, =*CH*$_2$ at 5', diast.: 5.05), 7.26-7.37 (m, 5H, aromatic). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 18.3 (+, 2'-CH_3, diast.: 18.2), 22.2 (+, 3"-CH_3), 29.2 (-, 3-C, diast.: 32.4), 40.1 (-, 4'-C, diast.: 40.3), 41.1 (+, 2'-C, diast.: 40.6), 42.3 (+, 4-C, diast.: 42.0), 43.9 (-, 2"-C, diast.: 43.4), 53.6 (+, 1'-C, diast.: 53.2), 68.2 (+, 1"-C, diast.: 70.0), 71.6 (-, O*CH*$_2$Ph, diast.: 71.7), 83.7 (+, 5-C, diast.: 83.5), 84.6 (+, 3'-C, diast.: 84.5), 111.4 (-, 5' =*CH*$_2$, diast.: 111.3), 114.6 (-, 3" =*CH*, diast.: 114.8), 127.6 (+,

para), 127.7 (+, *ortho*), 128.3 (+, *meta,* diast.: 138.4), 138.3 (quart., *ipso*), 141.3 (quart., 3"-C, diast.: 141.4), 147.1 (quart., 5'-C, diast.: 147.4), 176.8 (quart., *C*=O at 2, diast.: 176.7). **IR (Film, cm^{-1})**: 3453 (br), 3074(w), 3014(w), 2960 (w), 2931 (w), 2905 (w), 2871 (w), 1762 (s), 1651 (w), 1655 (s), 1454 (w), 1354 (w), 1198 (m), 1090 (m), 1028 (m), 895 (m), 750 (s), 698 (m), 667 (m). **MS (PI-EIMS, 70 eV)**: *m/z* (%) = 370.2 ($M^{+\cdot}$, 14), 209.1 (3), 184.1 (6), 169.1 ([M-$C_{14}H_{17}O$]$^{+\cdot}$, 5), 151.1 (4), 113.0 (8), 105.1 (11), 94.1 (12), 91.0 ($C_7H_7^+$, 100), 84.0 ([M-$C_{19}H_{26}O_2$]$^{+\cdot}$, 6). **HR-EIMS** Calcd. for $C_{23}H_{30}O_4$ [$M^{+\cdot}$]: 370.2144, Found: 370.2139. $[\alpha]_D^{21}$ +57.3 (c 1.78, $CHCl_3$)



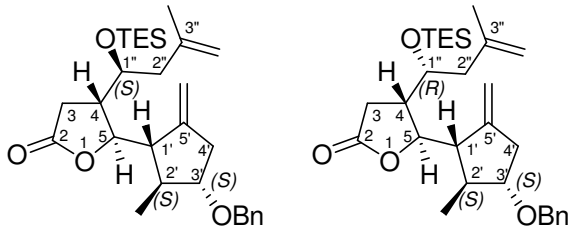
237

(4*R*,5*R*)-5-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-[1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (237)

200 (590 mg, 1.87 mmol) was dissolved in CH_2Cl_2 (10 ml), then it was cooled down to -68°C. **174** (701 µl, 3.88 mmol) was added and stirred for 15 min. $BF_3 \cdot Et_2O$ (270 µl, 2.13 mmol) was added over 10 min via a syringe. The reaction mixture was stirred for 80 h further at -68°C. Following the same procedure with **235**, the desired **237** (501 mg, 72 %, *dr* = 57:19:17:7) was obtained as pale yellow oil.

TLC $\mathbf{R}_f$ = 0.63 (PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.9 Hz, 3H, 2'-C*H*$_3$, diast.: 1.09), 1.67 (br s, 3H, 3"-C*H*$_3$, diast.: 1.72, 1.73, 1.76), 1.98-2.20 (m, 3H), 2.27-2.50 (m, 3H), 2.51-2.62 (m, 1H), 2.63-2.84 (m, 2H), 3.40-3.67 (m, 1H), 3.68-3.98 (m, 1H), 4.44 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$), 4.56 (d, *J* = 11.5 Hz, 1H, OC*H*$_2$), 4.64-4.85 (m, 2H), 4.85-4.96 (m, 1H), 4.97-5.04 (m, 1H), 5.05-5.18 (m, 1H). 7.24-7.39 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 19.0 (+, *C*H$_3$, diast.: 18.4), 22.3 (+, *C*H$_3$, diast.: 22.4), 29.0 (-), 39.5 (-), 41.7 (+), 42.4 (+), 44.1 (-), 53.0 (+), 68.4 (+, diast.: 68.0), 71.8 (-, -O*C*H$_2$Ph), 83.9 (+), 84.7 (+), 111.0 (-, diast.: 111.6), 114.5 (-, diast.: 114.8), 127.8 (+, aromatic), 127.9 (+, aromatic), 128.6 (+, aromatic), 138.4 (quart.), 141.5 (quart.), 147.0 (quart.), 176.7 (quart., *C*=O, diast.: 176.3). **IR (Film, cm^{-1})**: 3418, 3020, 1770, 1714, 1216, 756, 669. **MS (EI-MS, 70 eV)**: *m/z* (%) = 371.2 ($MH^{+\cdot}$, 1), 315.1 (17), 279.1 (48), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{23}H_{30}O_4$ [$M^{+\cdot}$]: 370.2144, Found: 370.2142. $[\alpha]_D^{20}$ -

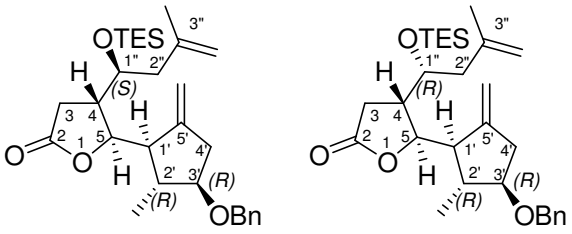
25.0 (c 0.53, $CHCl_3$).



236

(4*S*,5*R*)-5-[(1'*S*,2'*S*,3'*S*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-{3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (236)

235 (500 mg, 1.35 mmol) was dissolved in CH_2Cl_2 (10 ml), then DMAP (180 mg, 1.47 mmol) and Et_3N (281 µl, 2.02 mmol) were added subsequently at rt. TESCl (457 µl, 2.67 mmol) was added and the reaction mixture was stirred for 44 h at rt. CH_2Cl_2 (30 ml) and 5 % $NaHCO_3$ solution (3 ml) were poured into the mixture under ice bath. Org. phase was separated and aqueous phase was extracted with CH_2Cl_2 (2×10 ml). The combined org. phase was dried over Na_2SO_4, filtrated, concentrated, and subjected to SiO_2 column chromatography (PE:EA = 9:1). **236** (583 mg, 89 %, *dr* = 77:23) was obtained as colorless oil. TLC $\mathbf{R}_f$ = 0.56 (minor) and 0.64 (major) (PE:EA = 5:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.45-0.64 (quart., *J* = 8.0 Hz, 6H, SiC*H*$_2$), 0.88-0.98 (t, *J* = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$), 1.04 (d, *J* = 6.6 Hz, 3H, 2'-C*H*$_3$), 1.71 (s, 3H, 3"-C*H*$_3$), 2.07 (dd, *J* = 13.4 Hz, 10.2 Hz, 1H), 2.11-2.37 (m, 4H), 2.40 (dd, *J* = 16.5 Hz, 9.5 Hz, 1H), 2.47-2.57 (m, 1H), 2.64-2.77 (m, 2H), 3.49 (ddd, *J* = 7.7 Hz, 6.6 Hz, 6.3 Hz, 1H), 3.93 (ddd, *J* = 10.2 Hz, 4.7 Hz, 1.4 Hz, 1H), 4.47-5.59 (m, 3H), 4.70 (br s, 1H, =C*H*$_2$), 4.81 (m, 1H, =C*H*$_2$), 4.91 (m, 1H, =C*H*$_2$), 5.03 (m, 1H, =C*H*$_2$), 7.24-7.38 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 5.3 (-, 3×*C*H_2), 7.0 (+, 3×*C*H_3), 18.6 (+, *C*H), 22.8 (+, *C*H), 28.2 (-, *C*H_2), 40.2 (-, *C*H_2), 41.0 (+, *C*H), 41.2 (+, *C*H), 44.7 (-, *C*H_2), 53.8 (+, *C*H), 70.7 (+, O*C*H), 71.5 (-, O*C*H_2), 84.4 (+, O*C*H), 84.6 (+, O*C*H), 111.3 (-, =*C*H_2), 114.2 (-, =*C*H_2), 127.6 (+, *para*), 127.7 (+, *ortho*), 128.5 (+, *meta*), 138.7 (quart., *ipso*), 141.5 (quart.), 147.4 (quart.), 177.3 (quart., *C*=O). **IR (Film, cm^{-1})**: 3073, 2956, 2877, 1778, 1651, 1455, 1184, 1099, 1071, 1005, 735. **MS (CI-MS, NH$_3$)**: *m/z* (%) = 502.4 ([M+NH_4]$^{+\cdot}$, 100), 485.4 (MH$^{+\cdot}$, 9), 132.2 (10), 108.1(11). **HR-EIMS** Calcd. for $C_{29}H_{44}O_4Si$ [M$^{+\cdot}$]: 484.3009, Found: 484.3009. $[\alpha]_D^{20}$ + 59.9 (c 0.84, $CHCl_3$).



238

(4*S*,5*R*)-5-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-{3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (238)

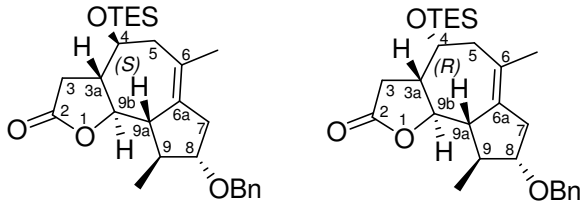
237 (491 mg, 1.32 mmol) was dissolved in CH_2Cl_2 (10 ml), then DMAP (178 mg, 1.46 mmol) and Et_3N (276 µl, 1.99 mmol) were added subsequently at rt. TESCl (449 µl, 2.65 mmol) was added and the reaction mixture was stirred for 48 h at rt. After the same work-up process with **236**, SiO_2 column chromatography (PE:EA = 9:1) afforded **238** (510 mg, 80 %, *dr* = 68:12:10:9) as colorless oil.

TLC $\mathbf{R}_f$ = 0.71 (PE:EA = 5:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.51-0.67 (m, 6H, Si-C*H*$_2$), 0.88-1.01 (m, 9H, Si(CH_2C*H*$_3$)$_3$), 1.04-1.15 (d, *J* = 6.6 Hz, 3H, 2'-C*H*$_3$, diast.: 1.06, 1.12), 1.67 (br s, 3H, 3"-C*H*$_3$, diast.: 1.71), 1.84-1.99 (quart., *J* = 7.3 Hz, 1H), 2.06 (dd, *J* = 13.7 Hz, 10.4 Hz, 1H), 2.12-2.43 (m, 3H), 2.44-2.57 (m, 2H), 2.57-2.80 (m, 2H), 3.34-3.57 (m, 1H), 3.82-4.01 (m, 1H), 4.44-4.64 (m, 3H), 4.64-4.72 (m, 1H), 4.74-4.84 (m, 1H), 4.86-4.99 (m, 1H), 5.00-5.14 (m, 1H), 7.23-7.39 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 5.3 (-, 3×Si*C*H$_2$, diast.: 5.9), 7.0 (+, 3×Si*C*H$_3$, diast.: 6.7), 18.7 (+, diast.: 18.5), 22.6 (+, diast.: 22.8), 28.1 (-, diast.: 28.1), 40.0 (+, diast.: 41.0), 40.2 (-, diast.: 40.3), 41.8 (+, diast.: 41.2), 44.8 (-, diast.: 45.1), 52.2 (+, diast.: 53.9), 71.9 (+, O*C*H, diast.: 70.7), 72.0 (-, O*C*H$_2$, diast.: 71.6), 84.3 (+, O*C*H, diast.: 84.4), 85.0 (+, O*C*H, diast.: 84.6), 110.4 (-, =*C*H$_2$, diast.: 111.3), 113.9 (-, =*C*H$_2$, diast.: 114.1), 127.7 (+, aromatic, diast.: 127.7), 127.8 (+, aromatic, diast.: 127.6), 128.5 (+, aromatic, diast.:128.4), 138.5 (quart.), 141.5 (quart.), 146.9 (quart., diast.: 147.3), 177.2 (quart., *C*=O, diast.: 177.0, 177.2, 177.3). **IR (Film, cm^{-1})**: 3019, 2958, 1770, 1715, 1215, 757. **MS (EI-MS, 70 eV)**: *m/z* (%) = 485.3 ([MH]$^{+\cdot}$, 2), 455.2 ([M-C_2H_5]$^{+\cdot}$, 30), 429.2 ([M-C_7H_7]$^{+\cdot}$, 61), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{29}H_{44}O_4Si$ [M$^{+\cdot}$]: 484.3009, Found: 484.3001. $[\alpha]_D^{20}$ - 27.2 (c 1.14, $CHCl_3$).

General Procedure for Ring Closing Metathesis reaction using Grubbs (II) catalyst, (4,5-DihydroIMES)(PCy$_3$)Cl$_2$Ru=CHPh, under Microwave irradidation. (GWP 5)

The corresponded TES protected γ-butyrolactone derivatives were dissolved in toluene (3 ml) into quartz microwave reaction vessel then it was fixed into the synthesizer. The cooler was also equipped and Ar gas was sparged *via* Teflon tube. The reactions were carried out using

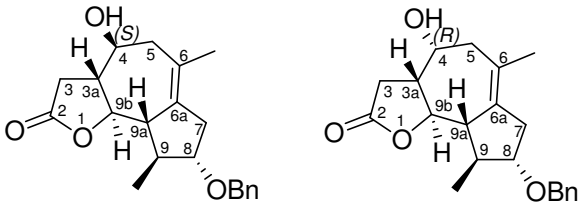
Microwave synthesizer Synthewave™ S 402 (monocavity) under ambient pressure. Being circulate the cooling water, the reaction was start to irradiate microwave conduction. The Grubbs (Ⅱ) catalyst **221** (5 mol% / every injection) dissolved in toluene (0.5 ml) were injected using syringe and Teflon® tube, another portion of toluene (0.5 ml) was used for rinse. The other portions (totally up to 15 ~ 20 mol%) of **221** were injected subsequently. The end of the irradiation was the reaction checked by TLC (PE:EA = 9:1). The reaction mixture was concentrated under reduced pressure and the concentrate was subjected to deprotection of TES using Bu_4NF (1.25 eq.) dissolved in THF (10 ml / mmol). The reaction was checked by TLC (PE:EA = 1:1). The concentrated reaction mixture was subjected to SiO_2 column chromatography (PE:EA = 2:1).



239

(3a*S*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-4-[(triethylsilyl)oxy]-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (239)

TLC $\mathbf{R}_f$ = 0.33 and 0.44 (PE:EA = 9:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.53-0.67 (quart., *J* = 7.7 Hz, 6H, $Si(CH_2CH_3)_3$), 0.94 (m, 9H, $Si(CH_2CH_3)_3$), 1.16 (d, *J* = 6.3 Hz, 9-CH_3, diast.: 1.14), 1.72 (s, 3H, 6-CH_3, diast.: 1.75), 2.15-2.82 (m, 9H), 3.37-3.96 (m, 1H), 3.99-4.13 (m, 1H), 4.16-4.32 (m, 1H), 4.44-4.65 (m, 2H, OCH_2), 7.22- 7.38 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 5.1 (-, 3×CH_2, SiCH_2, diast.: 5.3), 7.1 (+, 3×CH_3, $SiCH_2CH_3$), 18.9 (+, CH_3, diast.: 16.0), 25.3 (+, CH_3, diast.: 23.3), 33.5 (-, CH_2, diast.: 33.0), 37.2 (-, CH_2, diast.: 39.3), 42.4 (-, CH_2, diast.: 41.2), 43.7 (+, CH, diast.: 44.0), 53.3 (+, CH, diast.: 59.2), 53.8 (+, CH, diast.: 59.2), 66.4 (+, CH, diast.: 70.2), 71.4 (-, CH_2, diast.: 73.1), 81.7 (+, CH, diast.: 81.3), 84.4 (+, CH, diast.: 90.3), 127.0 (quart.), 127.5 (+, aromatic), 127.6 (+, aromatic), 128.4 (+, aromatic), 133.4 (quart.), 138.9 (quart.), 176.1 (quart., diast.: 176.2). **IR (Film, cm^{-1})**: 3408, 3018, 2957, 1770, 1455, 1204, 1107, 1003, 755. **MS (EI-MS, 70 eV)**: *m/z* (%) = 456.0 ($M^{+\cdot}$, 2), 365.1 ([M-C_7H_7]$^{+\cdot}$, 3), 324.0 ([M-$HOSiEt_3$]$^{+\cdot}$, 5), 227.1 (100). **HR-EIMS** Calcd. for $C_{27}H_{40}O_4Si$ [$M^{+\cdot}$]: 456.2696, Found: 456.2699. $[\alpha]_D^{20}$ - 8.7 (c 1.04, $CHCl_3$).

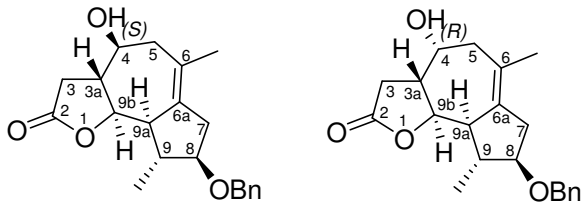


240

(3a*R*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-4-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (240)

RCM of **236** (1.0 g, 2.06 mmol) was carried out in 30 ml of toluene using Grubbs (II) (**221**, 0.41 mmol, 20 mol%) under Ar sparging and ambient pressure following the GWP5. Addition of **221** (4×5 mol%) as solution dissolved in toluene and the silmultaneous microwave (max. 300W power) irradiation for 8 h afforded **239** first. The subsequent desilylation of **239** using TBAF (592 mg, 2.26 mmol) and column chromatography (PE:EA = 1:1) afforded **240** (72 %, *dr* = 4:1) as pale brown oil.

TLC $\mathbf{R}_f$ = 0.15 and 0.21 (PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.09 (d, *J* = 7.3 Hz, 3H, 9-C*H*$_3$, diast.: 1.10), 1.74 (s, 3H, 6-C*H*$_3$, diast.: 1.76), 2.16 (dd, *J* =14.1 Hz, *J* = 2.4 Hz, 1H, 3), 2.19-2.28 (m, 1H, 3a), 2.30-2.36 (m, 1H, 5), 2.36-2.56 (m, 4H, 7, 3, 9a, 9), 2.62-2.70 (m, 1H, 5), 2.70-2.77 (m, 1H, 7), 3.43-3.50 (m, 1H, 4, diast.: 4.01), 3.50-3.57 (m, 1H, 8, diast.: 3.55), 3.86 (dd, *J* = 11.4 Hz, 9.4 Hz, 1H, 9b, diast.: 4.13), 4.49-4.59 (m, 2H, OC*H*$_2$Ph), 7.25-7.37 (m, 5H, aromatic). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 19.0 (+, 9-*C*H$_3$, diast.: 19.1), 24.0 (+, 6-*C*H$_3$, diast.: 25.5), 35.6 (-, 7-C, diast.: 33.6), 37.2 (-, 5-C, diast.: 37.3), 42.3 (+, 9-C, diast.: 42.2), 45.4 (-, 3-C, diast.: 41.8), 52.6 (+, 9a-C, diast.: 53.5), 56.0 (+, 3a-C, 53.8), 69.7 (+, 4-C, diast.: 65.9), 71.1 (-, O*C*H$_2$Ph, diast.: 71.2), 84.0 (+, 9b-C, diast.: 80.7), 84.4 (+, 8-C, diast.: 84.6), 126.6 (quart., 6-C, diast.: 126.4), 127.7 (+, aromatic, diast.: 127.8), 128.8 (+, aromatic, diast.: 127.9), 128.5 (+, aromatic, diast.: 128.6), 135.9 (quart., 6a-C, diast.: 136.5), 138.6 (quart., *ipso*, diast.: 138.5), 175.6 (quart., *C*=O, diast.: 175.8). **IR (Film, cm^{-1})**: 3416, 3019, 2926, 2400, 1774, 1215, 757, 699. **MS (EI-MS, 70 eV)**: *m/z* (%) = 342.0 ($M^{+\cdot}$, 1), 324.1 ($[M\text{-}H_2O]^{+\cdot}$, 6), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{21}H_{26}O_4$ [$M^{+\cdot}$]: 342.1831, Found: 342.1831. $[\alpha]_D^{20}$ + 38.7 (c 0.96, $CHCl_3$).

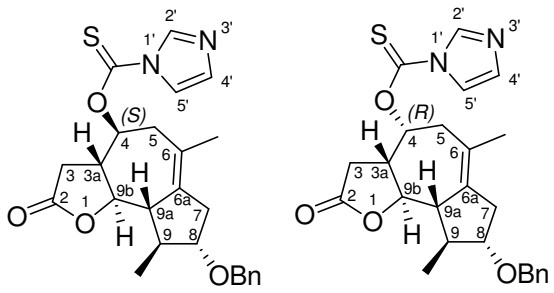


241

(3a*R*,4*S*,8*R*,9*R*,9a*R*,9b*R*)-8-(benzyloxy)-4-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (241)

RCM of **238** (470 mg, 0.97 mmol) was carried out in 5 ml of toluene using Grubbs (II) (**221**, 20 mol%) under Ar sparging and ambient pressure following the GWP5. Addition of **221** (4×5 mol%) as solution dissolved in toluene and the silmultaneous microwave (max. 300W power) irradiation for 8 h, then desilylation with TBAF (317 mg, 1.21 mmol), and a subsequent column chromatography (PE:EA = 1:1) afforded **241** (69 %, *dr* = 69:12:8:6:5), which was recrystallized with CH_2Cl_2 and Et_2O as a colorless crystal.

TLC $\mathbf{R}_f$ = 0.30 and 0.22 (PE:EA = 1:1, Mostain). **m.p.** = 140-141°C. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.10-1.32 (d, *J* = 6.3 Hz, 3H, 9-C*H*$_3$, diast.: 1.13), 1.68-1.82 (br s, 3H, 6-C*H*$_3$), 1.97-2.54 (m, 6H), 2.64-2.89 (m, 1H), 2.90-3.17 (m, 1H), 3.33-3.63 (m, 1H), 3.65-3.97 (m, 1H), 4.32-4.70 (m, 3H), 7.24-7.42 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 18.8 (+, 9-*C*H$_3$), 22.9 (+, 6-*C*H$_3$), 34.9 (-), 36.4 (-), 40.2 (-), 41.7 (+), 43.7 (+), 49.1 (+), 71.6 (-), 74.1 (+), 78.9 (+), 83.6 (+), 124.7 (quart.), 127.5 (+, aromatic), 127.6 (+, aromatic), 128.3 (+, aromatic), 133.3 (quart.), 138.5 (quart.), 176.6 (quart., *C*=O). **IR (Film, cm^{-1})**: 3488, 2922, 1757, 1456, 1263, 1118, 1026, 956, 739. **MS (EI-MS, 70 eV)**: *m/z* (%) = 342.1 ($M^{+\cdot}$, 4), 324.1 ($[M\text{-}H_2O]^{+\cdot}$, 10), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{21}H_{26}O_4$ [$M^{+\cdot}$]: 342.1831, Found: 342.1831. $[\alpha]_D^{20}$ - 22.9 (c 3.27, $CHCl_3$).



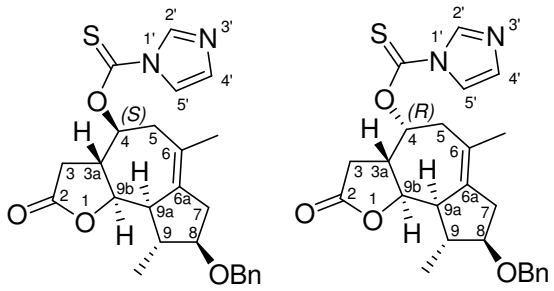
243

***O*-[(3a*S*,4*S*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-*b*]furan-4-yl] 1*H*-imidazole-1-carbothioate (243)**

240 (198 mg, 0.62 mmol) was dissolved in CH_2Cl_2 (6 ml) under N_2, then **242** (356 mg, 2.0 mmol) and DMAP (29 mg, 0.24 mmol) were added subsequently. The reaction mixture was stirred for 50 h at rt. SiO_2 (220 mg) was added into reaction mixture and it was concentrated and subjected to column chromatography (PE:EA = 3:1) to give **243** (quant. yield, *dr* = 79:21 = 4S: 4R) as two separated diastereomers.

TLC $\mathbf{R}_f$ = 0.48 (4R-**243**), 0.36 (4S-**243**) (PE:EA = 1:1, Mostain), **^{1}H-NMR** of (4S)-**243** (300MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.9 Hz, 3H, 9-C*H*$_3$), 1.81 (br d, *J* = 1.1 Hz, 3H, 6-C*H*$_3$), 2.36-2.87 (m, 9H), 3.58 (m, 1H), 4.05 (dd, *J* = 11.0 Hz, 9.3 Hz, 1H), 4.54 (m, 2H, OC*H*$_2$Ph), 5.42 (ddd, *J* = 10.4 Hz, 9.9 Hz, 3.3 Hz, 1H), 7.09 (m, 1H, imidazole), 7.27-7.39 (m, 5H, aromatic), 7.61 (br s, 1H, imidazole), 8.45 (br s, 1H, imidazole). **^{13}C-NMR** (4S)-**243** (75.5 MHz, $CDCl_3$): δ 19.0 (+, *C*H$_3$), 23.4 (+,*C*H$_3$), 35.3 (-), 37.1 (-), 40.2 (-), 41.8 (+), 52.7 (+), 53.1 (+), 71.1 (-), 80.5 (+), 83.3 (+), 84.4 (+), 118.0 (+, imidazole), 125.5 (quart.), 127.8 (+, aromatic), 127.9 (+, aromatic), 128.6 (+, aromatic), 130.5 (+, imidazole), 136.7 (+, imidazole), 137.8 (quart.), 138.4 (quart.), 138.5 (quart.), 173.9 (quart., *C*=O), 182.4 (quart., *C*=S):

^{1}H-NMR of (4R)-**243** (300 MHz, $CDCl_3$): δ 1.09 (d, *J* = 7.1 Hz, 3H, 9-C*H*$_3$), 1.63 (br s, 3H, 6-C*H*$_3$), 2.35-2.59 (m, 6H), 2.60-2.74 (m, 2H), 2.80 (dd, *J* = 15.4 Hz, 6.6 Hz, 1H), 3.60 (m, 1H), 4.28 (dd, *J* = 11.0 Hz, 9.1 Hz, 1H), 4.55 (m, 2H, OC*H*$_2$Ph), 5.88 (br d, *J* = 6.6 Hz, 1H), 6.93 (m, 1H, imidazole), 7.22-7.34 (m, 5H, aromatic), 7.35 (m, 1H, imidazole), 8.27 (m, 1H, imidazole). **^{13}C-NMR** of (4R)-**243** (75.5 MHz, $CDCl_3$): δ 19.0 (+, *C*H$_3$), 24.7 (+, *C*H$_3$), 33.4 (-), 37.1 (-), 41.9 (+), 51.4 (+), 53.7 (+), 70.8 (-), 77.0 (+), 81.3 (+), 84.5 (+), 117.2 (+), 125.9 (quart.), 127.6 (+, aromatic), 127.7 (+, aromatic), 128.5 (+, aromatic), 131.1 (+, imidazole), 136.5 (quart.), 137.2 (+, imidazole), 138.5 (quart.), 173.9 (quart., *C*=O), 183.2 (quart., *C*=S). **IR (Film, cm^{-1})**: 2961 (w), 2928 (w), 2904 (w), 2876 (w), 2857 (w), 1780 (s), 1466 (m), 1387 (m), 1329 (m), 1284 (m), 1229 (s), 1101 (m), 990 (m), 970 (m), 771 (s), 752(s), 698 (m), 657 (m), 642 (m). **MS** of (4R)-**243 (EI-MS, 70 eV)**: *m/z* (%) = 452.1 ($M^{+\cdot}$, 3), 346.1 (10), 233.1 (16), 218.1 (26), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{25}H_{28}N_2O_4S$ [$M^{+\cdot}$]: 452.1770, Found: 452.1770: **MS** of (4S)-**243 (EI-MS, 70 eV)**: *m/z* (%) = 452.3 ($M^{+\cdot}$, 1), 324.2 (8), 233.1 (15), 218.0 (29), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{25}H_{28}N_2O_4S$ [$M^{+\cdot}$]: 452.1770, Found: 452.1761. $[\alpha]_D^{20}$ + 78.6 ((4S)-**243**, c 0.37, $CHCl_3$): $[\alpha]_D^{20}$ - 87.6 ((4R)-**243**, c 0.37, $CHCl_3$)

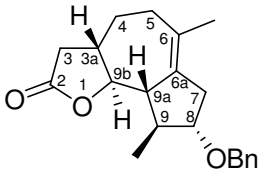


245

***O*-[(3a*S*,4*S*,8*R*,9*R*,9a*R*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-*b*]furan-4-yl] 1*H*-imidazole-1-carbothioate (245)**

241 (220 mg, 0.64 mmol) was dissolved in CH_2Cl_2 (7 ml) under N_2, then **242** (412 mg, 2.31 mmol) and DMAP (35 mg, 0.28 mmol) were added subsequently. The reaction mixture was stirred for 36 h at rt. SiO_2 (200 mg) was added into reaction mixture and it was concentrated and subjected to column chromatography (PE:EA = 1:1) to give **245** (92 %, *dr* = 67:14:13:6) as a mixture of diastereomers.

TLC $\mathbf{R}_f$ = 0.49 (4R-**245**), 0.38 (4S-**245**) (PE:EA = 1:1, Mostain), **^{1}H-NMR** (300MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.6 Hz, 3H, 9-C*H*$_3$, diast.: 1.05-1.31), 1.69 (br s, 3H, 6-C*H*$_3$, diast.: 1.61-1.85), 2.11-2.30 (m, 1H), 2.31-2.79 (m, 6H), 2.80-2.96 (m, 1H), 3.36-3.65 (m, 1H), 4.37-5.01 (m, 2H, OC*H*$_2$Ph), 5.29-6.04 (m, 1H), 7.04 (m, 1H, imidazole), 7.22-7.38 (m, 5H, aromatic), 7.51-7.66 (m, 1H, imidazole), 8.20-8.38 (m, 1H, imidazole). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 19.1 (+, *C*H$_3$), 22.5 (+, *C*H$_3$), 34.4 (-), 36.2 (-), 36.7 (-), 41.2 (+), 41.7 (+), 49.6 (+), 71.6 (-), 77.6 (+), 83.5 (+), 84.8 (+), 117.8 (+), 123.0 (quart.), 127.6 (+, aromatic), 127.7 (+, aromatic), 128.5 (+, aromatic), 131.2 (+, imidazole), 136.3 (quart.), 136.9 (+, imidazole), 138.5 (quart.), 174.6 (quart., *C*=O), 182.8 (quart., *C*=S). **IR (Film, cm^{-1})**: 3158, 3018, 1779, 1387, 1216, 755. **MS (EI-MS, 70 eV)**: *m/z* (%) = 452.2 ($M^{+\cdot}$, 1), 346.1 (1), 233.1 (8), 91.1 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{25}H_{28}N_2O_4S$ [$M^{+\cdot}$]: 452.1770, Found: 452.1774 $[\alpha]_D^{22}$ -13.0 (c 0.46, $CHCl_3$).

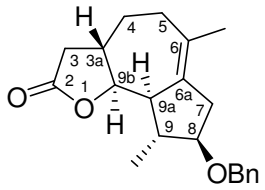


244

(3a*S*,8*S*,9*S*,9a*S*,9b*S*)-8-(benzyloxy)-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (244)

243 (230 mg, 0.51 mmol) was dissolved in toluene (8 ml) into 3-neck round bottom flask under N_2 atmosphere and AIBN (33 mg, 0.20 mmol) was added at 40°C. The reaction mixture was warmed to 90°C and Bu_3SnH (404 µl, 1.52 mmol) was dropwise injected using a syringe. It was refluxed for 4 h at 90°C. The reaction mixture was concentrated under reduced pressure. Column chromatography (SiO_2, PE:EA = 5:1) afforded **244** (128 mg, 0.39 mmol, 77 %) as colorless oil.

TLC $\mathbf{R}_f$ = 0.35 (PE:EA = 3:1, Mostain). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.11 (d, $J_{9\text{-}Me/9}$ = 6.8 Hz, 3H, 9-C*H*$_3$), 1.29 (m, 1H, 4B), 1.72 (s, 3H, 6-C*H*$_3$), 1.83 (m, 1H, 4A), 2.05 (m, 1H, 5B), 2.13-2.19 (m, 2H, 3a, 5A), 2.20-2.27 (m, 1H, 3B), 2.28-2.33 (m, 1H, 7B), 2.34-2.39 (m, 1H, 9a), 2.43 (m, 1H, 9), 2.52 (ddd, *J* = 15.9 Hz, 6.2 Hz, 0.8 Hz, 1H, 3A), 2.67 (dd, *J* = 16.0 Hz, 5.6 Hz, 1H, 7A), 3.52 (m, 1H, 8), 3.82 (dd, *J* = 10.0 Hz, 10.0 Hz, 1H, 9b), 4.56 (s, 2H, -OC*H*$_2$Ph), 7.24-7.36 (m, 5H, aromatic). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 19.0 (+, 9-*C*H$_3$), 23.8 (+, 6-*C*H$_3$), 28.2 (-, 4-C), 34.8 (-, 5-C), 37.1 (-, 7-C), 37.3 (-, 3-C), 42.7 (+, 9-C), 49.5 (+, 3a-C), 53.2 (+, 9a-C), 71.2 (-,O*C*H$_2$Ph), 84.5 (+, 8-C), 87.3 (+, 9b-C), 127.6 (+, *para*), 127.7 (+, *ortho*), 128.4 (+, *meta*), 132.5 (quart., *ipso*), 133.6 (quart., 6-C), 138.8 (quart., 6a-C), 175.8 (quart., 2-C). **IR (Film, cm^{-1})**: 3028 (w), 2957 (w), 2924 (w), 2874 (w), 2853 (w), 1778 (s), 1454 (m), 1207 (m), 1190 (m), 1150 (w), 1099 (m), 1071 (m), 1009 (w), 984 (m), 752 (s), 699 (m), 667 (w), 645 (w). **MS (CI-MS, NH_3)**: *m/z* (%) = 344.2 ($[M+NH_4]^{+\cdot}$, 100), 327.1 ($MH^{+\cdot}$, 14), 221.1 (4), 219.0 (9). **HR-EIMS** Calcd. for $C_{21}H_{26}O_3$ [$M^{+\cdot}$]: 326.1882, Found: 326.1881. $[\alpha]_D^{21}$ + 54.9 (c 1.58, $CHCl_3$).

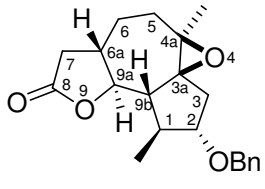


246

(3a*S*,8*R*,9*R*,9a*R*,9b*S*)-8-(benzyloxy)-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (246)

245 (250 mg, 0.55 mmol) was dissolved in toluene (8 ml) into 3-neck round bottom flask under N_2 atmosphere and AIBN (36 mg, 0.22 mmol) was added at 40°C. The reaction mixture was warmed to 90°C and Bu_3SnH (439 µl, 1.65 mmol) was dropwise injected using a syringe. It was refluxed for 60 h at 90°C. The reaction mixture was concentrated under reduced pressure. Column chromatography (PE:EA = 5:1) afforded **246** (134.3 mg, 75 %) as colorless oil.

TLC $\mathbf{R}_f$ = 0.45 (PE:EA = 3:1, Mostain). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.22-1.28 (d, *J* = 6.3 Hz, 3H, 9-C*H*$_3$, diast.: 1.14), 1.28-1.47 (m, 1H), 1.66-1.77 (m, 3H, 6-C*H*$_3$), 1.80-1.91 (m, 1H), 1.91-2.07 (m, 1H), 2.08-2.30 (m, 4H), 2.30-2.47 (m, 1H), 2.49-2.65 (dd, *J* = 16.2 Hz, 7.4, 1H), 2.66-2.79 (m, 1H), 2.79-3.11 (m, 1H, diast.: 3.05), 3.38-3.59 (m, 1H, 8, diast.: 3.83), 4.39-4.75 (m, 3H, OC*H*$_2$Ph, 9b), 7.25-7.40 (m, 5H, aromatic). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 18.9 (+, *C*H$_3$), 20.8 (+, *C*H$_3$), 28.3 (-, diast.: 26.8, 28.0), 30.8 (-, 27.8, 28.1), 36.3 (-, diast.: 34.6, 35.4), 36.4 (-, diast.: 37.0, 37.1), 41.7 (+, diast.: 40.4, 42.6), 49.3 (+, diast.: 53.0, 46.2), 71.6 (-, diast.: 71.0, 70.1), 81.4 (+, diast.:84.4, 83.6), 83.7 (+, diast.: 87.2, 85.3), 126.3 (quart., diast.:132.4, 131.4), 127.4 (+, aromatic, diast.: 127.5), 127.5 (+, aromatic, diast.: 127.6), 128.3 (+, aromatic, diast.: 128.4), 132.6 (quart., diast.: 133.4, 132.8), 138.7 (quart., 138.6, 138.5), 176.4 (quart., 176.3, 175.8). **MS (EI-MS, 70 eV)**: *m/z* (%) = 326.2 ($M^{+\cdot}$, 3), 308.2 ($[M\text{-}H_2O]^{+\cdot}$, 2), 91.1 ($C_7H_7^+$, 100). **HR-EIMS** Calcd. for $C_{21}H_{26}O_3$ [$M^{+\cdot}$]: 326.1882, Found: 326.1881. $[\alpha]_D^{22}$ - 44.3 (c 0.75, $CHCl_3$).



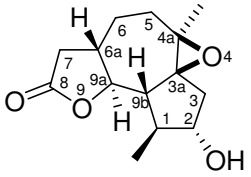
248

(1*S*,2*S*,3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-2-(benzyloxy)-1,4a-dimethyloctahydro-1*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (248)

244 (20 mg, 0.06 mmol) was dissolved in abs. CH_2Cl_2 (3 ml) and cooled down to -10°C.

*m*CPBA (18 mg, 0.10 mmol) was added at -10°C. The reaction mixture was warmed to ambient temperature slowly and stirred for 13 h. Et_2O (5 ml) was poured into the reaction mixture. Org. phase was separated and aqueous phase was extracted with Et_2O (5 ml). The combined org. phase was washed with sat. $NaHCO_3$ (3 ml) and brine (5 ml) successively. It was dried over Na_2SO_4, filtrated, concentrated under reduced pressure and purified by SiO_2 column chromatography (PE:EA = 2:1 + 0.5 % of Et_3N). **248** (12 mg, 57 %, *dr* = 82:18) was obtained as colorless oil.

TLC $\mathbf{R}_f$ = 0.58 (PE:EA = 1:1, Mostain). **^{1}H-NMR** (600MHz, $CDCl_3$): δ 1.12 (d, *J* = 7.1 Hz, 3H, 1-C*H*$_3$, diast.: 1.23), 1.31 (s, 3H, 4a-C*H*$_3$), 1.32-1.41 (m, 1H, 6B), 1.41-1.51 (m, 1H, 5A), 1.81-1.89 (m, 1H, 6A), 1.89-1.93 (m, 1H, 9b), 1.99-2.09 (m, 1H, 6a), 2.09 (dd, *J* = 15.4 Hz, 6.4 Hz, 1H, 3A, diast.: 1.75), 2.18 (dd, *J* = 15.4 Hz, 3.5 Hz, 1H, 3B, diast.: 2.38), 2.20-2.25 (m, 1H, 5B), 2.28 (dd, *J* = 16.5 Hz, 13.4 Hz, 1H, 7B, diast.: 2.22), 2.56 (dd, *J* = 16.5 Hz, 6.8 Hz, 1H, 7A, diast.: 2.47), 2.75-2.81 (m, 1H, 1), 3.82 (ddd, *J* = 6.4 Hz, 3.5 Hz, 2.8 Hz, 1H, 2, diast.: 3.50), 4.15 (dd, *J* = 10.8 Hz, 10.6 Hz, 1H, 9a, diast.: 4.05), 4.41 (d, *J* = 11.4 Hz, -OC*H*$_2$, diast.: 4.50), 4.63 (d, *J* = 11.4 Hz, -OC*H*$_2$, diast.: 4.57), 7.25-7.36 (m, 5H, aromatic). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 18.6 (+, 1-*C*H$_3$, diast.: 19.2), 21.3 (+, 4a-*C*H$_3$, diast.: 23.4), 25.8 (-, 6), 37.1 (-, 7, diast.: 36.4), 37.8 (-, 5), 38.1 (-, 3, diast.: 38.0), 40.5 (+, 1), 48.6 (+, 6a), 55.3 (+, 9b), 61.9 (quart., 4a), 71.0 (quart., 3a), 71.1 (-, -O*C*H$_2$, diast.: 71.2), 84.4 (+, 2), 85.4 (+, 9a, diast.: 86.0), 127.6 (+, *para*), 128.0 (+, *ortho*), 128.4 (+, *meta*), 138.2 (quart., *ipso*), 175.2 (quart., *C*=O). **IR (Film, cm^{-1})**: 3003, 2931, 2873, 1781, 1716, 1455, 1211, 1104, 991, 754. **MS (EI-MS, 70 eV)**: *m/z* (%) = 342.0 ($M^{+\cdot}$, 3), 252.9 (6), 236.0 (8), 218.0 (8), 180.9 (9), 91.0 ($C_7H_7^{+\cdot}$, 100). **HR-EIMS** Calcd. for $C_{21}H_{26}O_4$ [$M^{+\cdot}$]: 342.1831, Found: 342.1829. $[\alpha]_D^{22}$ + 123.1 (c 0.13, $CHCl_3$).



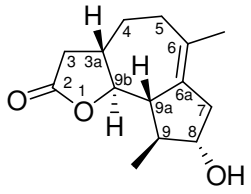
249

(1*S*,2*S*,3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-2-hydroxy-1,4a-dimethyloctahydro-1*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (249)

248 (10 mg, 0.03 mmol, *dr* = 82:18) was dissolved with abs. EtOH (1 ml) and this solution was purged through by N_2 for 2 min. The 20% $Pd(OH)_2$/C (3 mg) was poured at once into the reaction flask and N_2 was purged again for 2 min. It was stirred for 2.5 h at rt. Another portion of 20% $Pd(OH)_2$/C (2 mg) was added and the reaction mixture was stirred further for 1.5 h. It was filtrated through Celite® cake and the remained cake was washed with CH_2Cl_2

(3×5 ml). The combined filterate was washed with brine (2 ml), dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The desired product **249** (5.6 mg, 77 %, *dr* = 85:15) was obtained as white solid, which was recrystallized with CH_2Cl_2 and Et_2O.

TLC $\mathbf{R}_f$ = 0.17 (PE:EA = 1:1, Mostain). **m.p.**= 148-149 °C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.14 (d, $J_{1\text{-}Me/1}$ = 7.0 Hz, 3H, 1-CH_3), 1.34 (s, 3H, 4a-CH_3), 1.35-1.51 (m, 2H, 5B, 6B), 1.59 (br, OH), 1.87-1.94 (m, 2H, 6A, 9b), 2.01 (dd, $J_{3A/3B}$ = 15.1 Hz, $J_{3A/2}$ = 6.1 Hz, 3A), 2.00-2.08 (m, 1H, 6a), 2.13 (dd, $J_{3B/3A}$ = 15.1 Hz, $J_{3B/2}$ = 4.6 Hz, 3B), 2.25 (m, 1H, 5A), 2.32 (dd, $J_{7B/7A}$ = 16.7 Hz, $J_{7B/6a}$ = 13.4 Hz, 1H, 7B), 2.38 (ddq, $J_{1/1\text{-}Me}$ = 7.0 Hz, $J_{1/9b}$ = 3.7 Hz, $J_{1/2}$ = 3.4 Hz, 1H, 1), 2.58 (dd, $J_{7A/7B}$ = 16.7 Hz, $J_{7A/6a}$= 6.8 Hz, 1H, 7A), 4.13 (ddd, $J_{2/3A}$= 6.1 Hz, $J_{2/3B}$= 4.6 Hz, $J_{2/1}$= 3.4 Hz, 1H, 2), 4.18 (dd, $J_{9a/6a}$ = 11.2 Hz, $J_{9a/9b}$ = 10.3 Hz, 1H, 9a). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 18.3 (+, 1-CH_3), 21.2 (+, 4a-CH_3), 25.9 (-, 6-C), 37.1 (-, 7-C), 37.9 (-, 5-C), 39.7 (-, 3-C), 45.7 (+, 1-C), 48.5 (+, 6a-C), 55.2 (+, 9b-C), 62.0 (quart., 4a-C), 70.8 (quart., 3a-C), 77.5 (+, 2-C), 85.9 (+, 9a-C), 175.3 (quart., 8-C).). **IR (Film, cm^{-1})**: 3362, 2946, 2834, 1659, 1450, 1416, 1113, 1028. **MS (EI-MS, 70 eV)**: *m/z* (%) = 252.1 ($M^{+\cdot}$, 5), 234.0 ([M-H_2O]$^{+\cdot}$, 12), 205.9 (16), 180.9 (18), 148.9 (14), 139.1 (39), 138.0 (69), 110.9 (100), 96.8 (57), 69.1 (32), 55.0 (63), 41.0 (52). **HR-EIMS** Calcd. for $C_{14}H_{20}O_4$ [$M^{+\cdot}$]: 252.1362, Found: 252.1364. $[\alpha]_D^{22}$ + 42.6 (c 0.54, $CHCl_3$).



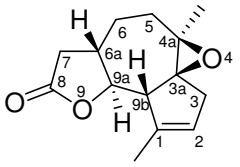
250

(3a*S*,8*S*,9*S*,9a*S*,9b*S*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (250)

249 (20 mg, 0.08 mmol) was added to the mixture solution of PPh_3 (23 mg, 0.09 mmol) and I_2 (17 mg, 0.07 mmol) in CH_3CN (2 ml). The reaction mixture was stirred at rt. for 17 h and concentrated under reduced pressure. It was diluted with H_2O, and extracted with Et_2O (2×5 ml). After washing with 10 % $NaHCO_3$ (2×3 ml), the dried org. phase was concentrated and subjected to column chromatography (PE:EA = 3:1) to give **250** (6.6 mg, 35 %) as an colorless oil.

TLC $\mathbf{R}_f$ = 0.36 (PE:EA = 1:1, Mostain). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.13 (d, 3H, 9-CH_3), 1.31 (m, 1H, 4B), 1.62 (br s, OH), 1.73 (m, 1H, 6-CH_3), 1.85 (m, 1H, 4A), 2.06 (ddd, *J* = 14.9 Hz, 5.9 Hz, 1.8 Hz, 1H, 5), 2.10 (m, 1H, 9), 2.14-2.22 (m, 2H, 3a, 5), 2.37 (m, 1H, 9a), 2.54 (dd, *J* = 16.1 Hz, 6.3 Hz, 1H, 3A), 2.68 (dd, *J* = 15.8 Hz, 5.6 Hz, 1H, 7A), 3.75 (ddd, *J* = 7.3 Hz, 6.3 Hz, 5.6 Hz, 1H, 8), 3.81 (dd, *J* = 11.1 Hz, 9.1 Hz, 1H, 9b). **^{13}C-NMR** (150.9 MHz,

$CDCl_3$): δ 18.6 (+, 9-*C*H_3), 32.9 (+, 6-*C*H_3), 28.3 (-, 4-C), 34.7 (-, 5-C), 37.2 (-, 3-C), 39.7 (-, 7-C), 46.4 (+, 9-C), 49.4 (+, 3a-C), 53.2 (+, 9a-C), 78.0 (+, 8-C), 87.7 (+, 9b-C), 132.7 (quart., 6-C), 133.0 (quart., 6a-C), 176.0 (quart., *C*=O). **IR (Film, cm^{-1})**: 3392, 3020, 1773, 1422, 1216, 1062, 757, 667. **MS (EI-MS, 70 eV)**: *m/z* (%) = 236.1 ($M^{+\cdot}$, 11), 218.1 ($[M-H_2O]^{+\cdot}$, 11), 203.1 ($[M-CH_3]^{+\cdot}$, 4), 28.1 (100). **HR-EIMS** Calcd. for $C_{14}H_{20}O_3$ [$M^{+\cdot}$]: 236.1412, Found: 236.1413. $[\alpha]_D^{21}$ + 39.4 (c 0.66, $CHCl_3$)

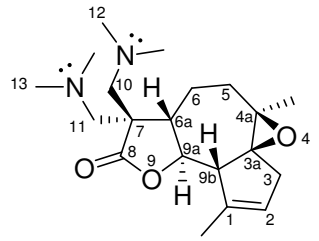


251

(3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (251)

To a solution of **249** (20 mg, 0.08 mmol) and anhyd. pyridine (64 µl, 0.79 mmol) in abs. CH_2Cl_2 (2 ml), which was cooled down to 0°C for 15 min. Tf_2O (40 µl, 0.238 mmol) was added by syringe at 0°C under Ar atmosphere. It was stirred for 19 h at rt. The reaction was quenched by sat. $NaHCO_3$ (2 ml) and the separated aqueous phase was extracted with CH_2Cl_2 (5 ml). The combined org. phase was washed with sat. $NaHCO_3$ (5 ml), brine (5 ml), dried over Na_2SO_4, filtrated and concentrated. The concentrated mixture was purified by column chromatography (SiO_2, PE:EA = 2:1). The desired **251** (7.5 mg, 41 %, *dr* = 100:0) was obtained as yellow oil.

TLC $\mathbf{R}_f$ = 0.55 (PE:EA = 1:1, Vanillin sulfuric acid). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.33 (s, 3H, 4a-CH_3), 1.36-1.45 (m, 1H, 6B), 1.46-1.53 (m, 1H, 5A), 1.90-1.96 (m, 4H, 6A, 1-CH_3), 2.11-2.21 (m, 2H, 3A, 6a), 2.25 (dd, $J_{7B/7A}$ = 16.2 Hz, $J_{7B/6a}$ = 13.2 Hz, 1H, 7B), 2.24-2.29 (m, 1H, 5B), 2.56 (dd, $J_{7A/7B}$ = 16.2 Hz, $J_{7A/6a}$= 6.6 Hz, 1H, 7A), 2.56-2.60 (m, 1H, 9b), 2.85 (br d, 1H, 3B), 3.82 (dd, *J* = 10.5 Hz, 10.3 Hz, 1H, 9a), 5.56 (br s, 1H, 2). **^{13}C-NMR** (75.5 MHz, $CDCl_3$): δ 18.1 (+, 1-*C*H_3), 20.8 (+, 4a-*C*H_3), 26.2 (-, 6-C), 36.4 (-, 7-C), 37.9 (-, 5-C), 38.4 (-, 3-C), 48.4 (+, 6a-C), 57.0 (+, 9b-C), 62.7 (quart., 4a-C), 72.1 (quart., 3a-C), 86.6 (+, 9a-C), 124.5 (+, 2-C), 141.2 (quart., 1-C), 175.4 (quart., 8-C). **IR (Film, cm^{-1})**: 2959, 2928, 2859, 1726, 1460, 1269, 1123, 1073, 797. **MS (PI-EIMS, 70 eV)**: *m/z* (%) = 234.2 ($M^{+\cdot}$, 58), 96.1 (100). **HR-EIMS** Calcd. for $C_{14}H_{20}O_4$ [$M^{+\cdot}$]: 234.1256, Found: 254.1254. $[\alpha]_D^{22}$ + 55.2 (c 0.67, $CHCl_3$).

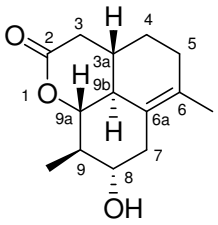


263

(3a*S*,4a*R*,6a*S*,9a*R*,9b*R*)-7,7-bis[(dimethylamino)methyl]-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (263)

LDA (5.0 eq.) in 0.5 ml of THF was freshly prepared at 0°C and cooled down to -78°C. The solution of **251** (17 mg, 0.07 mmol) in THF (0.8 ml) was transferred into LDA solution at -78°C and it was stirred for 15 min at the same temperature. *Eschenmoser*'s salt (10 eq.) was dissolved with 2 ml of THF. The solution was syringed carefully from the remaining emulsion and injected into the reaction mixture at -78°C. The reaction mixture was stirred for 5 h till the temperature reached at rt. The reaction was quenched with sat. $NaHCO_3$ (2 ml) and it was extracted with CH_2Cl_2 (5×10 ml). The combined org. phase was washed with sat. $NaHCO_3$ (10 ml), brine (10 ml). Column chromatography on a flash silica gel was carried out (EA + 1% of Et_3N). **263** (7.8 mg, 31%) was obtained light brown oil.
TLC $\mathbf{R_f}$ = 0.19 (EA, Vanillin sulfuric acid). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 1.15-1.22 (m, 1H, 6A), 1.31-1.35 (s, 3H, 4a-C*H*$_3$), 1.49-1.54 (m, 1H, 5A), 1.53-1.67 (m, 1H, 6B), 1.92-2.00 (m, 3H, 1-C*H*$_3$), 2.07-2.13 (d, *J* = 13.9 Hz, 1H, 10), 2.08-2.16 (m, 1H, 3A), 2.20 (s, 6H, 12/13-C*H*$_3$), 2.22 (s, 6H, 13/12-C*H*$_3$), 2.23-2.29 (d, *J* = 13.8 Hz, 1H, 11), 2.26-2.33 (m, 1H, 5B), 2.37-2.42 (d, *J* = 13.8 Hz, 1H, 11), 2.44-2.51 (m, 1H, 6a), 2.48-2.53 (d, *J* = 11.0 Hz, 1H, 9b), 2.59-2.65 (d, *J* = 13.9 Hz, 1H, 10), 2.82-2.90 (m, 1H, 3B), 4.33 (dd, 1H, 9a), 5.55 (m, 1H, 2). **^{13}C-NMR** (100.6 MHz, $CDCl_3$): δ 18.3 (+, 1-*C*H$_3$), 21.0 (+, 4a-*C*H$_3$), 21.5 (-, 6-C), 38.4 (-, 5-C), 38.5 (-, 3-C), 47.7 (+, 2×*C*H$_3$, 12/13), 48.1 (+, 2×*C*H$_3$, 13/12), 51.1 (+, 6a-C), 52.2 (quart., 7-C), 58.2 (+, 9b-C), 61.2 (-, 10-C), 62.3 (-, 11-C), 63.1 (quart., 4a-C), 72.4 (quart., 3a-C), 83.7 (+, 9a-C), 124.1 (+, 2-C), 141.8 (quart., 1-C), 180.3 (quart., 8-C). **IR (Film, cm^{-1})**: 3410, 2930, 2775, 1768, 1456, 1379,1019, 874. **MS (CI-MS, NH$_3$)**: *m/z* (%) = 349.3 ($MH^{+\cdot}$, 100), 292.2 (4), 102.3 (4). **HR-PI-EIMS** Calcd. for $C_{20}H_{32}N_2O_3$ [$M^{+\cdot}$]: 348.2413, Found: 348.2405.

$[\alpha]_D^{22}$ + 23.1 (c 0.13, $CHCl_3$).



247

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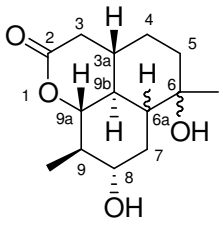


265

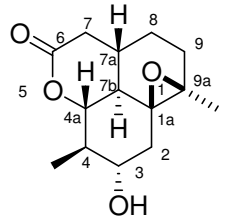
(3a*S*,8*R*,9*R*,9a*R*,9b*R*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (247)

244 (60 mg, 0.18 mmol) was dissolved in abs. CH_2Cl_2 (5 ml) under Ar atmosphere, and then it was cooled down to 0°C. Anhyd. $FeCl_3$ (29 mg, 0.18 mmol) was added under Ar atmosphere at 0°C. Another portions of anhyd. $FeCl_3$ (1 eq. and 3 eq.) were added in the reaction time of 14 h and 18 h, respectively. H_2O (1.0 ml) and CH_2Cl_2 (10 ml) were poured into the reaction mixture. Org. phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 ml). The combined org. phase was washed with brine (10 ml), dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Flash column chromatography (PE:EA = 1:1) afforded **247** (31 mg, 71 %) and **265** (29 %) as solid.
TLC $\mathbf{R}_f$ = 0.31 (**247**, PE:EA = 1:1, Mostain). **^{1}H-NMR** of **247** (300 MHz, $CDCl_3$): δ 1.20 (d, $J_{9\text{-}Me/9}$ = 6.4 Hz, 3H, 9-C*H*$_3$), 1.66 (s, 3H, 6-C*H*$_3$), 1.68-1.78 (m, 2H), 1.79 1.90 (m, 2H), 1.91-2.17 (m, 4H), 2.20 (dd, *J* = 18.3 Hz, 12.2 Hz, 1H, 7B), 2.73 (dd, *J* = 18.3 Hz, 5.2 Hz, 1H, 7A), 2.92 (dd, *J* = 14.0 Hz, 4.7 Hz, 1H, 3A), 3.11 (ddd, *J* = 10.8 Hz, 10.4 Hz, 4.6 Hz , 1H, 8), 3.42 (dd, *J* = 10.4 Hz, 10.4 Hz, 1H, 9a). **^{13}C-NMR** of **247** (75.5 MHz, $CDCl_3$): δ 13.5 (+, 9-*C*H$_3$), 19.2 (+, 6-*C*H$_3$), 27.6 (-), 31.6 (-), 34.9 (+), 36.9 (-), 37.8 (-), 44.7 (+), 44.9 (+), 72.5 (+, 8-C), 86.6 (+, 9a-C), 122.0 (quart., 6-C), 130.7 (quart., 6a-C), 170.9 (quart., 2-C). **MS** of **247** **(EI-MS, 70 eV)**: *m/z* (%) = 236.0 ($M^{+\cdot}$, 4), 218.0 ($[M\text{-}H_2O]^{+\cdot}$, 7), 175.9 (19), 159.2 (100), 158.1 (94), 143.1 (44), 91.1 (26), 28.1 (62). **HR-EIMS** of **247** Calcd. for $C_{14}H_{20}O_3$ [$M^{+\cdot}$]: 236.1412, Found: 256.1408. $[\alpha]_D^{20}$ + 98.5 (c 0.54, $CHCl_3$).

(3a*S*,8*R*,9*R*,9a*R*,9b*R*)-6,8-dihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (265)

TLC $\mathbf{R}_f$ = 0.16 (**265**, PE:EA = 1:1, Mostain). **^{1}H-NMR** of **265** (300 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.3 Hz, 3H, 9-C*H*$_3$), 1.18-1.28 (m, 1H), 1.60 (s, 3H, 6-C*H*$_3$), 1.40-1.74 (m, 7H), 1.75-1.95 (br s, 1H, O*H*), 2.20-2.33 (m, 3H), 2.74 (dd, *J* = 18.5 Hz, 4.8 Hz, 1H), 3.30 (ddd, *J* = 11.0 Hz, 10.3 Hz, 4.4 Hz, 1H), 3.56 (dd, *J* = 10.2 Hz, 10.2 Hz, 1H, diast.: 3.65, *J* = 10.4 Hz). **^{13}C-NMR** of **265** (75.5 MHz, $CDCl_3$): δ 13.7 (+, 9-*C*H$_3$), 28.0 (-), 31.3 (+, 6-C*H*$_3$), 35.0 (-), 35.4 (+), 36.9 (-), 41.4 (-), 42.2 (+), 45.3 (+), 72.8 (quart., 6-C), 73.0 (+), 85.4 (+), 170.3 (quart., *C*=O). IR (Film, cm^{-1}): 3418, 2930, 1723, 1233, 1016, 756. **MS** of **265** **(EI-MS, 70 eV)**: *m/z*

(%) = 236.0 ($M^{+\cdot}$, 4), 218.0 ($[M\text{-}H_2O]^{+\cdot}$, 7), 175.9 (19), 159.2 (100), 158.1 (94), 143.1 (44), 91.1 (26), 28.1 (62).

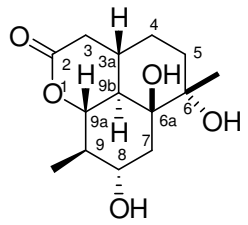


267

(1a*S*,3*R*,4*R*,4a*S*,7a*S*,7b*S*,9a*R*)-3-hydroxy-4,9a-dimethyloctahydro-2*H*-[1]benzoxireno[3,2,1a-*de*]chromen-6(7*H*)-one (267)

247 (25 mg, 0.11 mmol) was dissolved with abs. CH_2Cl_2 (3 ml) and the solution was cooled to -10°C. *m*CPBA (29.4 mg, 0.17 mmol) was added at the same temperature. The reaction mixture was stirred for 14 h at rt. Et_2O (5 ml) was poured into the mixture. The separated and combined org. phase was washed with sat. $NaHCO_3$ (2×3 ml), brine (5 ml) subsequently. It was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Column chromatography (SiO_2, PE/EA = 1:1 + 1% of Et_3N) afforded **267** (18 mg, 67 %, *dr* = 89:11) as white solid. It was recrystallized in Et_2O (2 ml) at -27°C.

TLC $\mathbf{R}_f$ = 0.49 (EA, Mostain). **m.p.** = 176-178°C. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 1.06 (dddd, $J_{8B/8A}$= 13.2 Hz, $J_{8B/7a}$= 12.3 Hz, $J_{8B/9A}$= 12.3 Hz, $J_{8B/9B}$= 7.3 Hz, 1H, 8B), 1.27 (d, J = 6.3 Hz, 3H, 4-CH_3), 1.35 (s, 3H, 9a-CH_3), 1.51-1.57 (m, 2H, 8A, 7b), 1.72 (ddq, $J_{4/3}$ = 10.3 Hz, $J_{4/4a}$ = 10.3 Hz, $J_{4/4\text{-}Me}$ = 6.3 Hz, 1H, 4), 1.82 (dd, $J_{2B/2A}$ = 13.3 Hz, $J_{2B/3}$ = 11.4 Hz, 1H, 2B), 1.88 (m, 1H, 9B), 1.94 (dd, $J_{2A/2B}$ = 13.3 Hz, $J_{2A/3}$ = 4.7 Hz, 1H, 2A), 1.98 (ddd, $J_{9A/9B}$ = 15.6 Hz, $J_{9A/8B}$ = 12.3 Hz, $J_{9A/8A}$ = 7.3 Hz, 1H, 9A), 2.09 (dd, $J_{7B/7A}$ = 18.3 Hz, $J_{7B/7a}$ = 12.4 Hz, 1H, 7B), 2.71 (dd, $J_{7A/7B}$ = 18.3 Hz, $J_{7A/7a}$ = 5.8 Hz, 1H, 7A), 3.56 (ddd, $J_{3/2B}$ = 11.3 Hz, $J_{3/4}$ = 10.3 Hz, $J_{3/2A}$ = 4.7 Hz, 1H, 3), 3.84 (dd, $J_{4a/7b}$ = 11.0 Hz, $J_{4a/4}$ = 10.3 Hz, 1H, 4a). **^{13}C-NMR** (150.9 MHz, $CDCl_3$): δ 13.5 (+, 4-CH$_3$), 20.7 (+, 9a-CH$_3$), 27.5 (-, 8-C), 28.7 (+, 7a-C), 29.2 (-, 9-C), 36.8 (-, 7-C), 37.7 (-, 2-C), 45.0 (+, 7b-C), 45.6 (+, 4-C), 61.2 (quart., 9a-C), 62.6 (quart., 1a-C), 71.4 (+, 3-C), 83.0 (+, 4a-C), 170.1 (quart., 6-C). **IR (KBr, cm^{-1})**: 3408, 3323, 2925, 1732, 1690, 1233, 1055, 799, 645. **MS (EI-MS, 70 eV)**: *m/z* (%) = 252.1 ($M^{+\cdot}$, 26), 234.1 ($[M\text{-}H_2O]^{+\cdot}$, 25), 194.1 (100), 165.9 (25), 79.0 (28), 43.0 (84). **HR-EIMS** Calcd. for $C_{14}H_{20}O_4$ [$M^{+\cdot}$]: 252.1362, Found: 252.1364. $[\alpha]_D^{21}$ + 44.8 (c 0.42, $CHCl_3$).



268

(3a*S*,6*R*,6a*S*,8*R*,9*R*,9a*S*,9b*S*)-6,6a,8-trihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (268)

267 (19 mg, 0.07 mmol) and PPh_3 (23.6 mg, 0.09 mmol) were dissolved with abs. THF (1 ml), and the resulting colorless solution was cooled down to 0°C. In 15 min stirring, DEAD (14.2 µl, 0.09 mmol) was added dropwise, and followed by addition of MeI (5.6 µl, 0.09 mmol). It was stirred for 4.5 h at rt. An additional MeI (5.6 µl) was added into reaction mixture. Another portion of PPh_3 (23.6 mg, 0.09 mmol), DEAD (14.2 µl, 0.09 mmol) and MeI (11 µl) were added sequentially at 0°C. The reaction mixture was stirred totally for 92 h at rt. The reaction mixture was concentrated under reduced pressure. Column chromatography (SiO_2, PE/EA = 1:1) afforded **268** (9 mg, 44 %) as white solid.
TLC $\mathbf{R}_f$ = 0.16 (EA, Mostain). **^{1}H-NMR** (600 MHz, Acetone-d_6): δ 1.14 (d, J = 6.2 Hz, 3H, 9-CH_3), 1.20 (s, 3H, 6-CH_3), 1.39 (m, 1H, 5), 1.41-1.51 (m, 3H, 4, 9), 1.70 (dd, $J_{9b/3a}$ = 11.2 Hz, $J_{9b/9a}$ = 10.6 Hz, 1H, 9b), 1.78 (dd, $J_{7B/7A}$ = 13.1 Hz, $J_{7B/8}$ = 11.6 Hz, 1H, 7B), 1.99 (m, 1H, 5), 2.03 (m, 1H, 3), 2.03-2.09 (m, 2H, 3a-H, 7A), 2.58 (m, 1H, 3), 3.50-3.54 (m, 6, 6a-OH), 3.54-3.61 (m, 1H, 8), 3.75 (m, 8-OH), 3.95 (dd, $J_{9a/9b}$ = 10.6 Hz, $J_{9a/9}$ = 10.6 Hz, 9a). **^{13}C-NMR** (150.9 MHz, Acetone-d_6): δ 14.3 (+, 9-CH$_3$), 23.8 (+, 6-CH$_3$), 28.4 (-, 4-C), 30.1 (+, 3a-C), 34.9 (-, 5-C), 37.7 (-, 3-C), 39.8 (-, 7-C), 44.3 (+, 9b-C), 46.9 (+, 9-C), 70.9 (+, 8-C), 72.9 (quart., 6-C), 74.4 (quart., 6a-C), 83.9 (+, 9a-C), 170.2 (quart., 2-C). **IR (KBr, cm^{-1})**: 3423, 2932, 2361, 1715, 1256, 1088, 1011, 903, 810. **MS (EI-MS, 70 eV)**: *m/z* (%) = 270.0 ($M^{+\cdot}$, 10), 252.0 ([M-H_2O]$^{+\cdot}$, 39), 234.1 ([M-2H_2O]$^{+\cdot}$, 36), 223.9 ([M$^{\cdot}$-H_2O-CO_2]$^{+\cdot}$, 20), 211.0 (42), 199.0 (100), 193.9 (96), 134.9 (38), 109.1 (50), 95.1 (32), 81.1 (39), 71.0 (59), 55.1 (44).

HR-EIMS Calcd. for $C_{14}H_{22}O_5$ [$M^{+\cdot}$]: 270.1467, Found: 270.1469. $[\alpha]_D^{21}$ - 5.5 (c 0.18, MeOH)

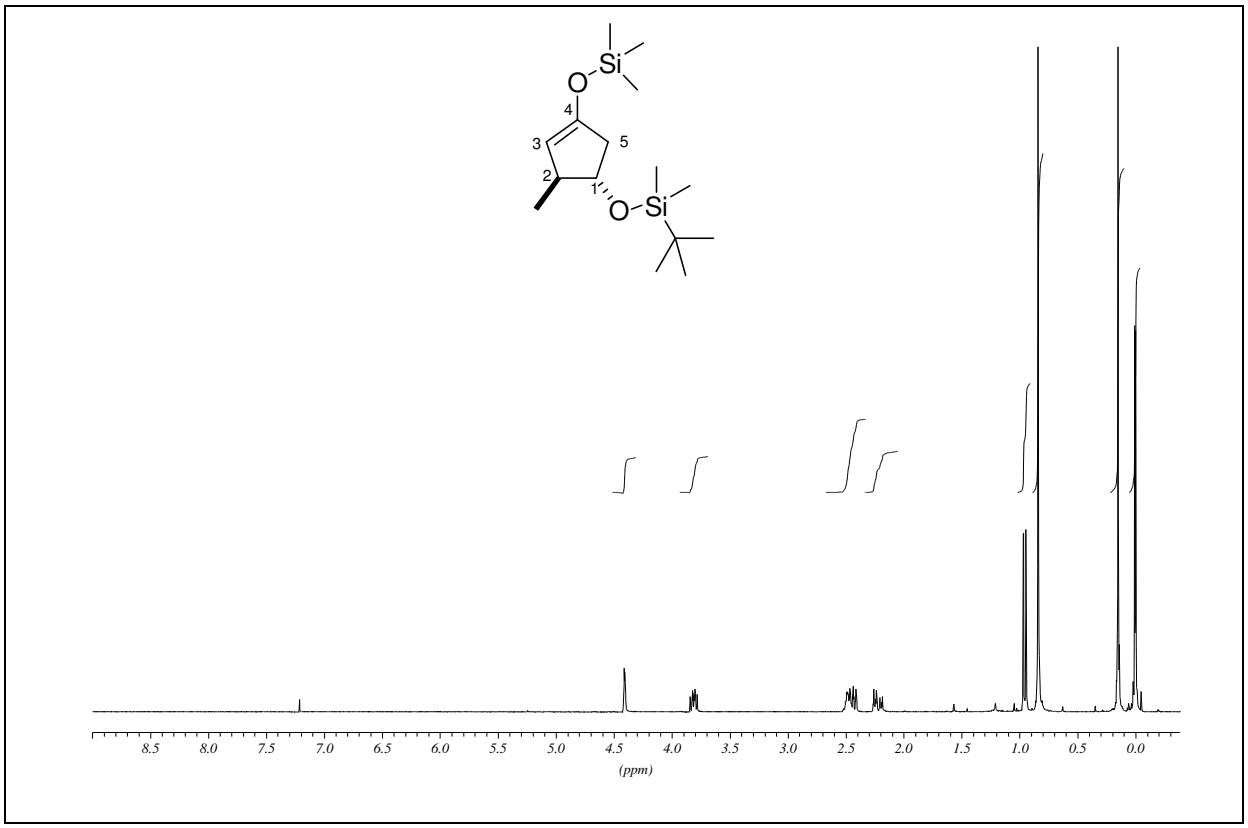
E. Appendix

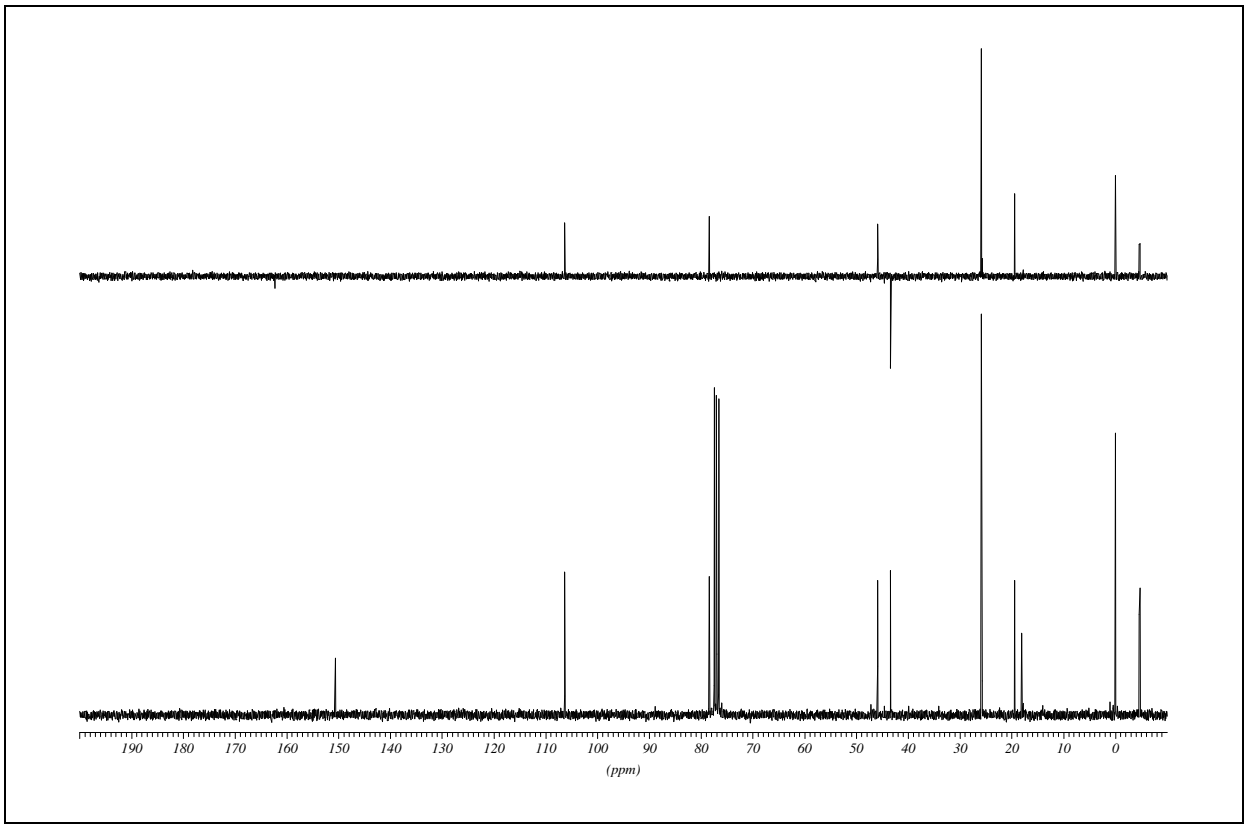
1. NMR spectra

^{1}H-NMR Spectra (Upper figure)

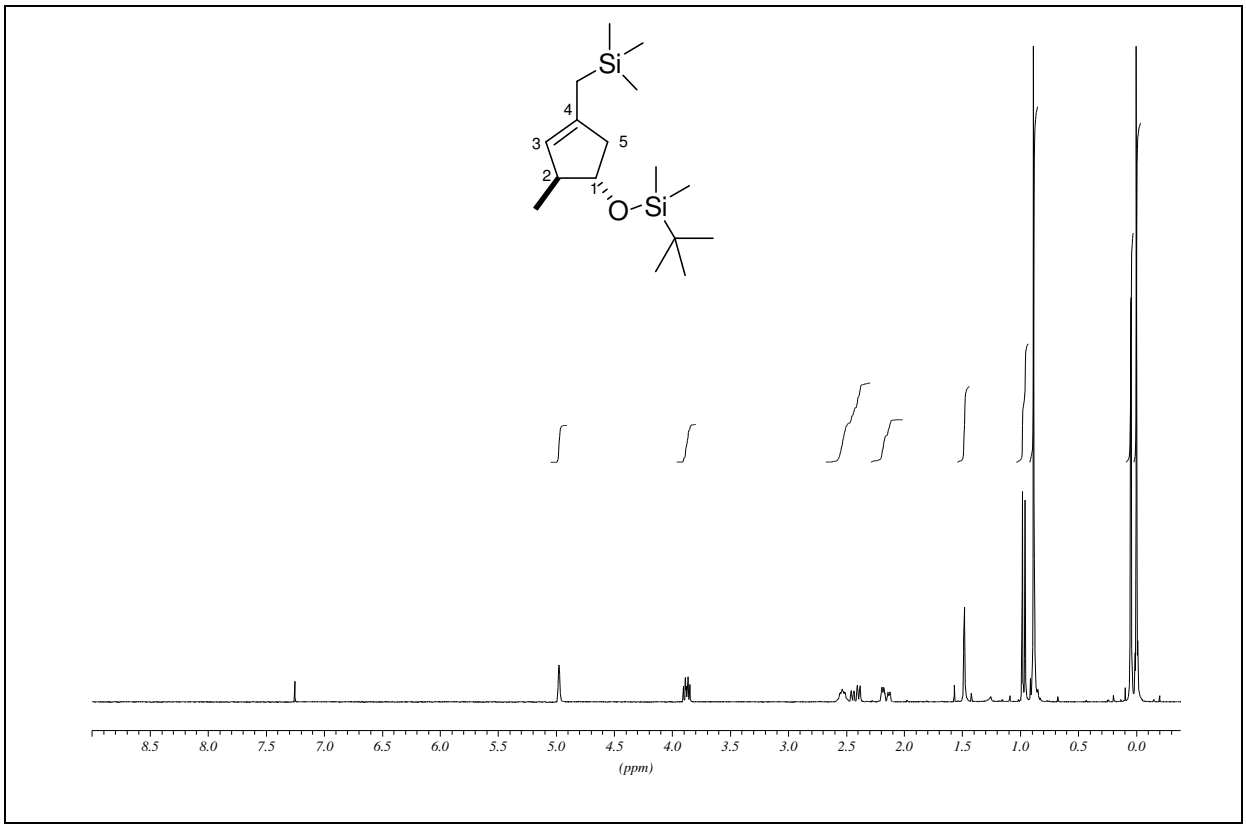
^{13}C-NMR and DEPT 135 Spectra (Down figure)

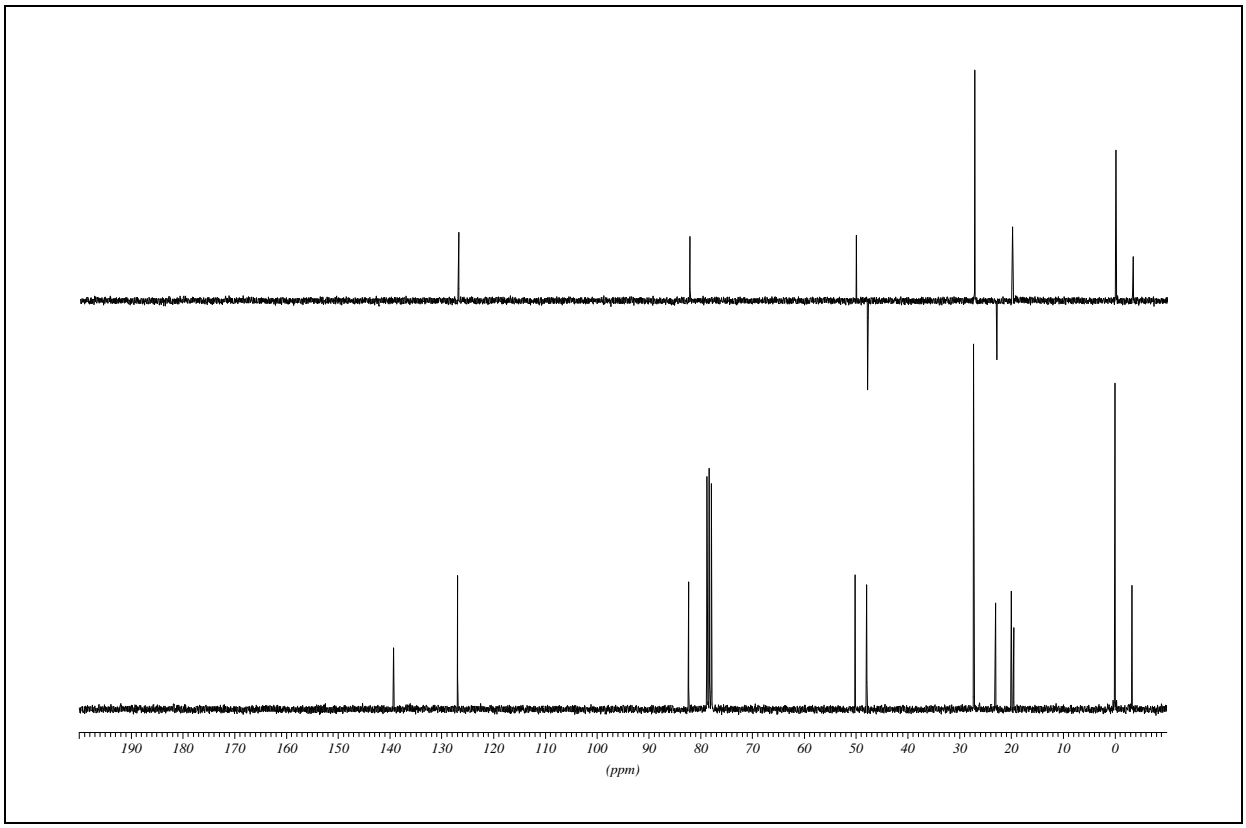
tert-butyl(dimethyl)({2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)silane ((*rac*)-**146b**)



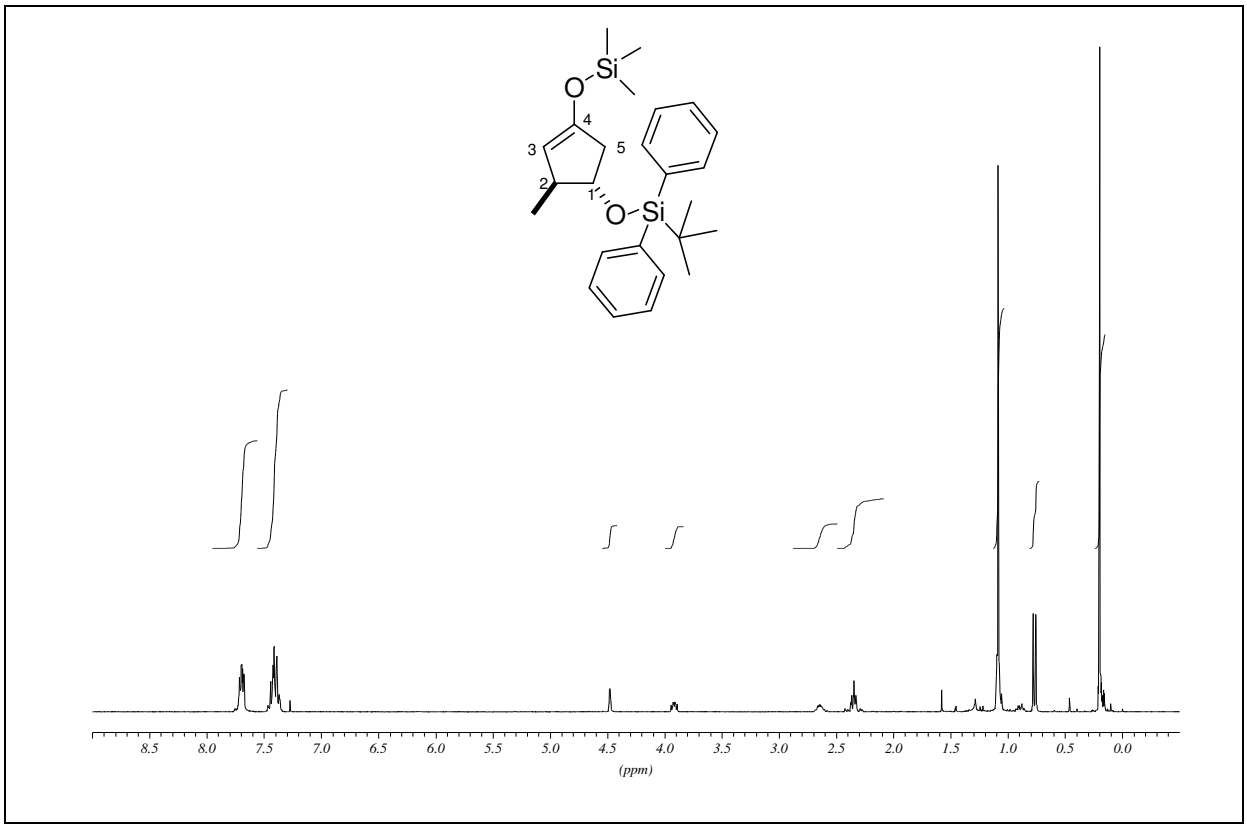


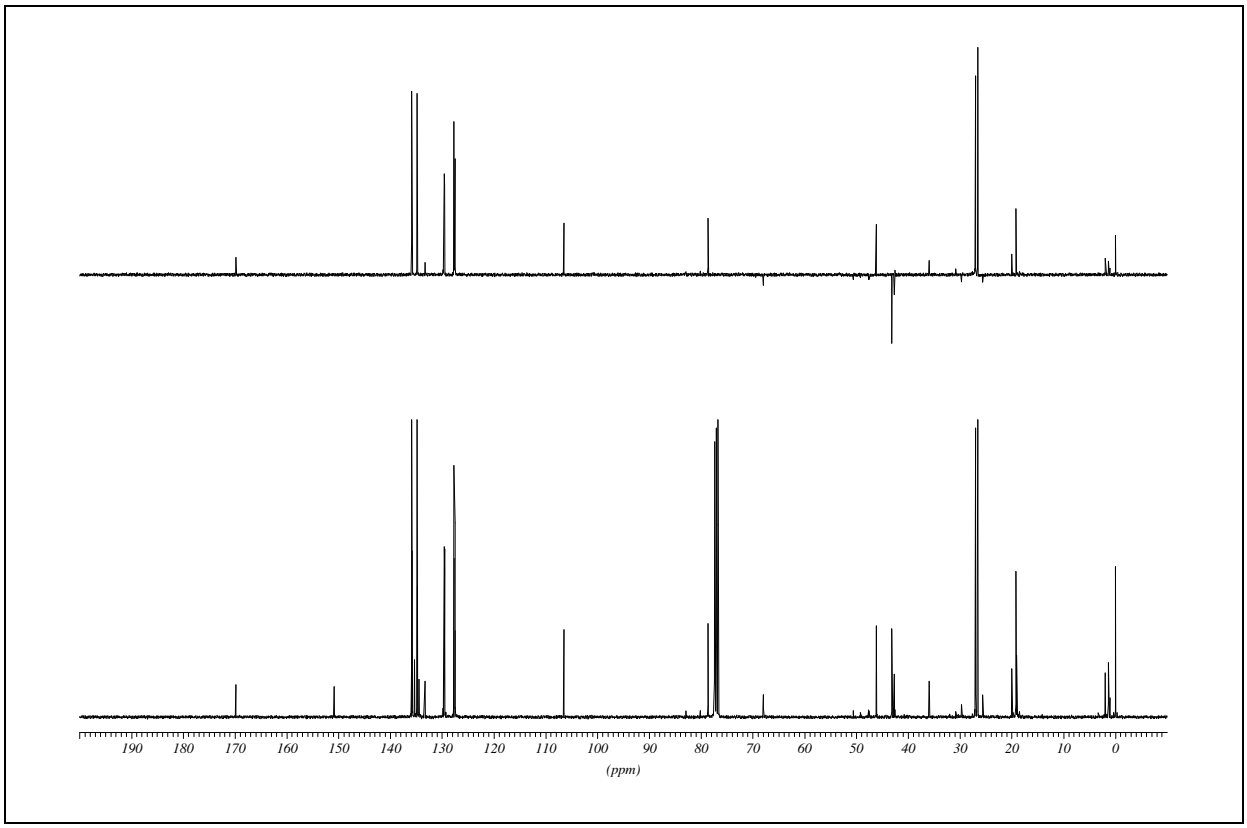
tert-butyl(dimethyl)({2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl}oxy)silane ((*rac*)-**103b**)



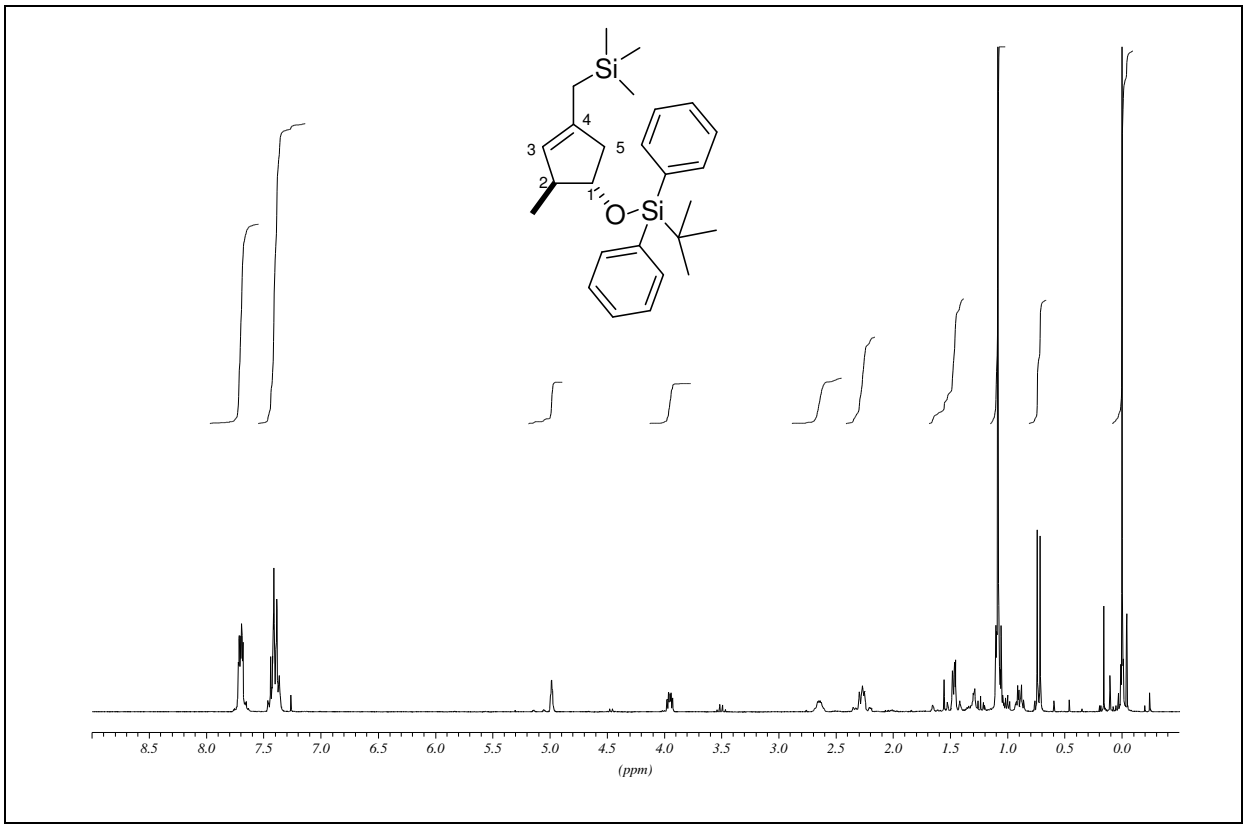


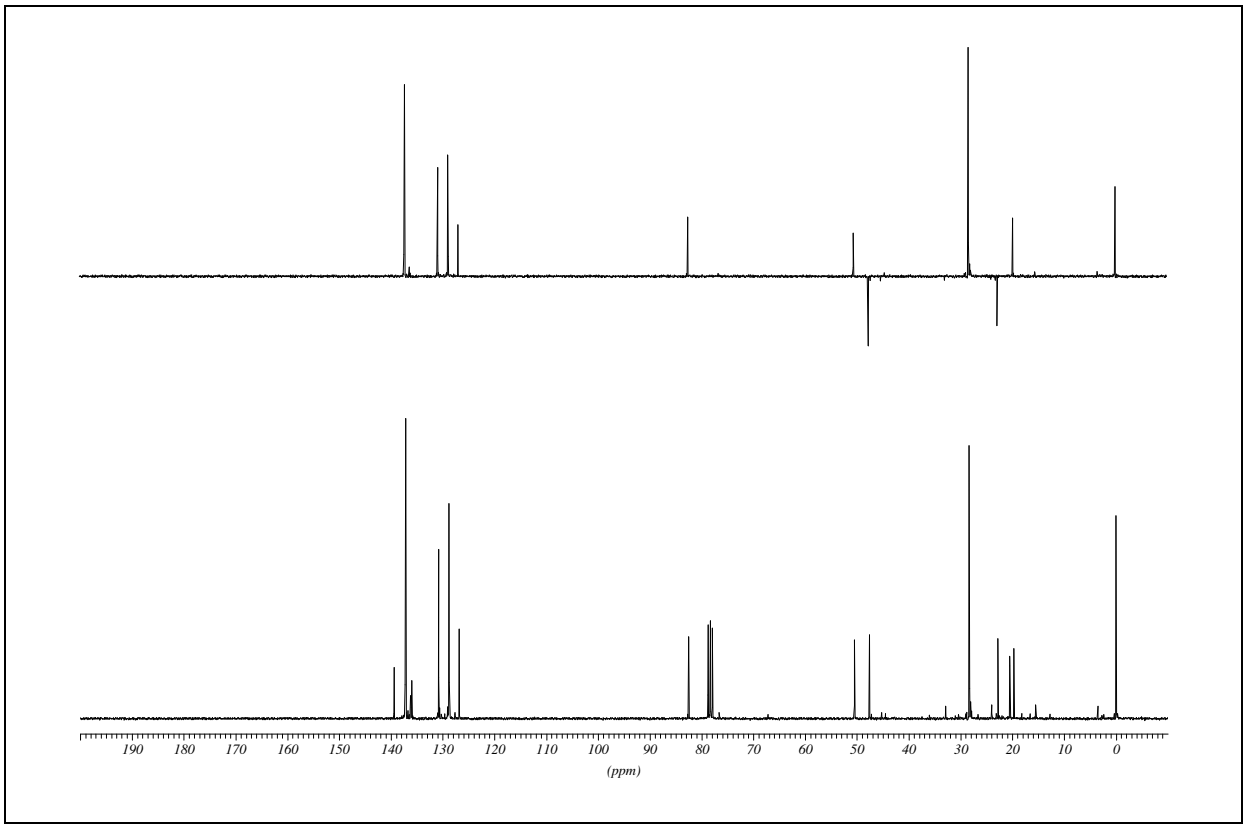
tert-butyl({2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl}oxy)diphenylsilane (**146a**)



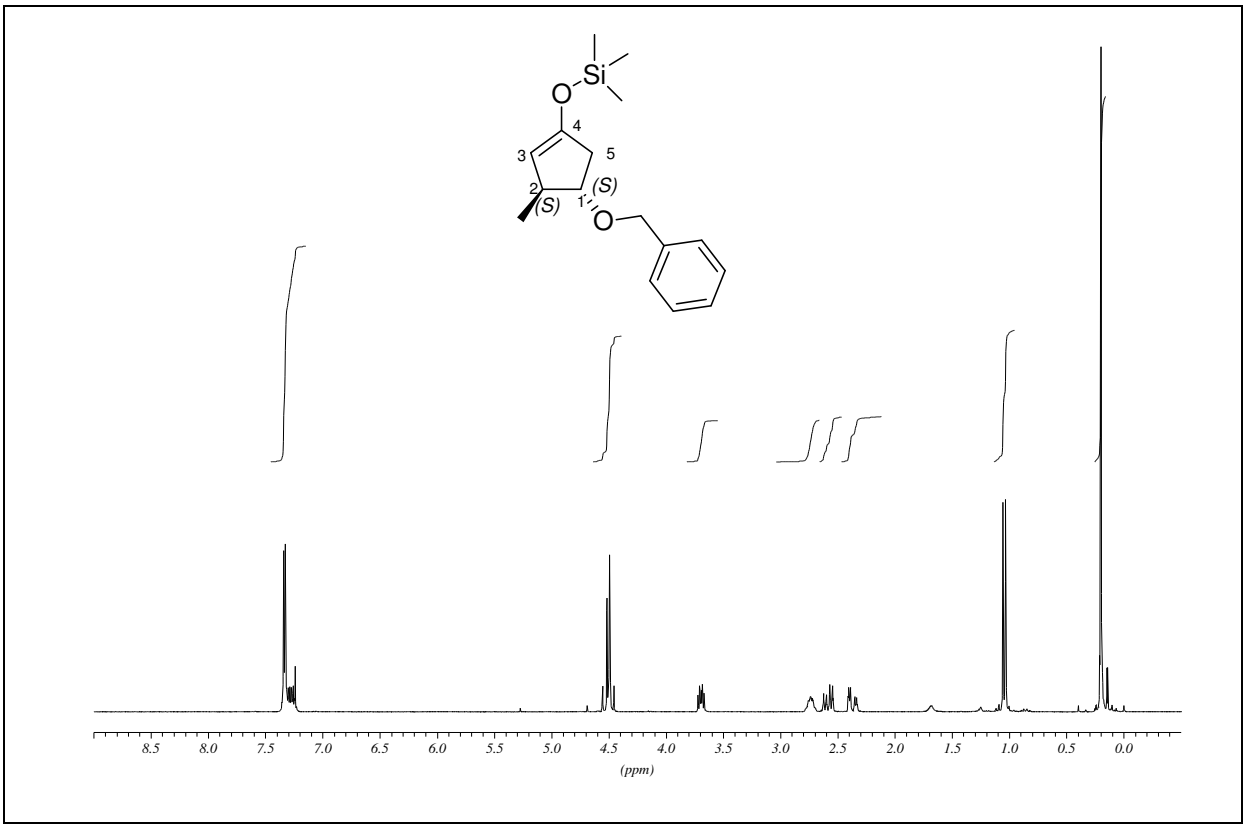


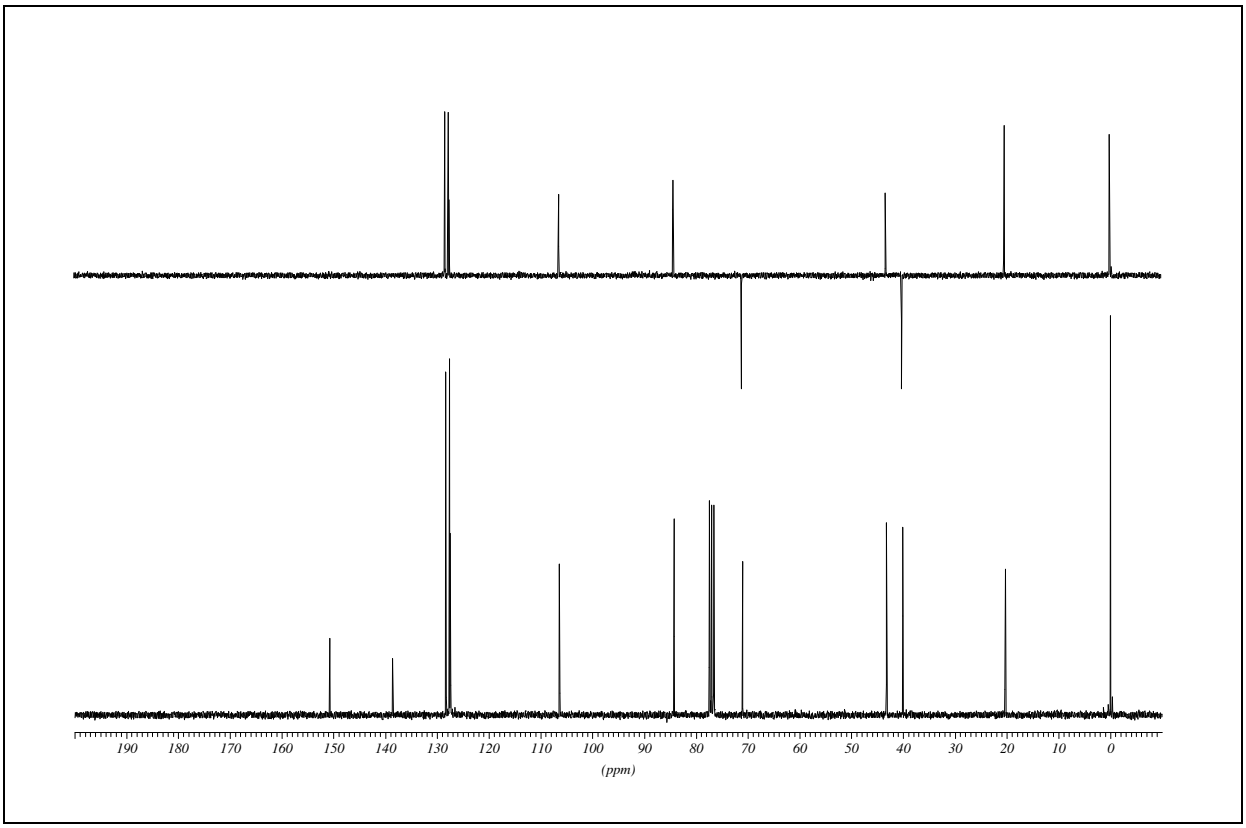
tert-butyl({2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl}oxy)diphenylsilane (**103a**)



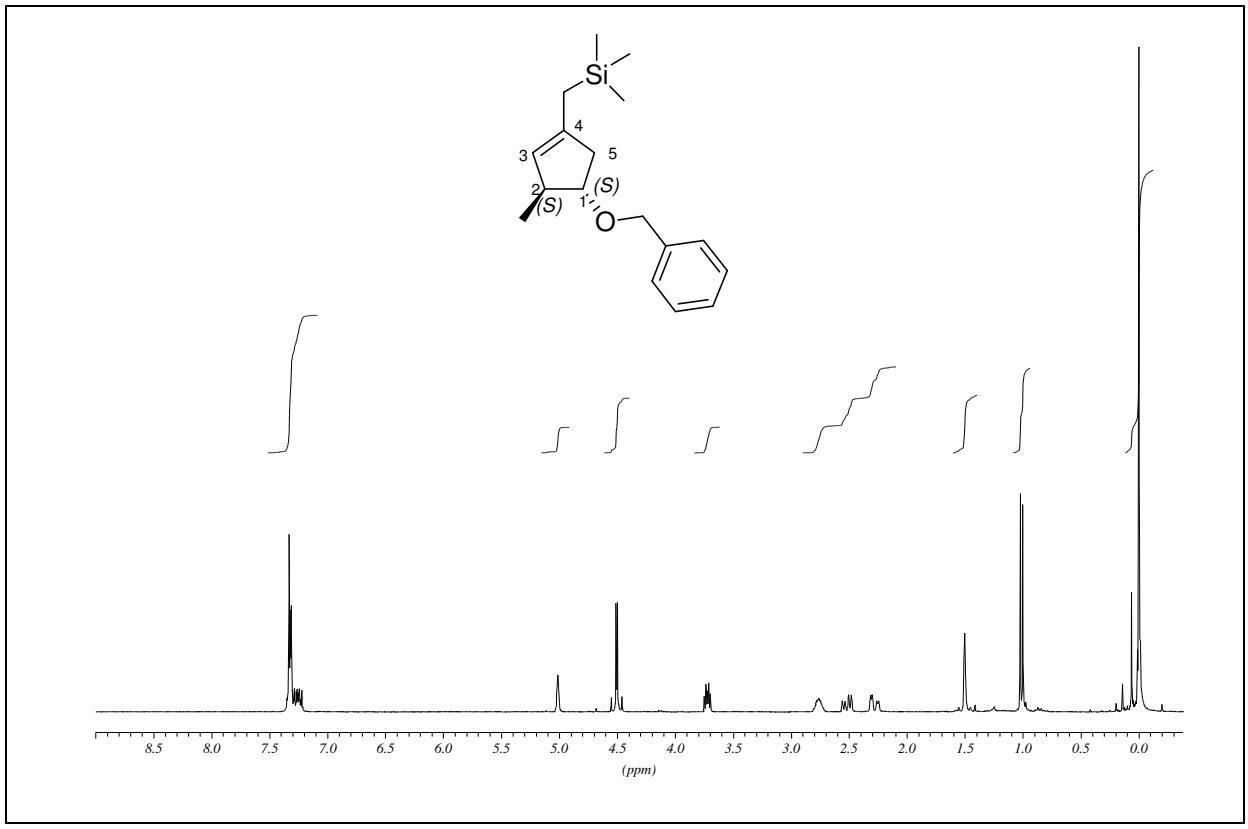


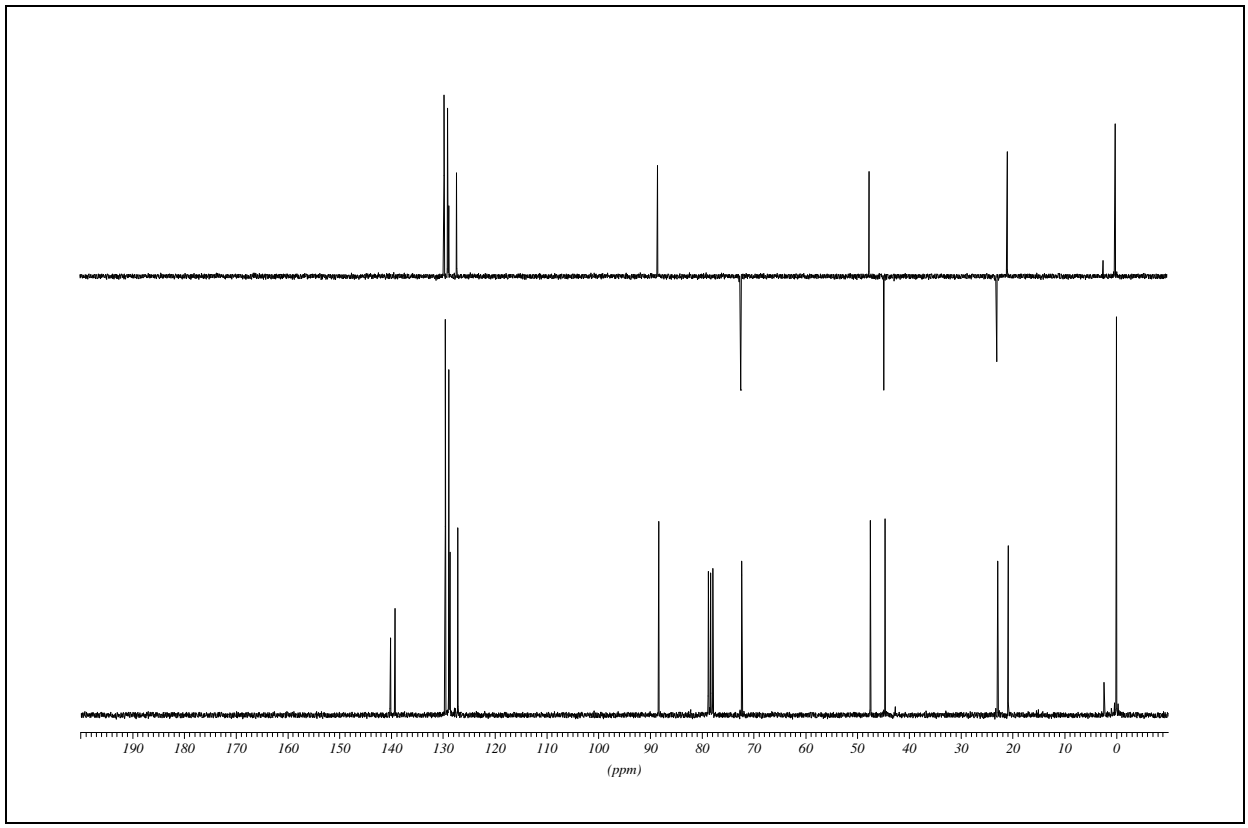
benzyl (1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)oxy]-3-cyclopenten-1-yl ether (**146f**)



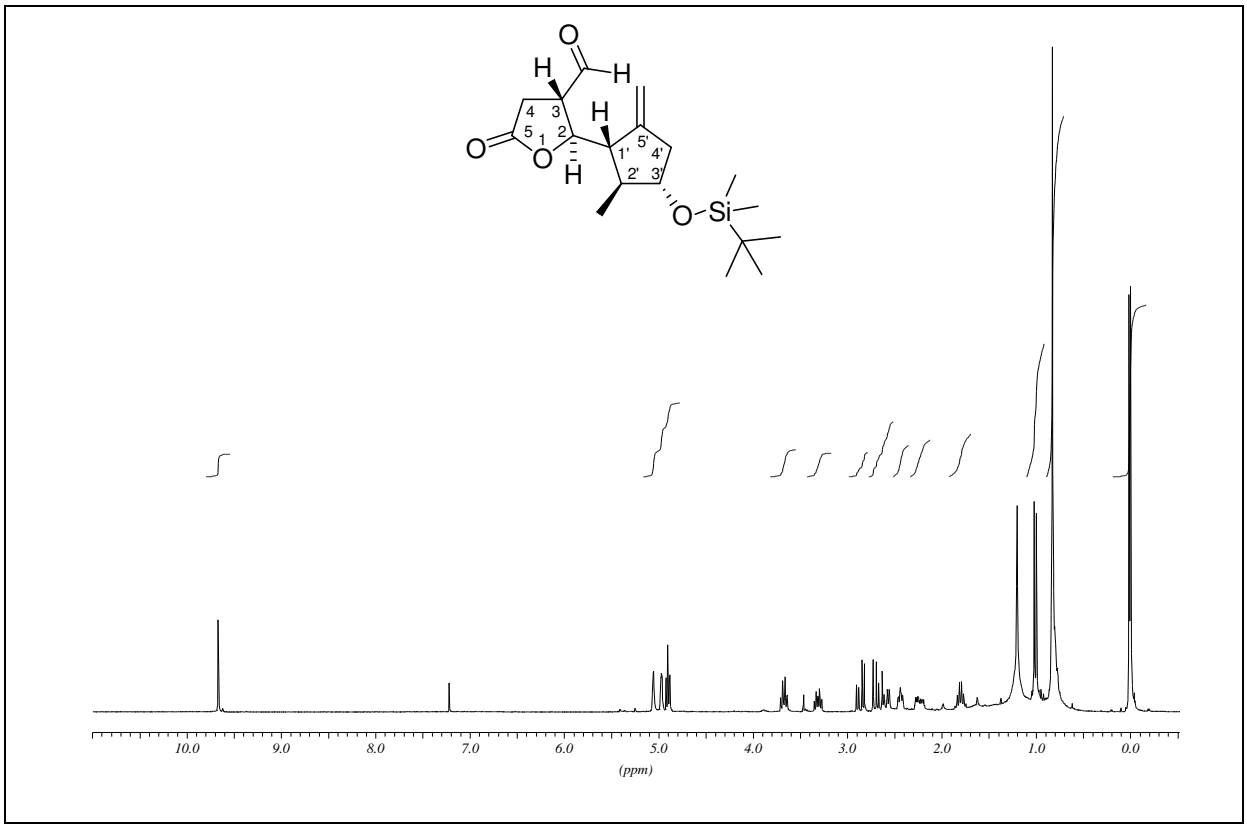


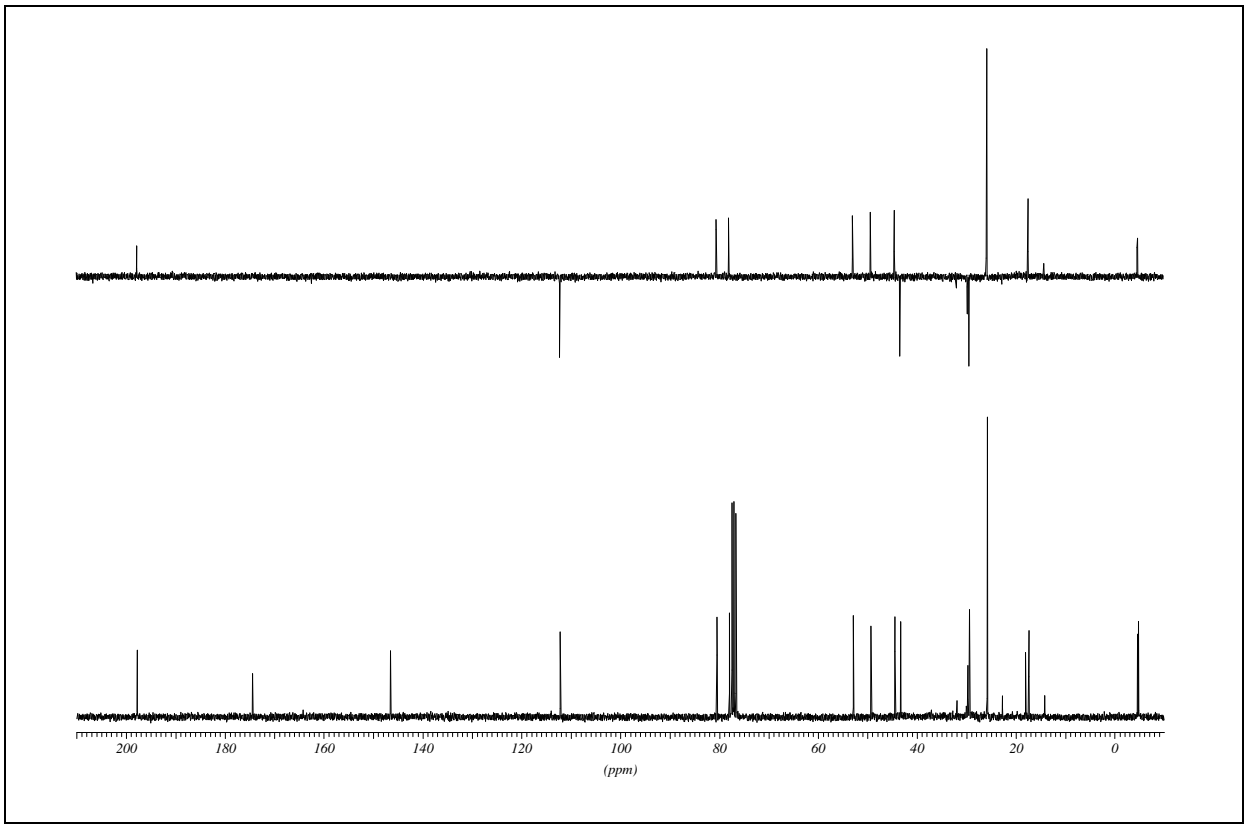
benzyl (1*S*,2*S*)-2-methyl-4-[(trimethylsilyl)methyl]-3-cyclopenten-1-yl ether (**103f**)



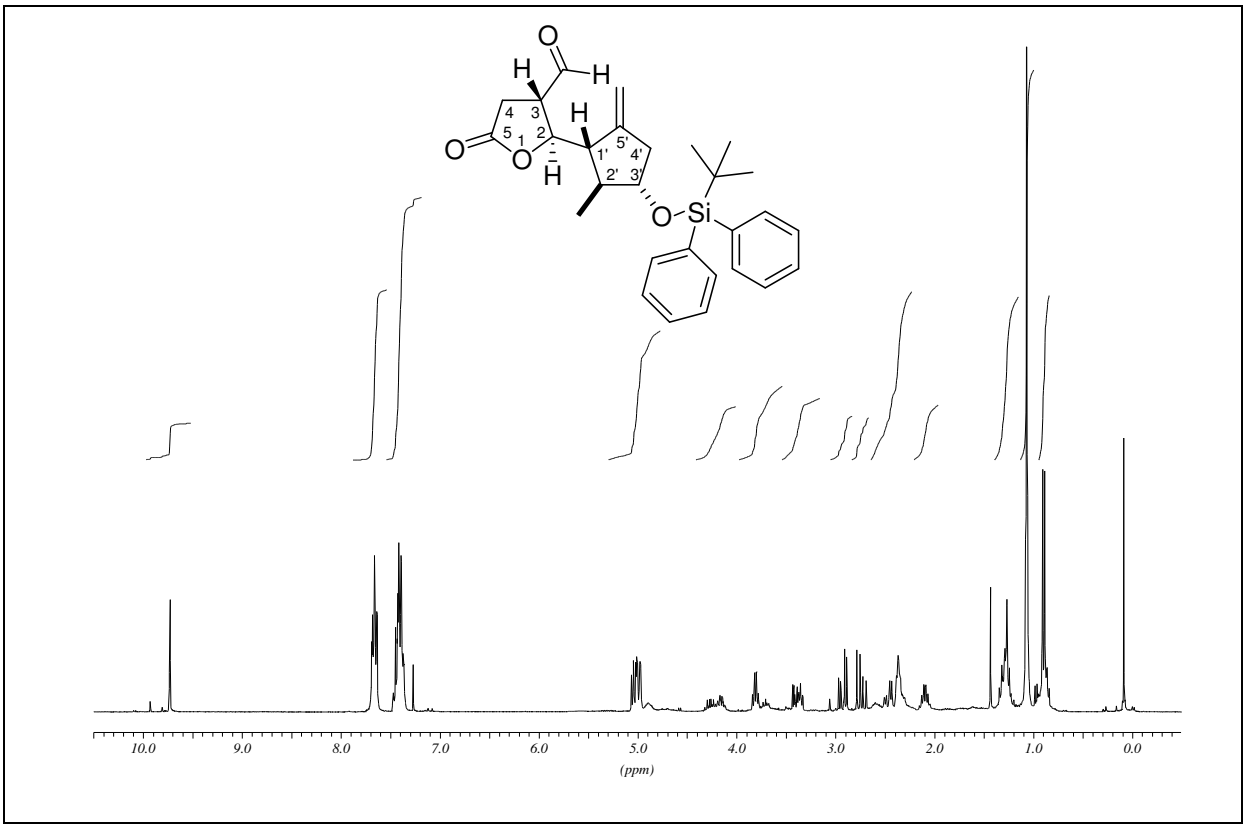


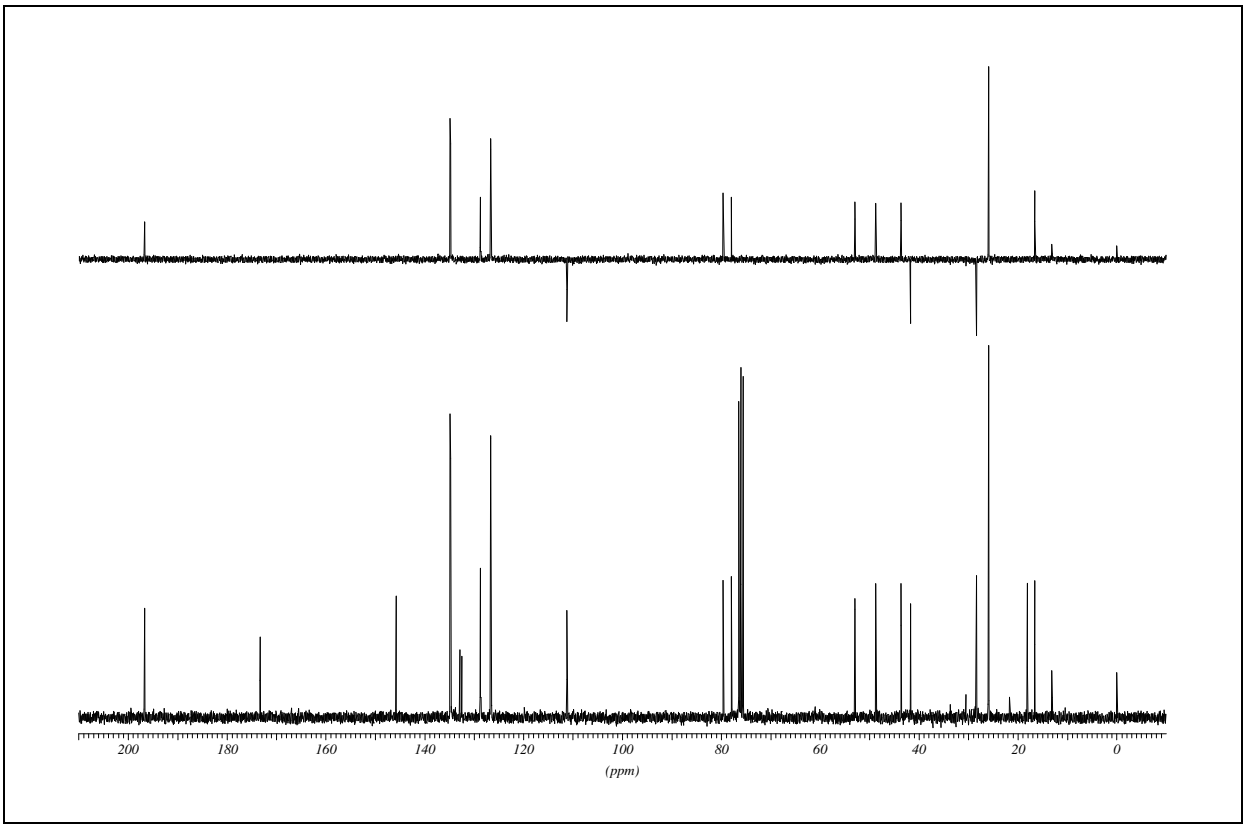
(2*R*,3*S*)-2-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-5-oxotetrahydro-3-furancarbaldehyde (**182**)



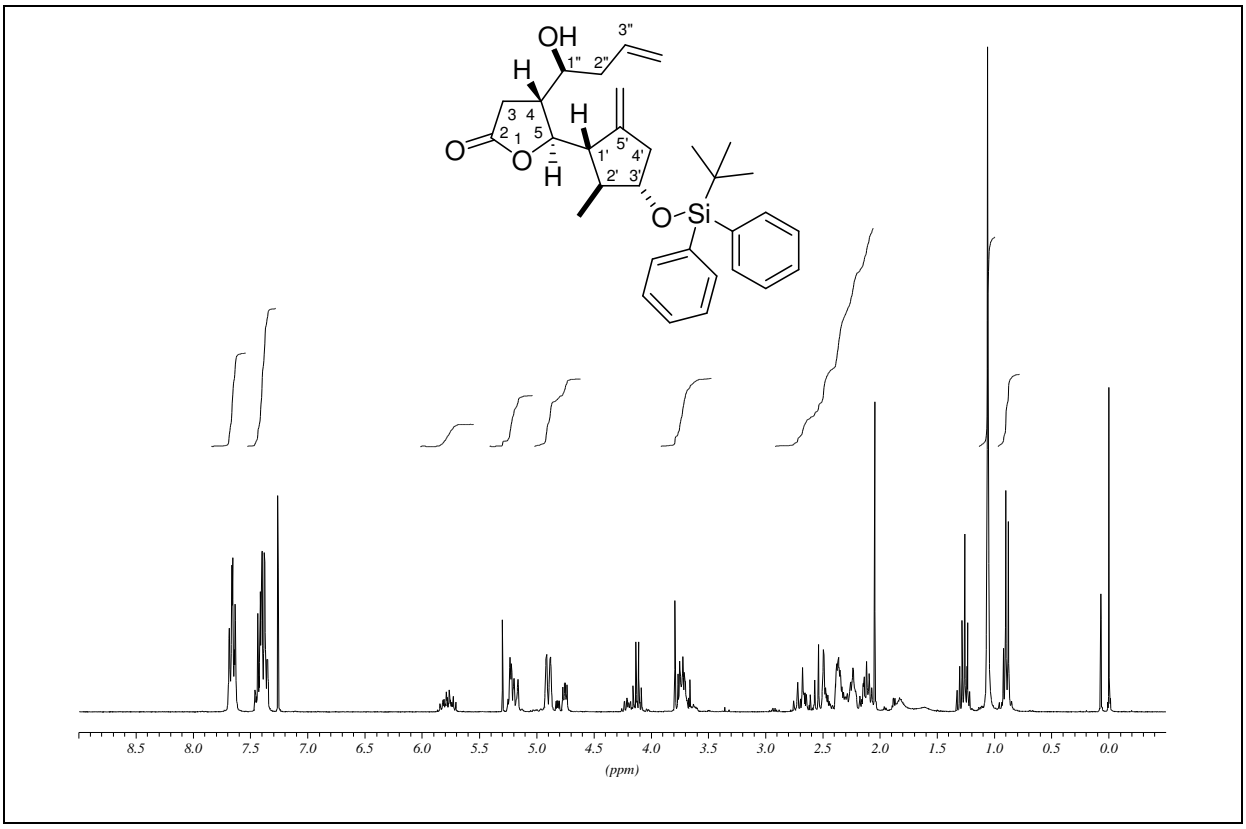


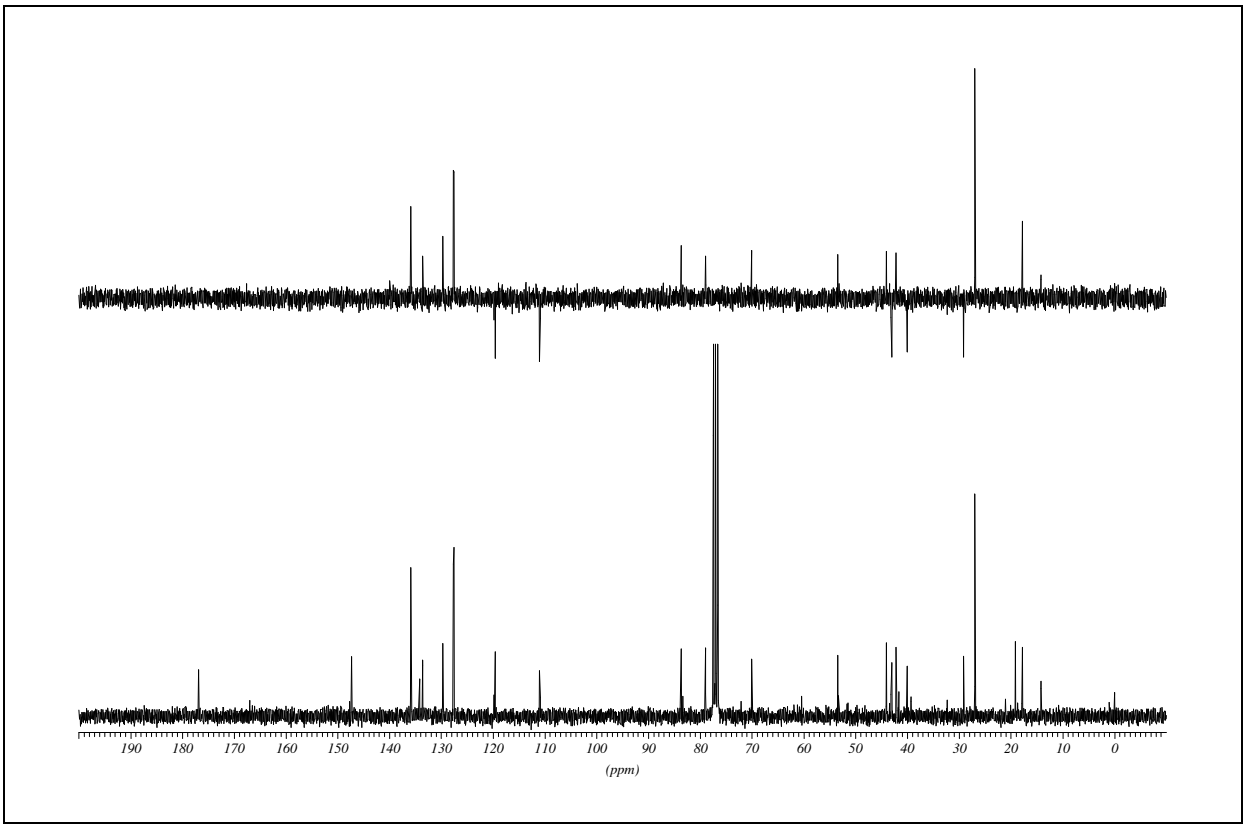
(2*R*,3*S*)-2-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-5-oxotetrahydro-3-furancarbaldehyde (**222**)



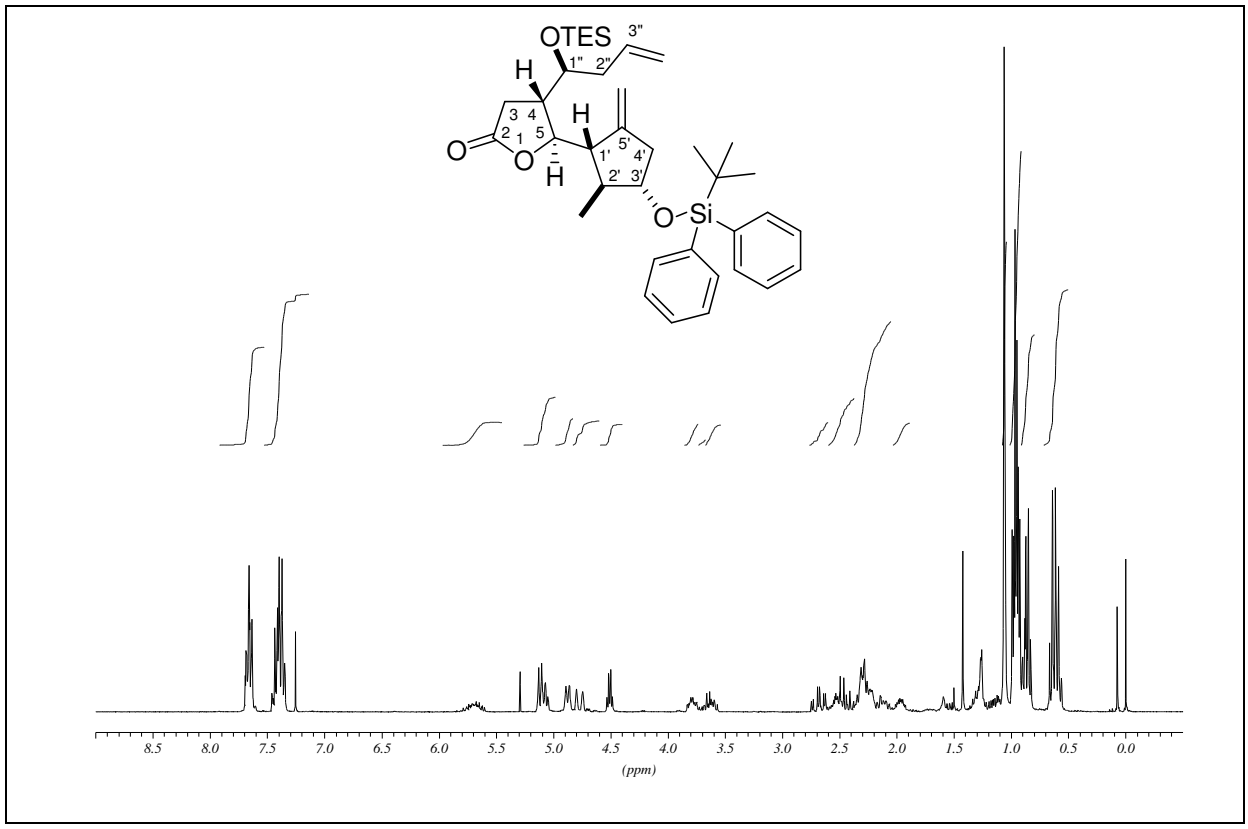


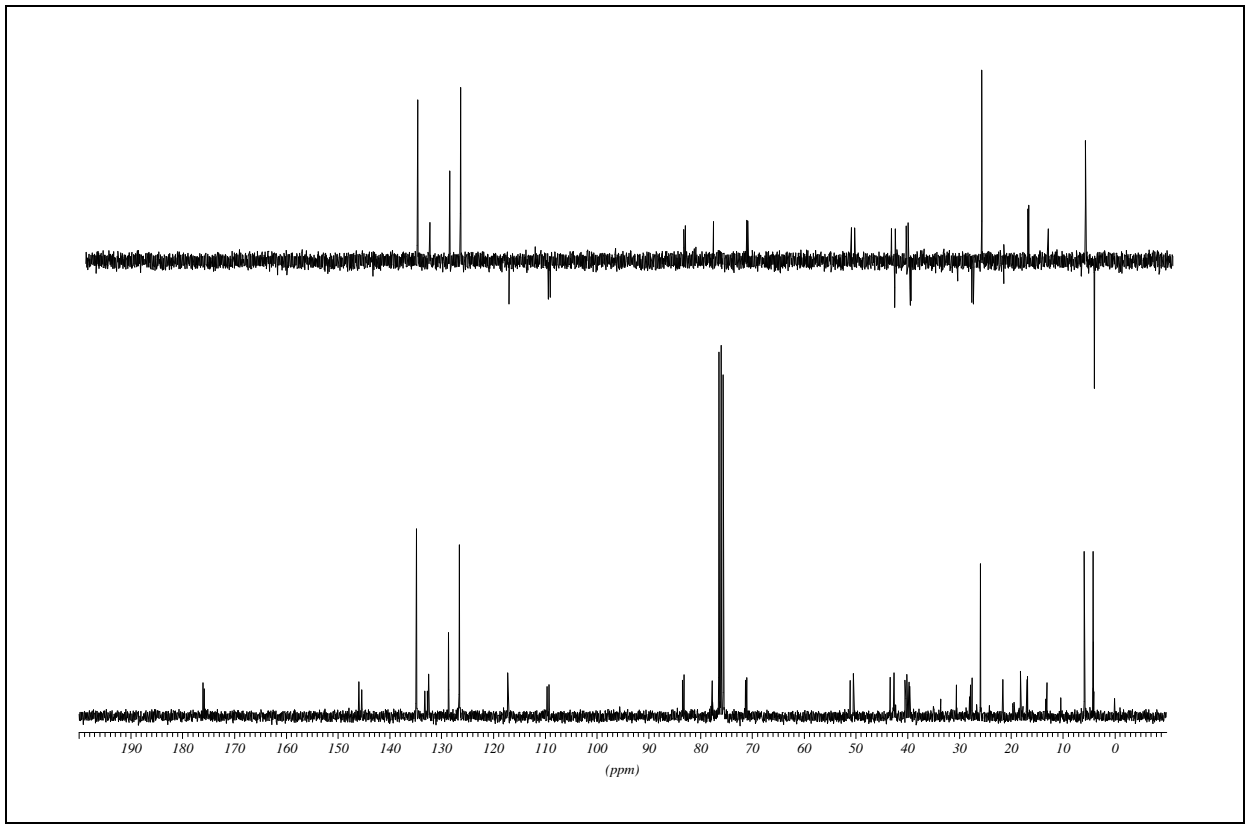
5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-(1"-hydroxy-3"-butenyl)dihydro-2(3*H*)-furanone (**223**)



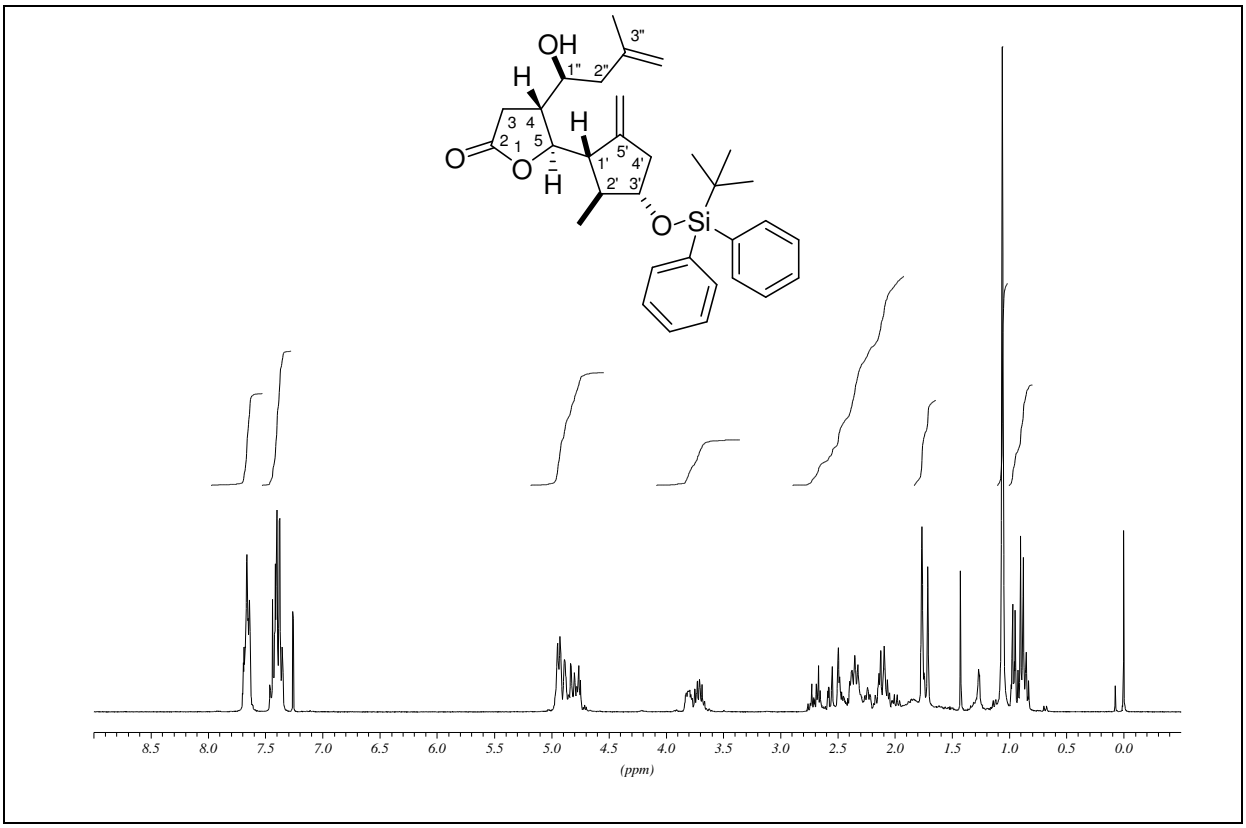


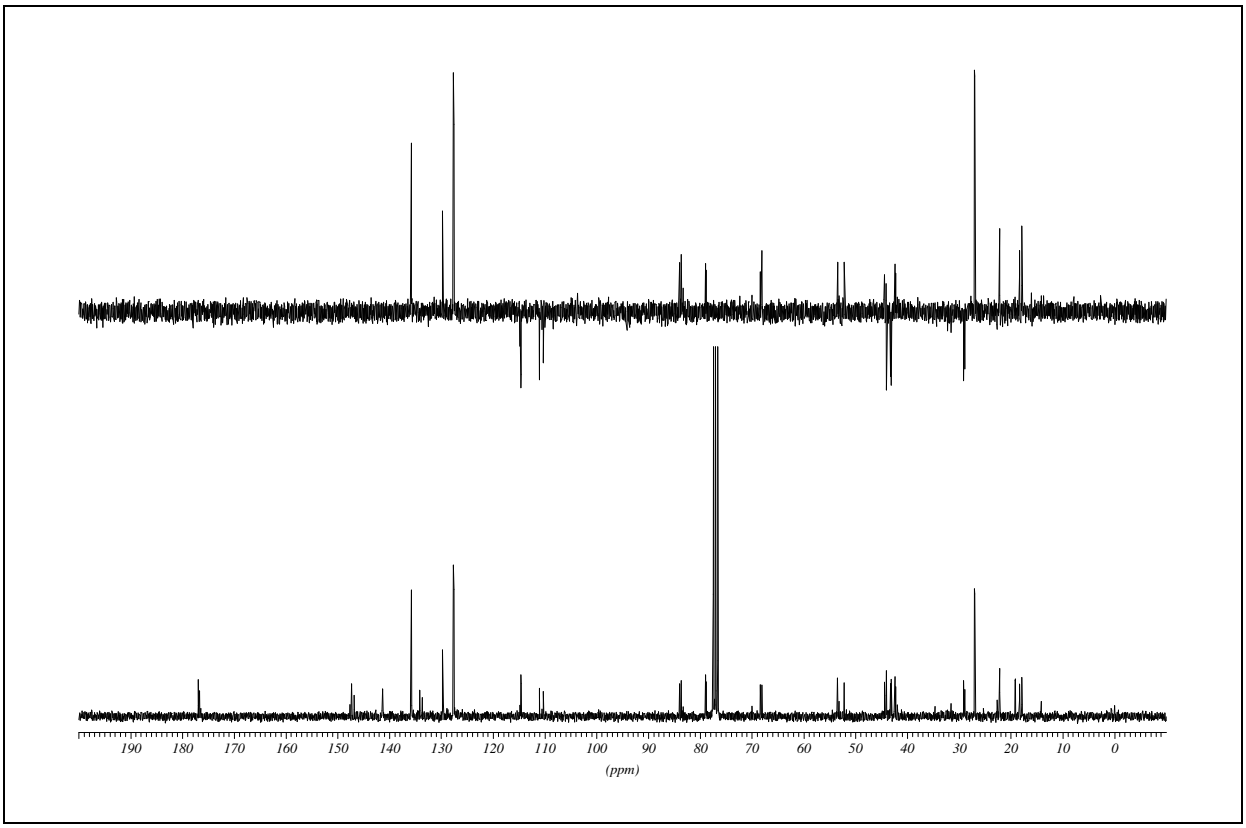
(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**224**)



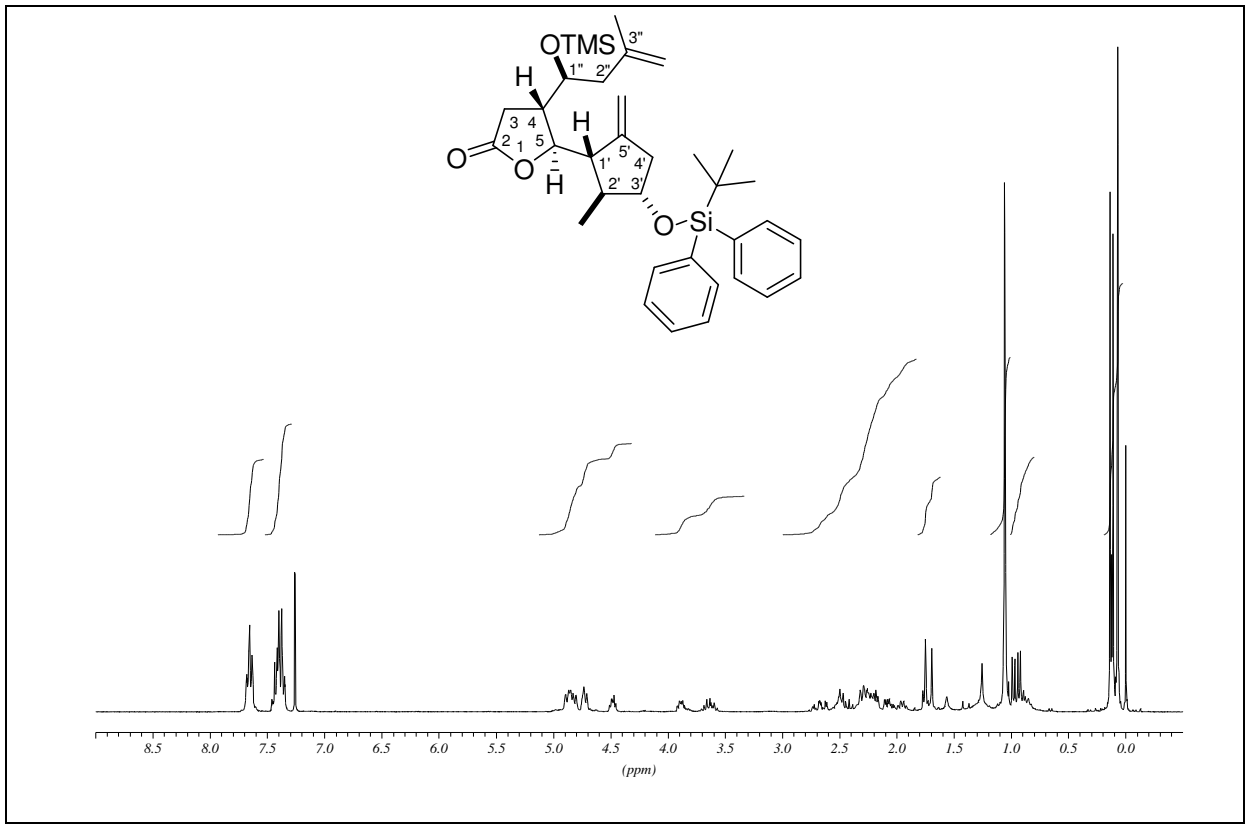


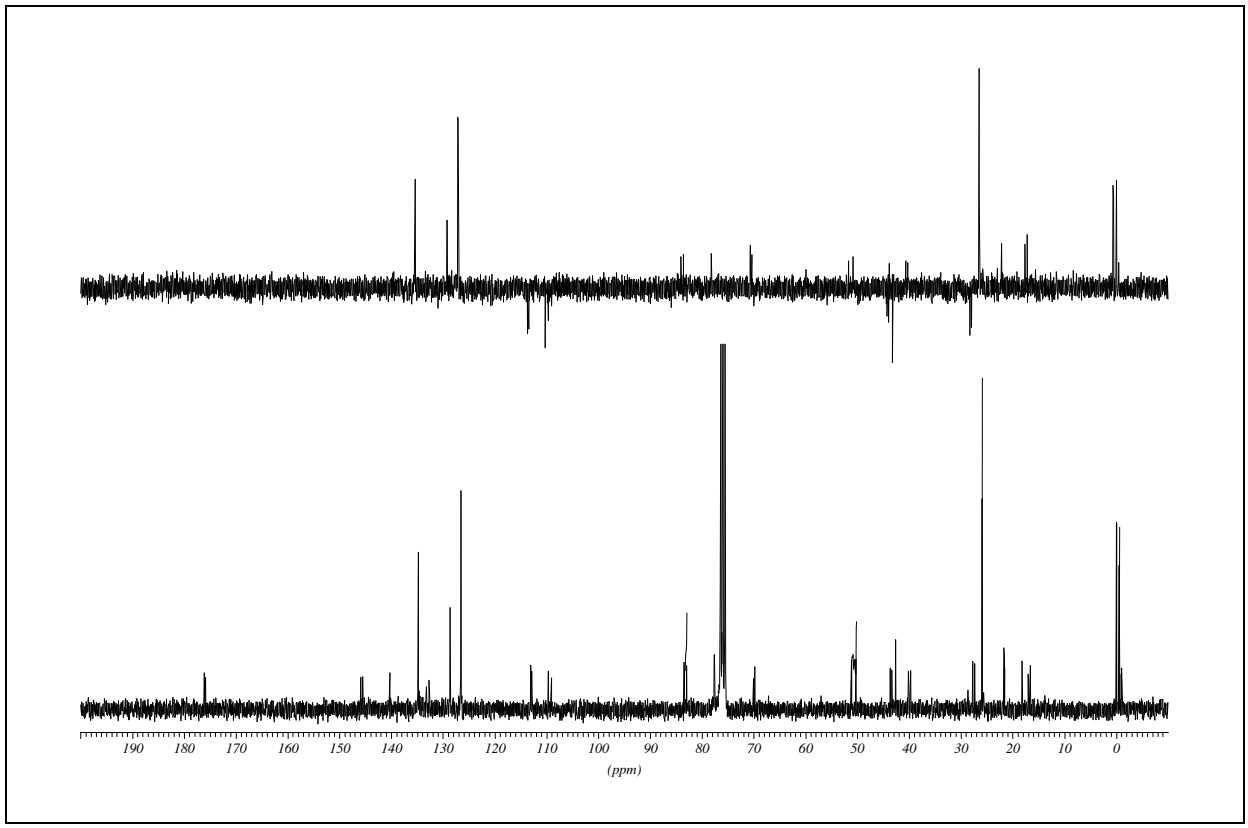
(4*R*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-[1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (**225**)



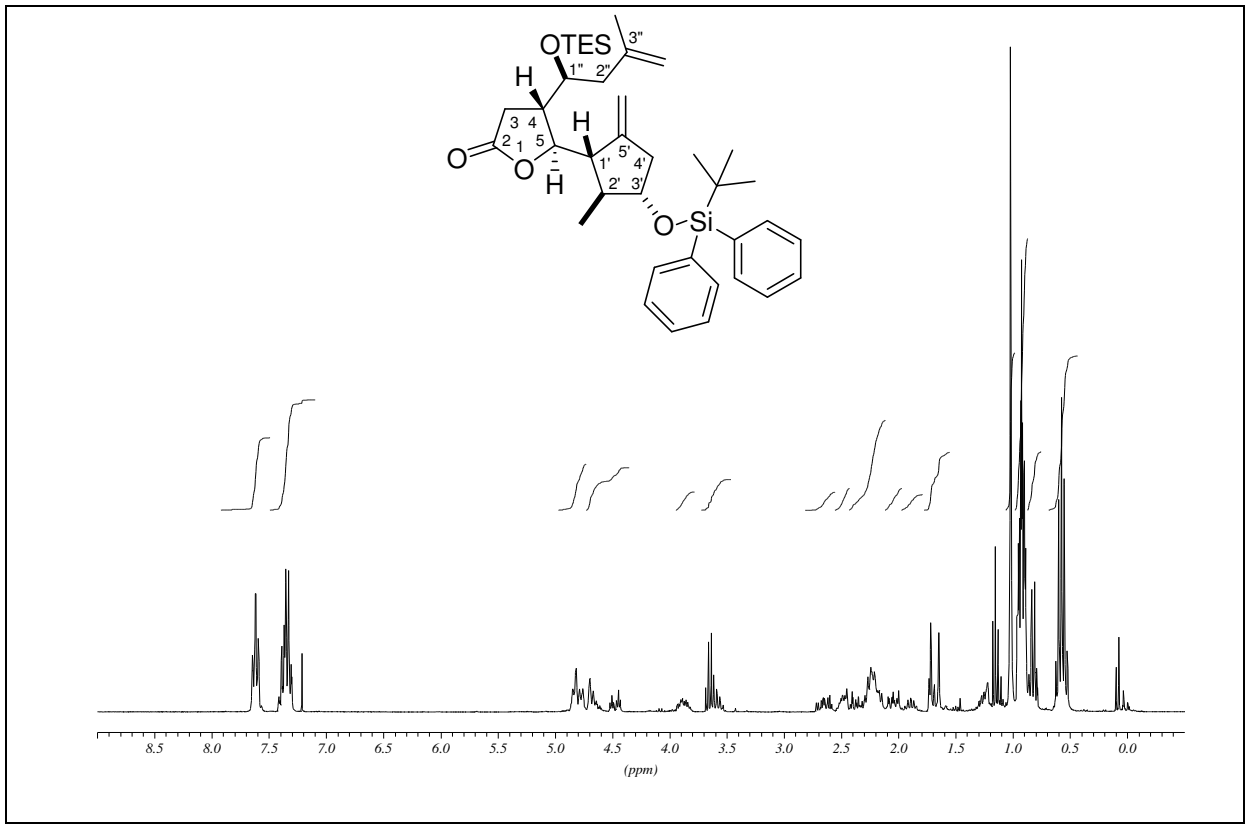


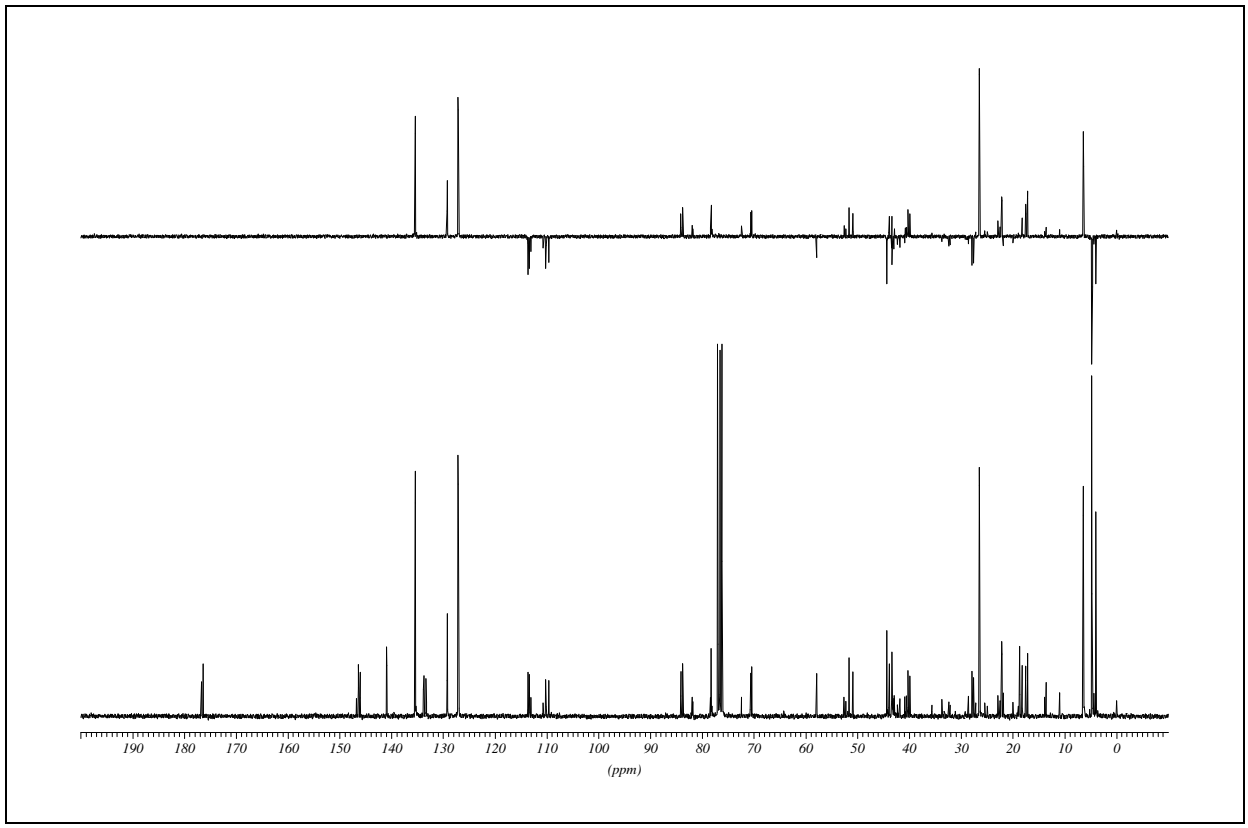
(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{3"-methyl-1"-[(trimethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**226**)



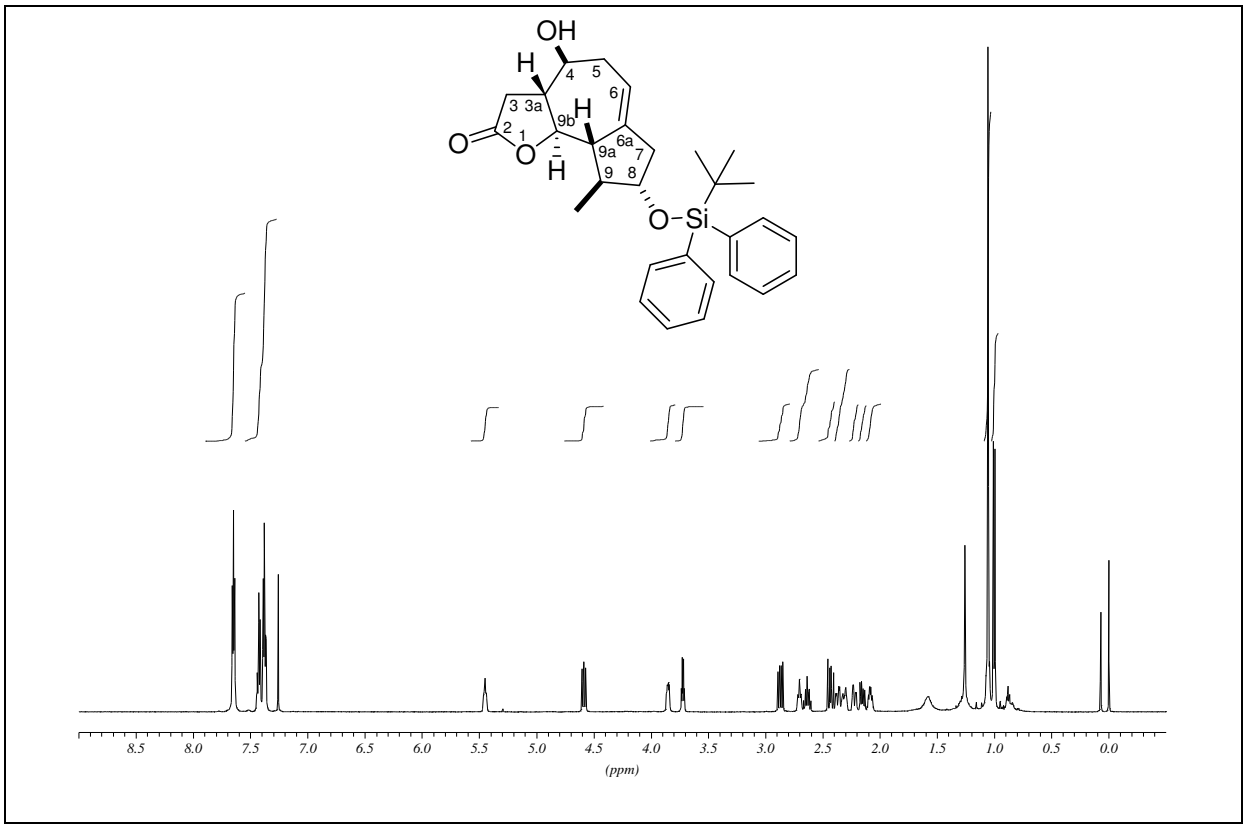


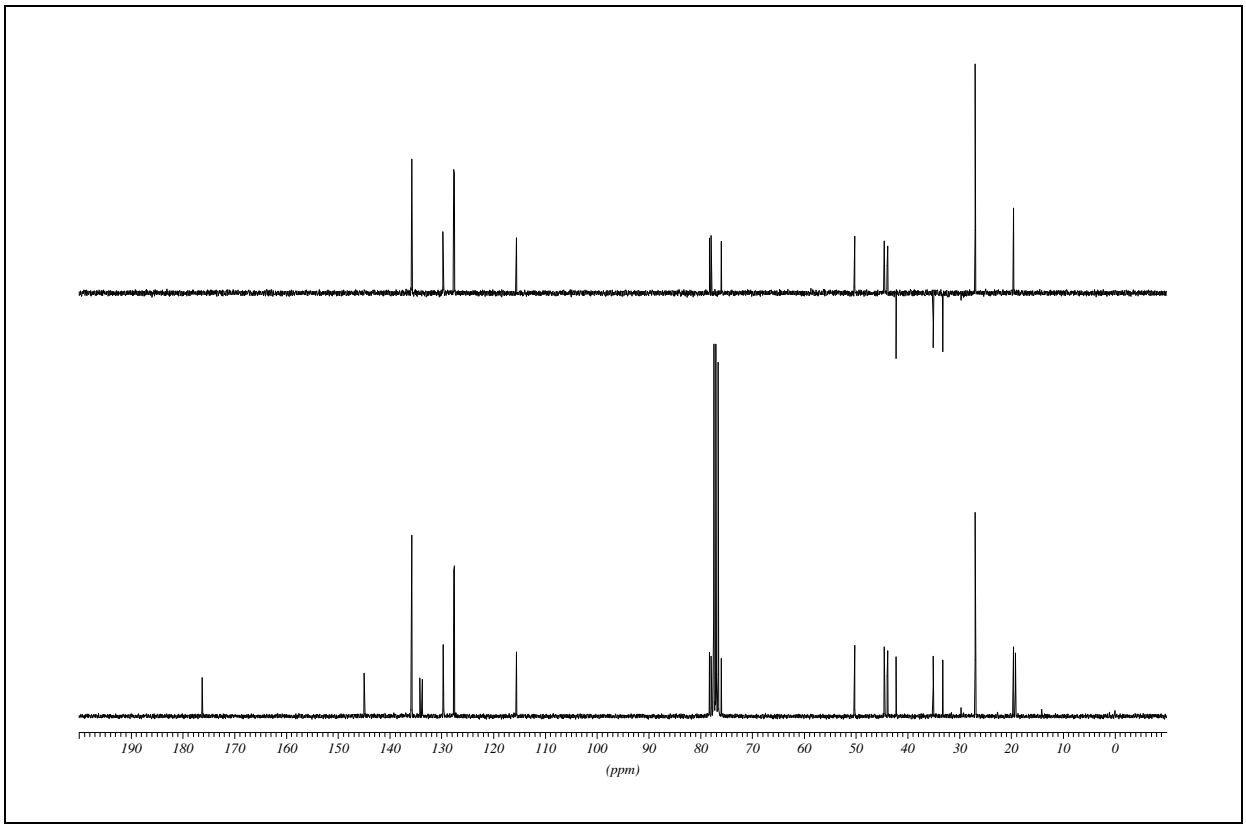
(4*S*,5*R*)-5-(3'-{[*tert*-butyl(diphenyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**227**)



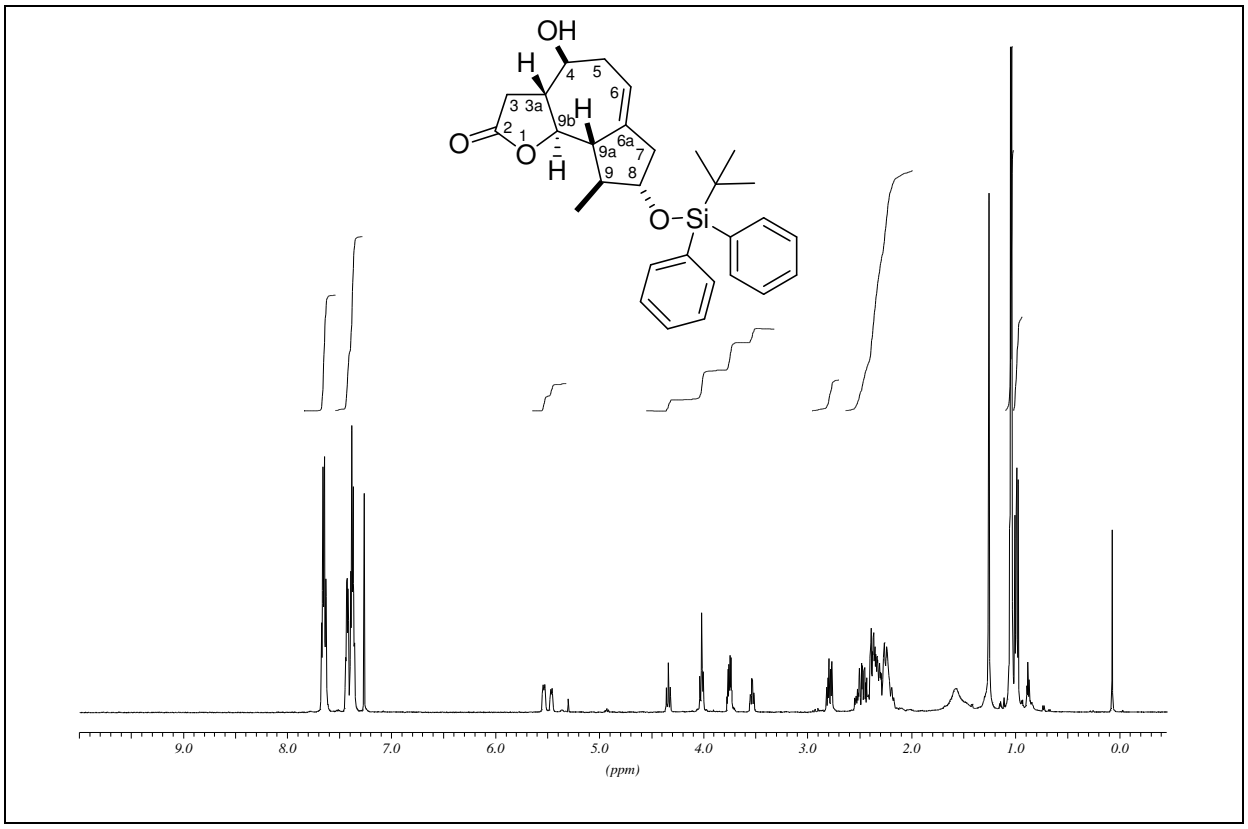


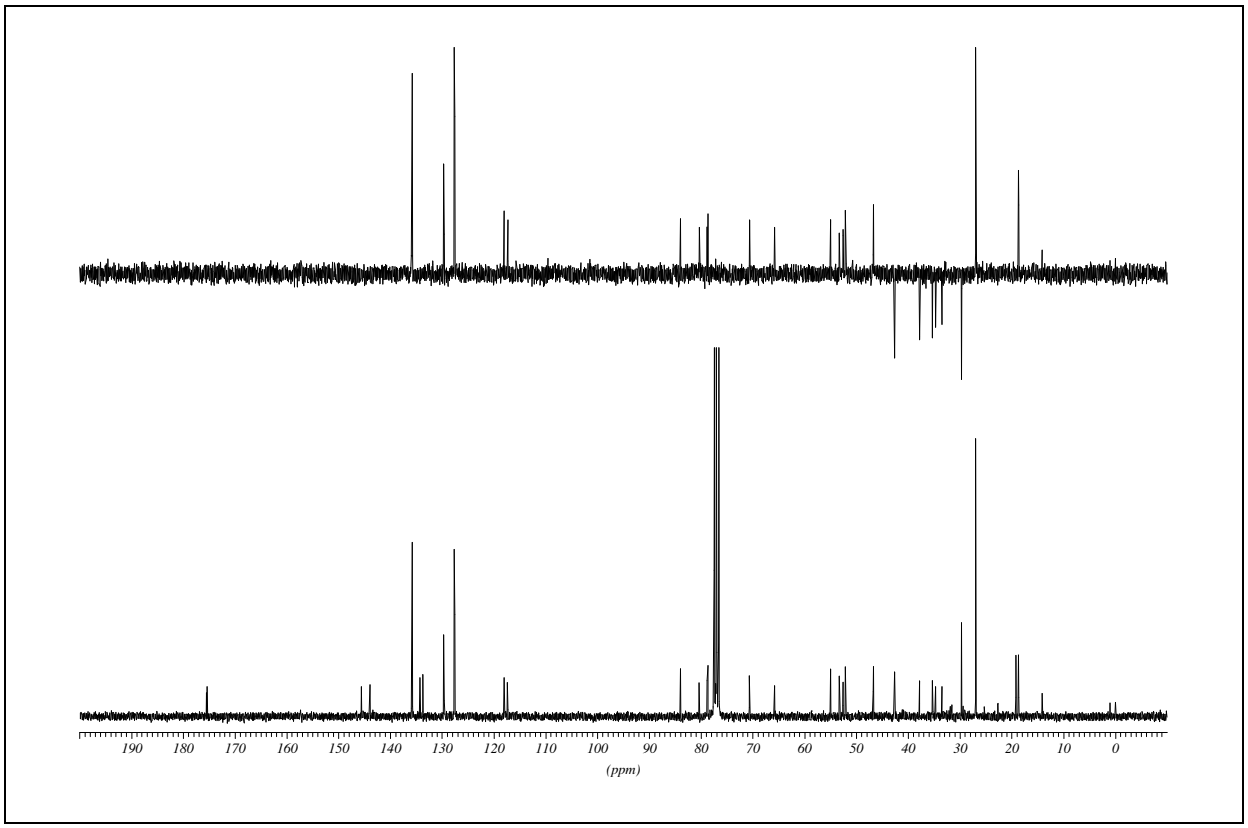
(3a*R*,9b*R*)-8-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxy-9-methyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**228**, 1st major diastereomer)



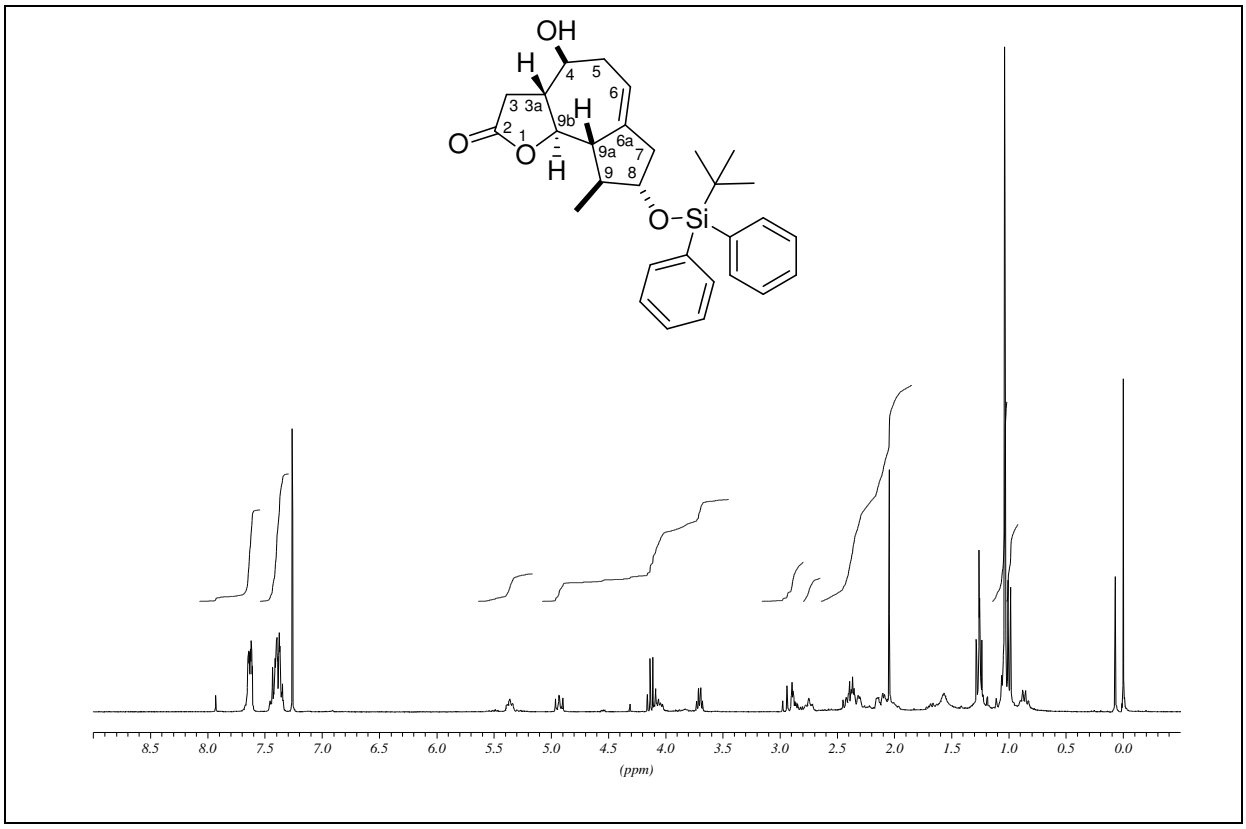


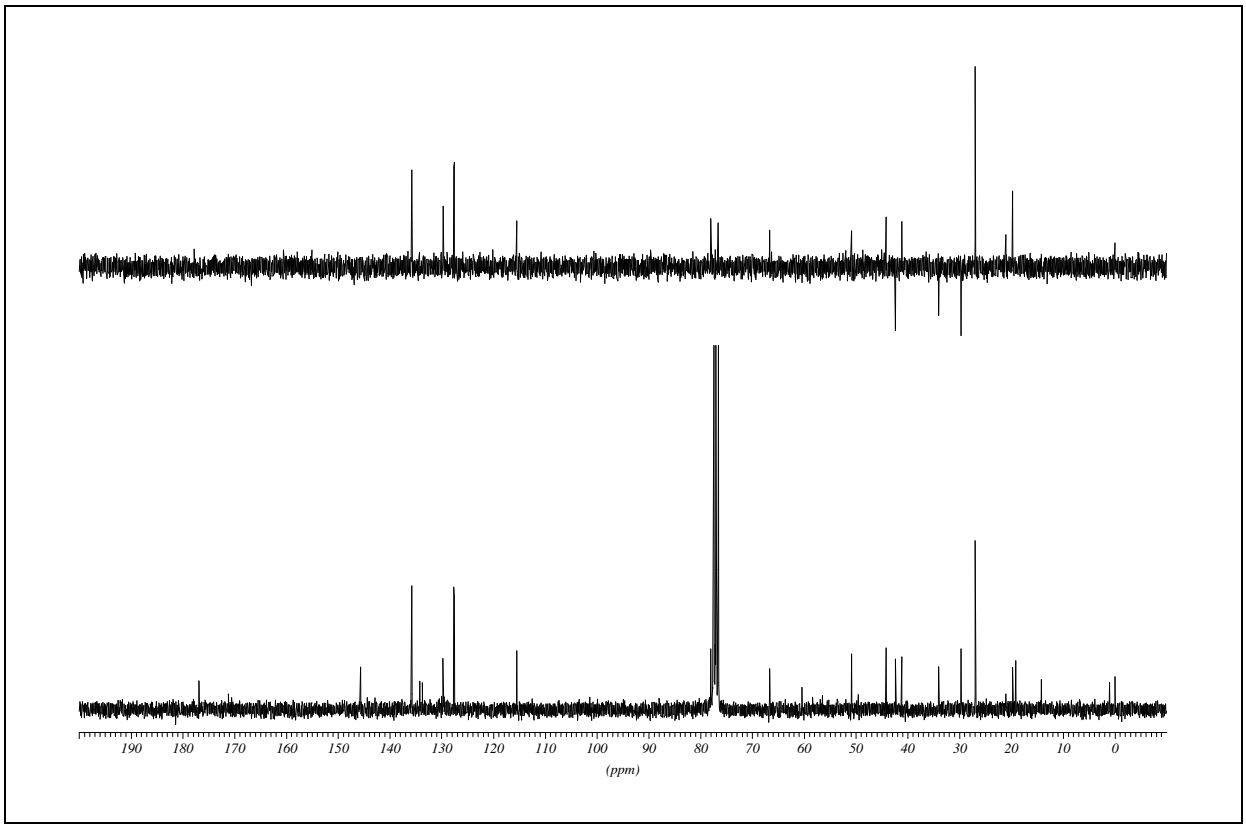
(3a*R*,9b*R*)-8-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxy-9-methyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**228**, 2nd + 3rd diastereomers)



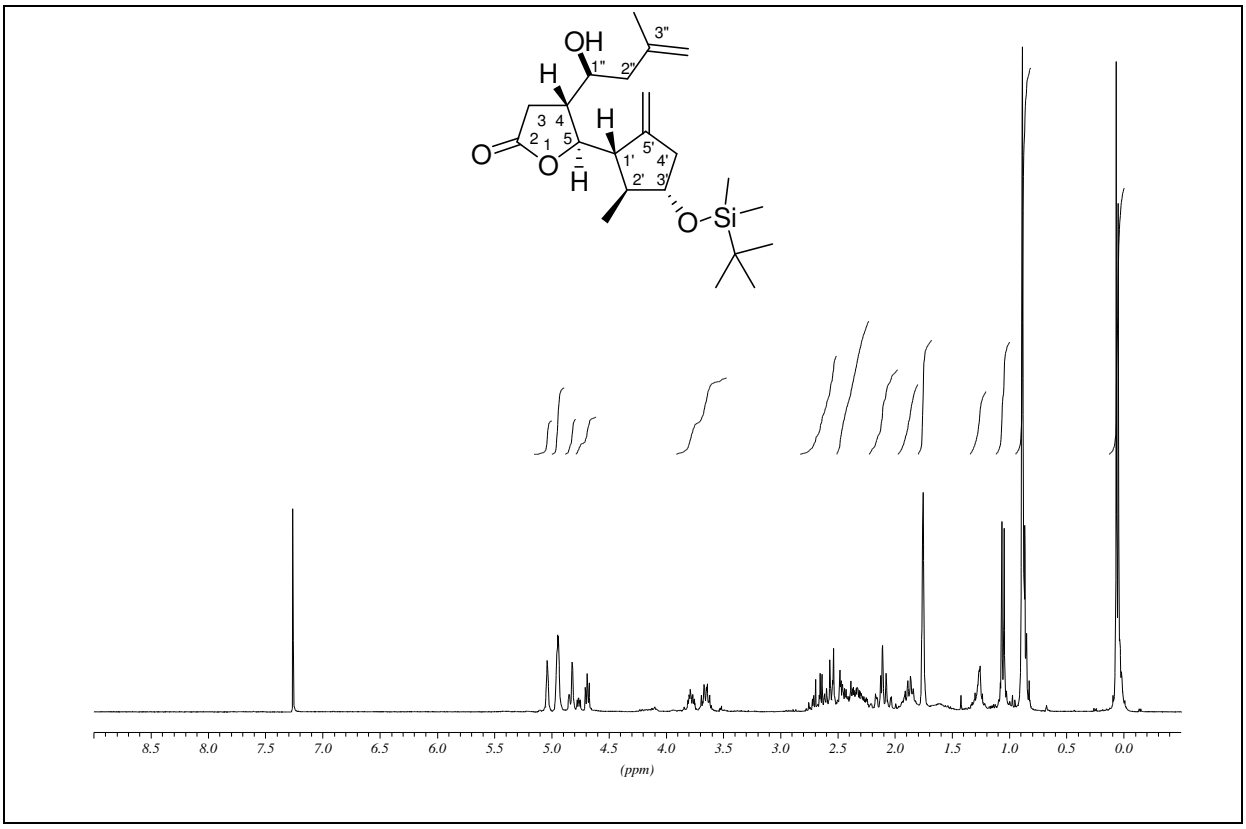


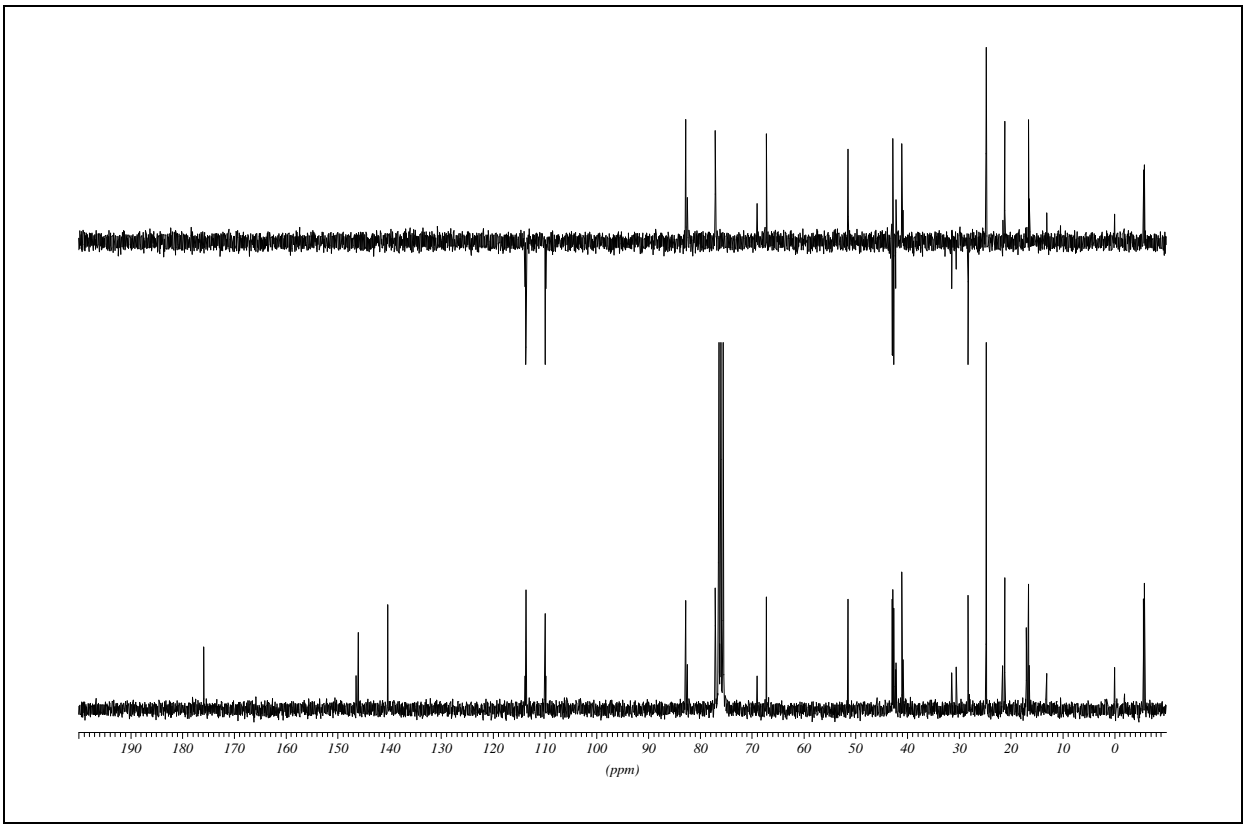
(3a*R*,9b*R*)-8-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxy-9-methyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**228**, 4th diastereomer)



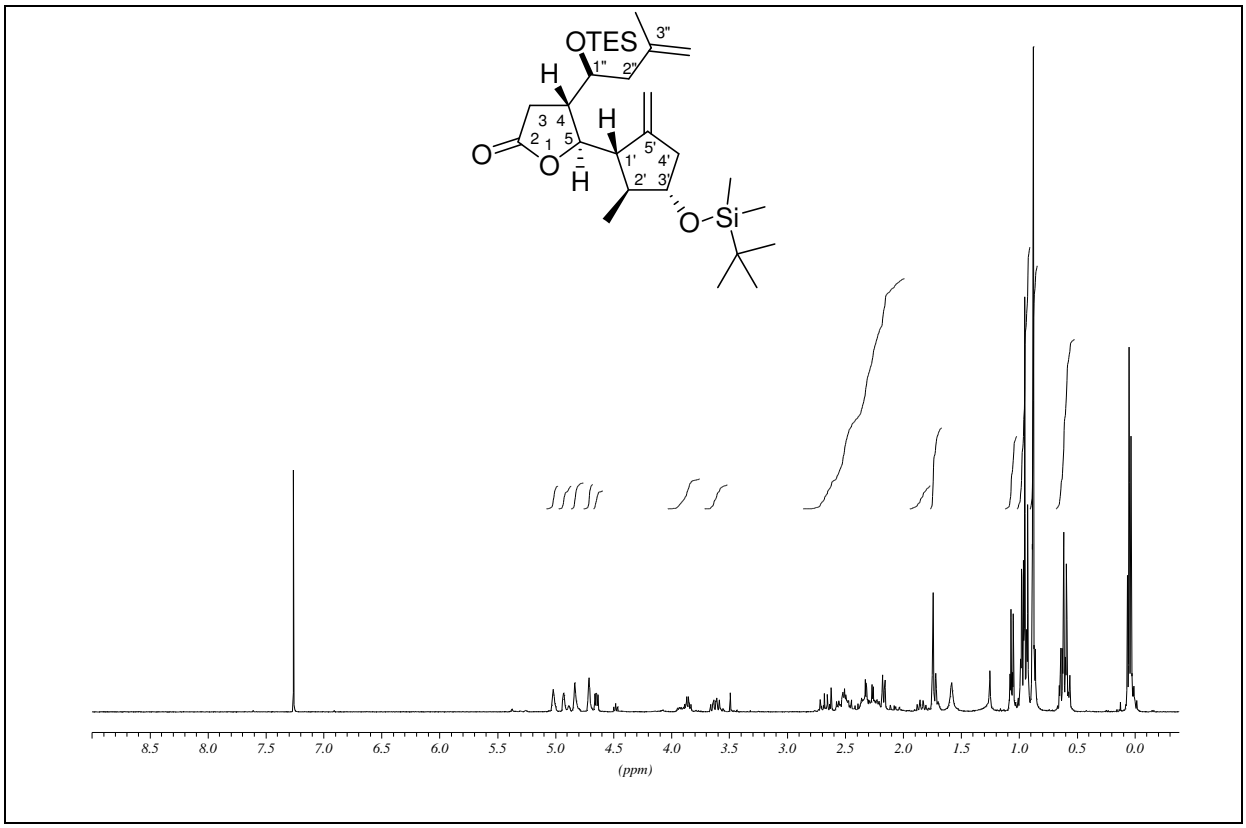


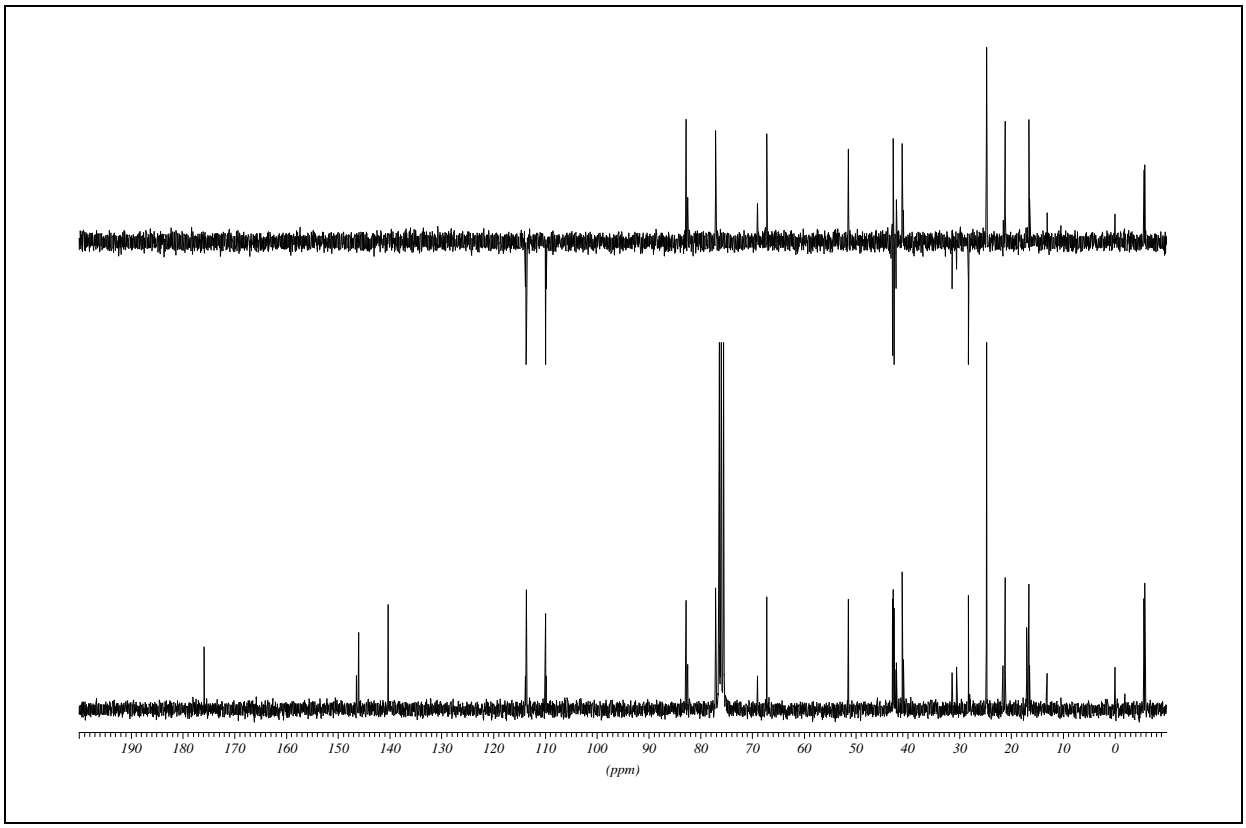
(4*R*,5*R*)-5-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-[(1"*S*)-1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (**233**)



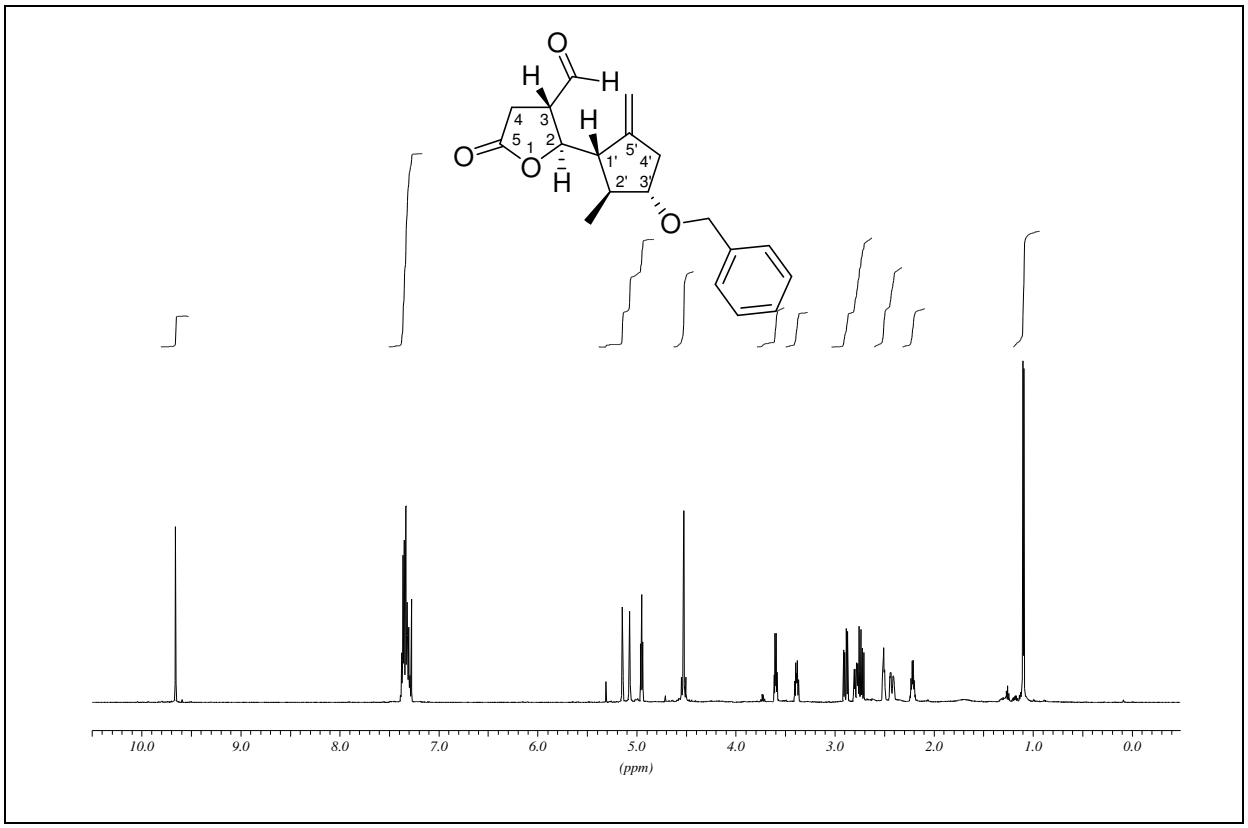


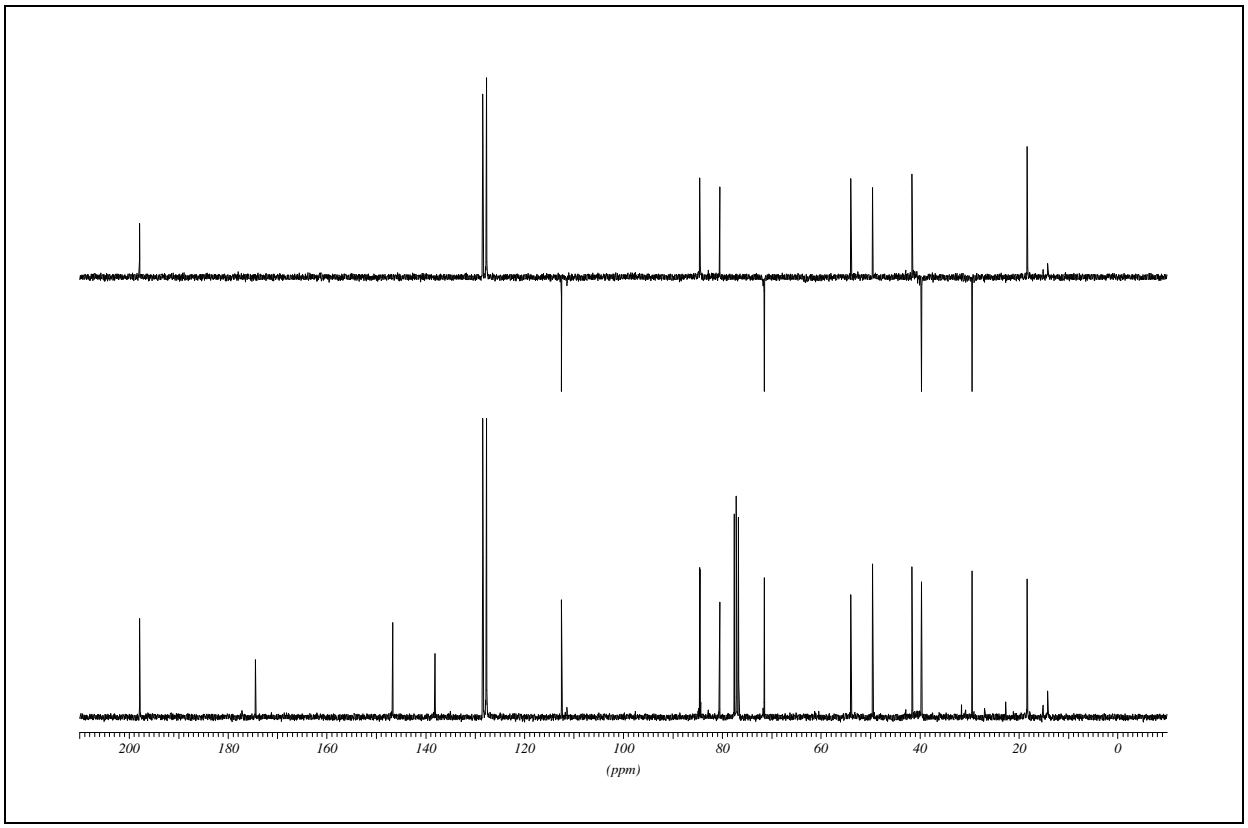
(4*S*,5*R*)-5-((1'*S*,2'*S*,3'*S*)-3'-{[*tert*-butyl(dimethyl)silyl]oxy}-2'-methyl-5'-methylenecyclopentyl)-4-{(1"*S*)-3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**234**)



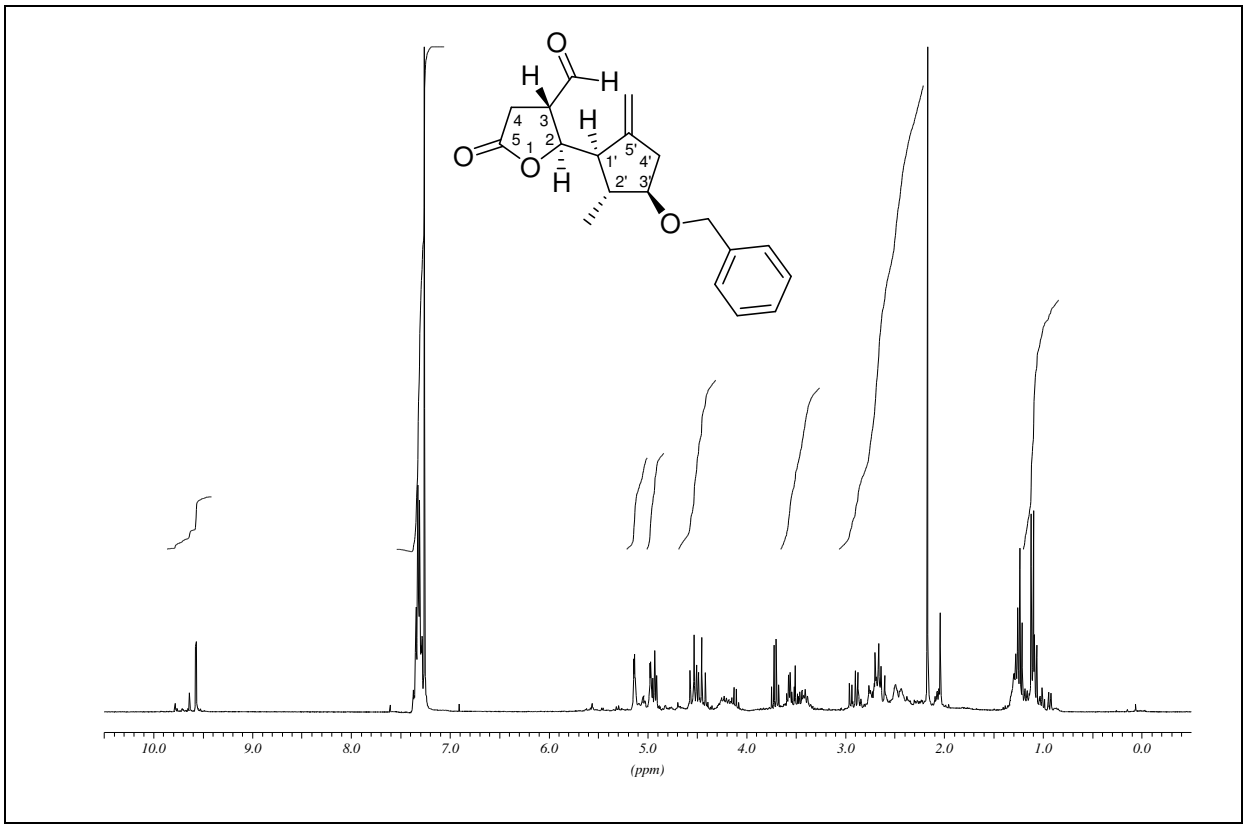


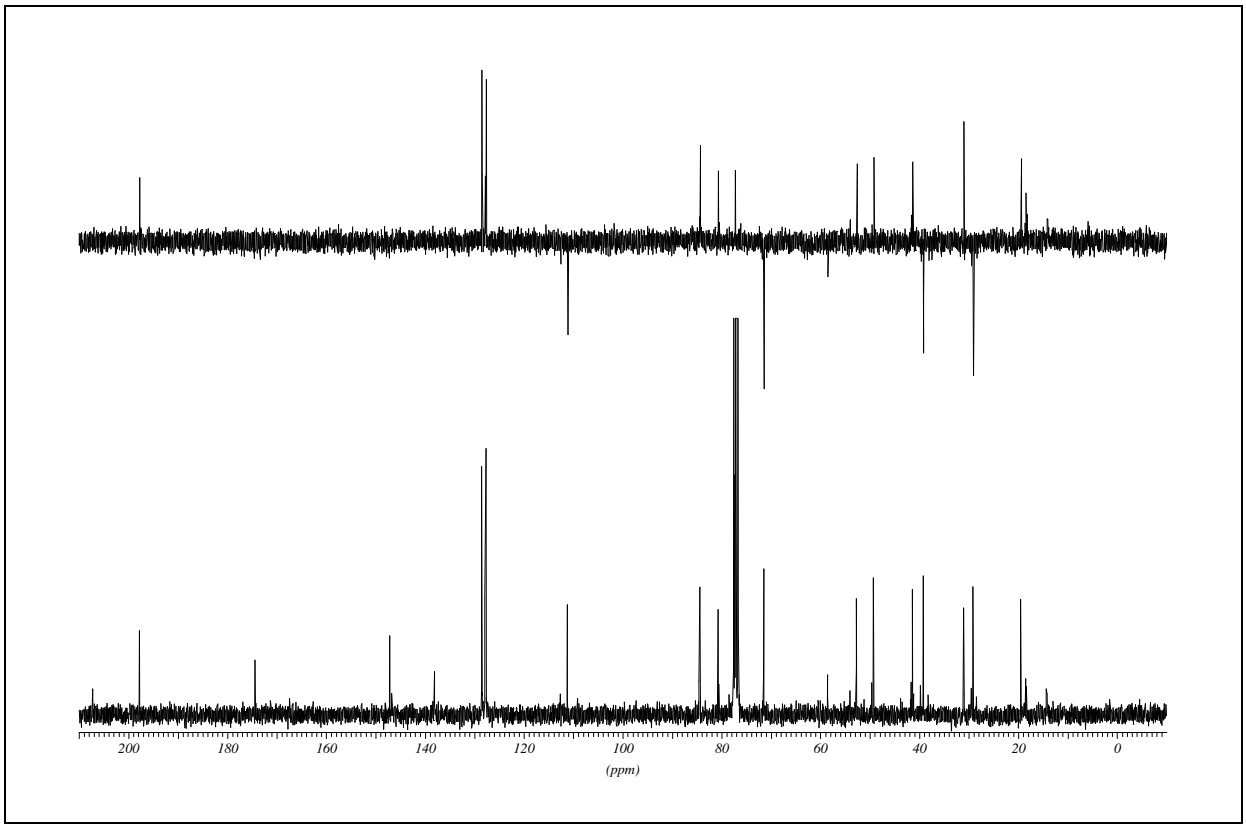
(2*S*,3*S*)-2-[(1'*S*,2'*S*,3'*S*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-5-oxotetrahydro-3-furancarbaldehyde (**183**)



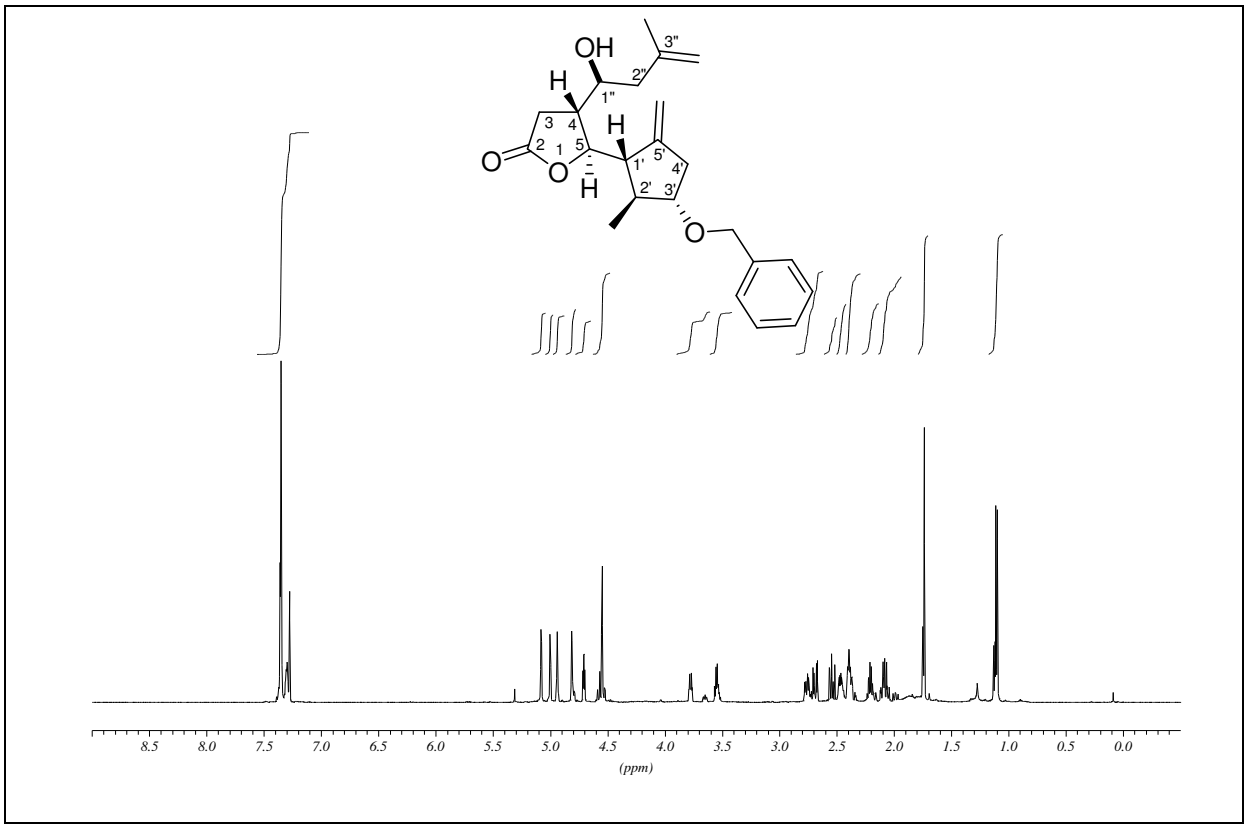


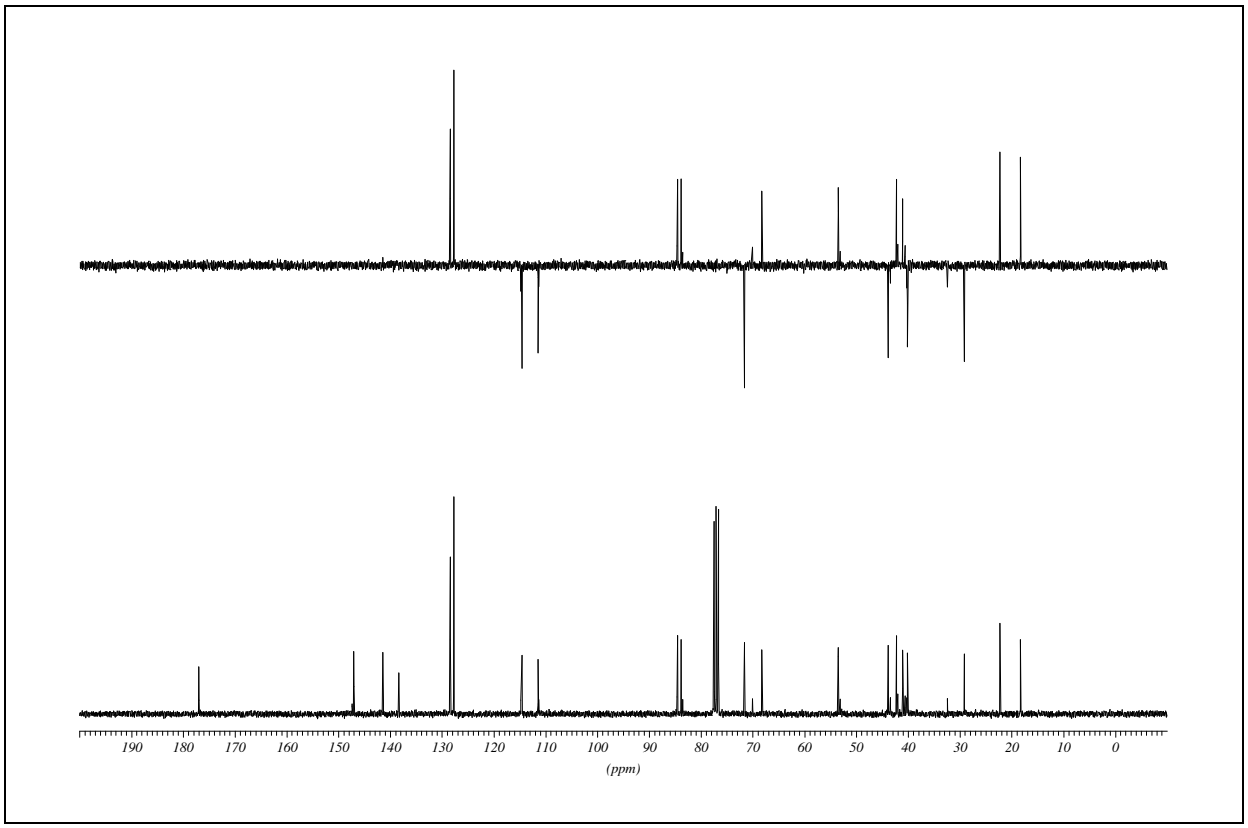
(2*S*,3*S*)-2-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-5-oxotetrahydro-3-furancarbaldehyde (**200**)



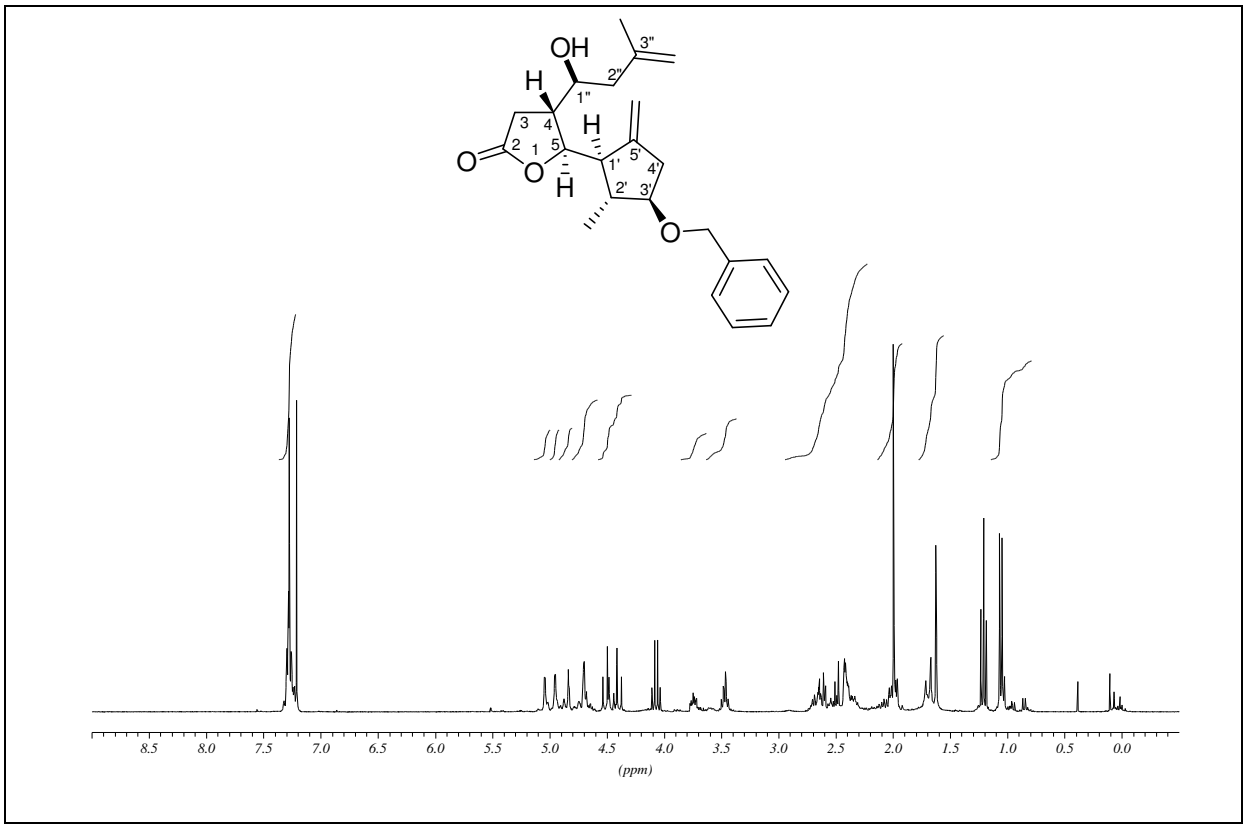


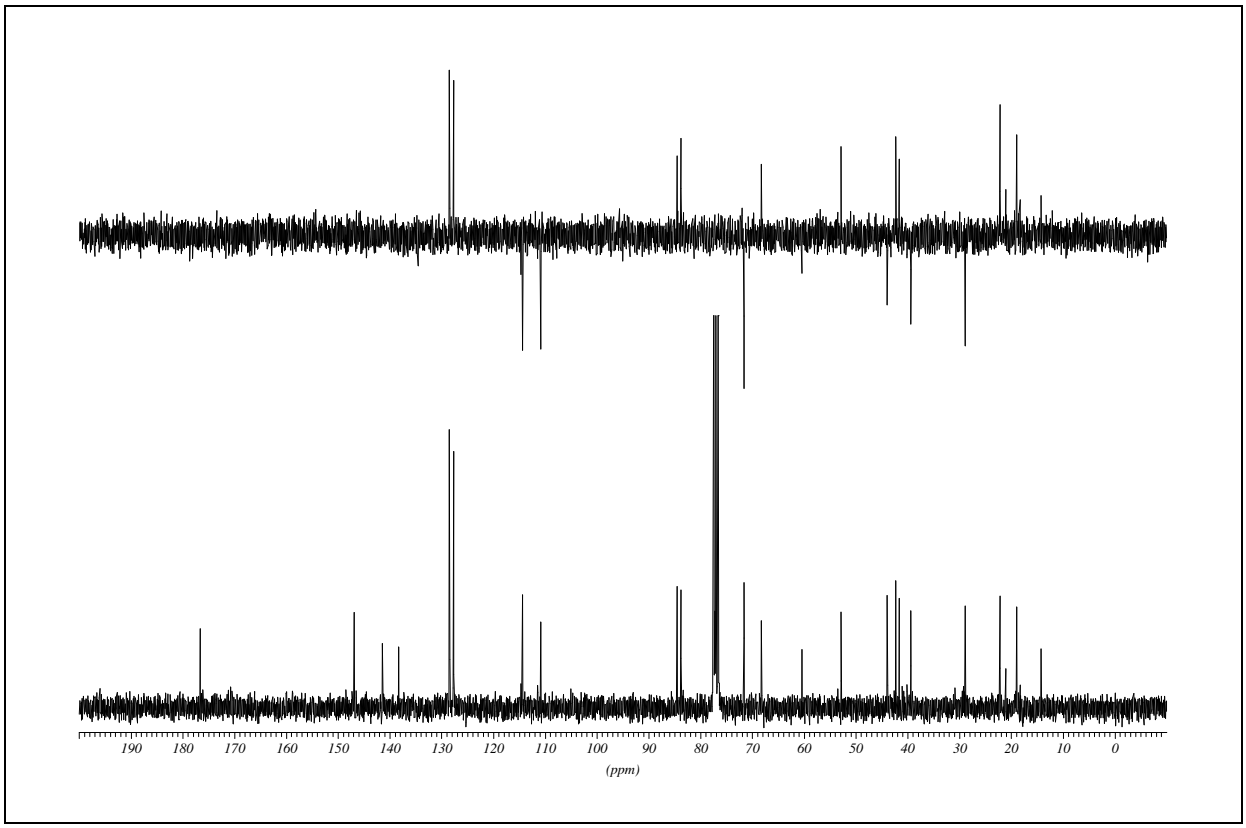
(4*R*,5*S*)-5-[(1'*S*,2'*S*,3'*S*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-(1''-hydroxy-3''-methyl-3''-butenyl)dihydro-2(3*H*)-furanone (**235**)



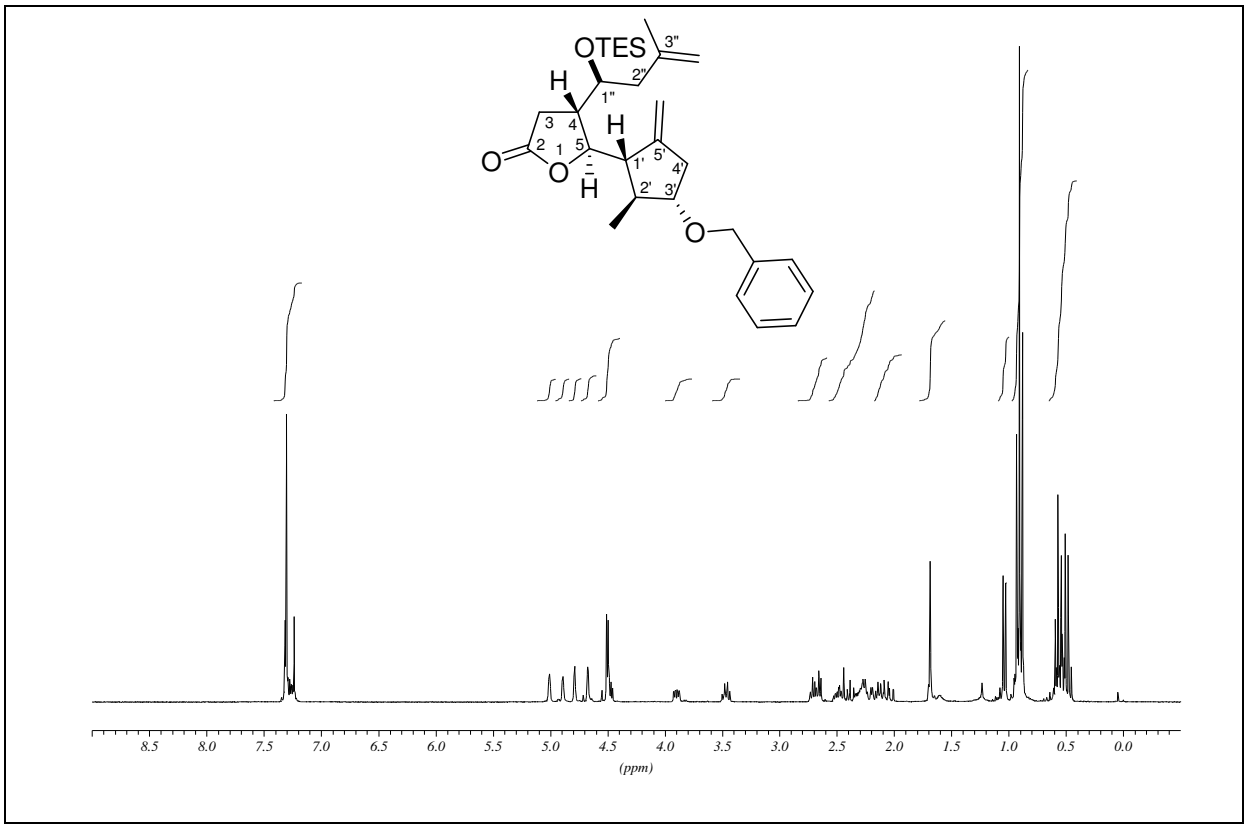


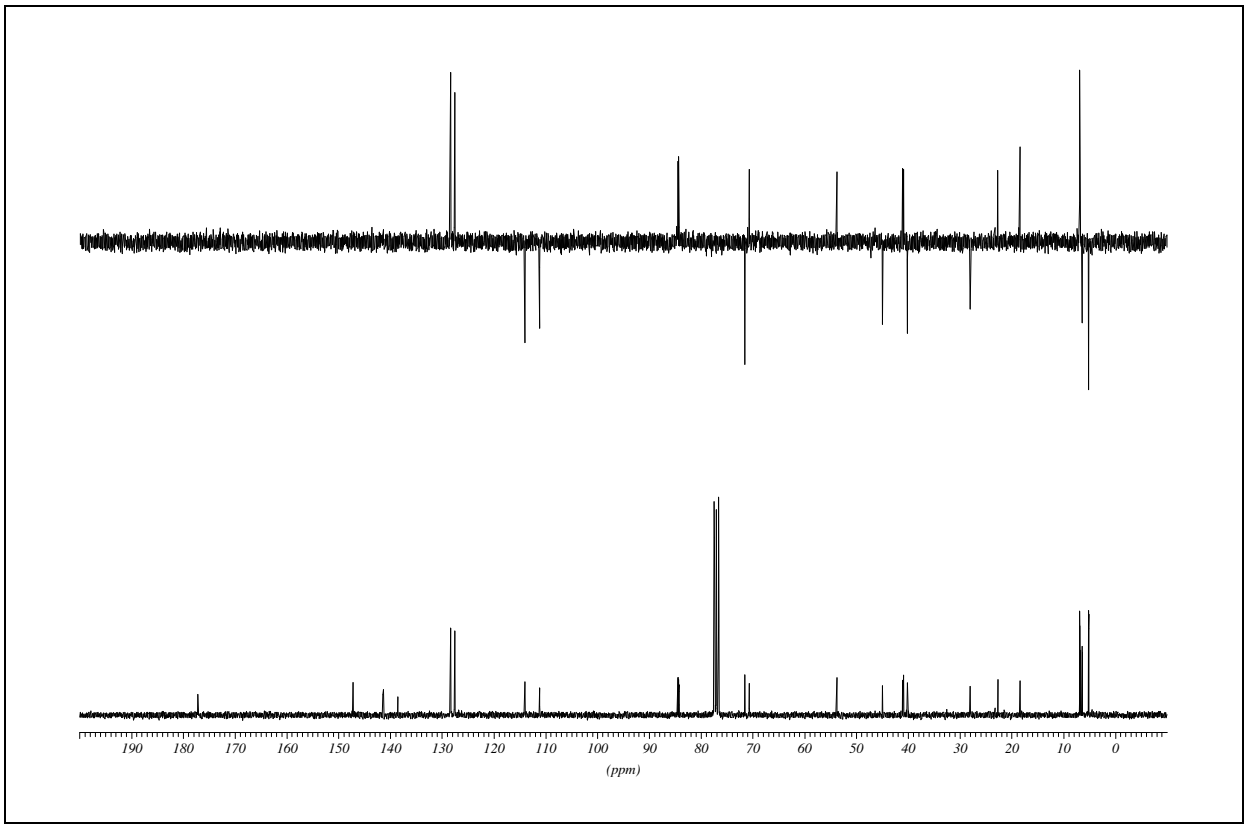
(4*R*,5*R*)-5-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-[1"-hydroxy-3"-methyl-3"-butenyl]dihydro-2(3*H*)-furanone (**237**)



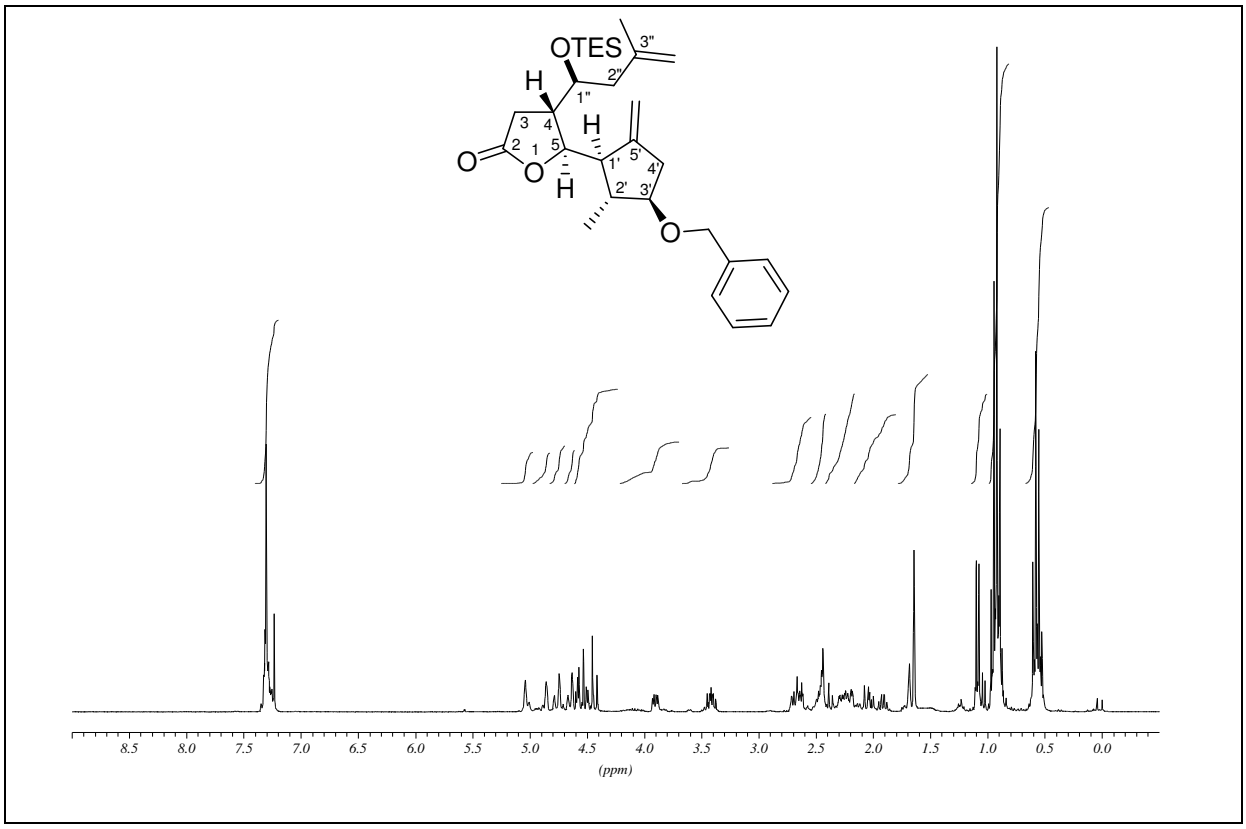


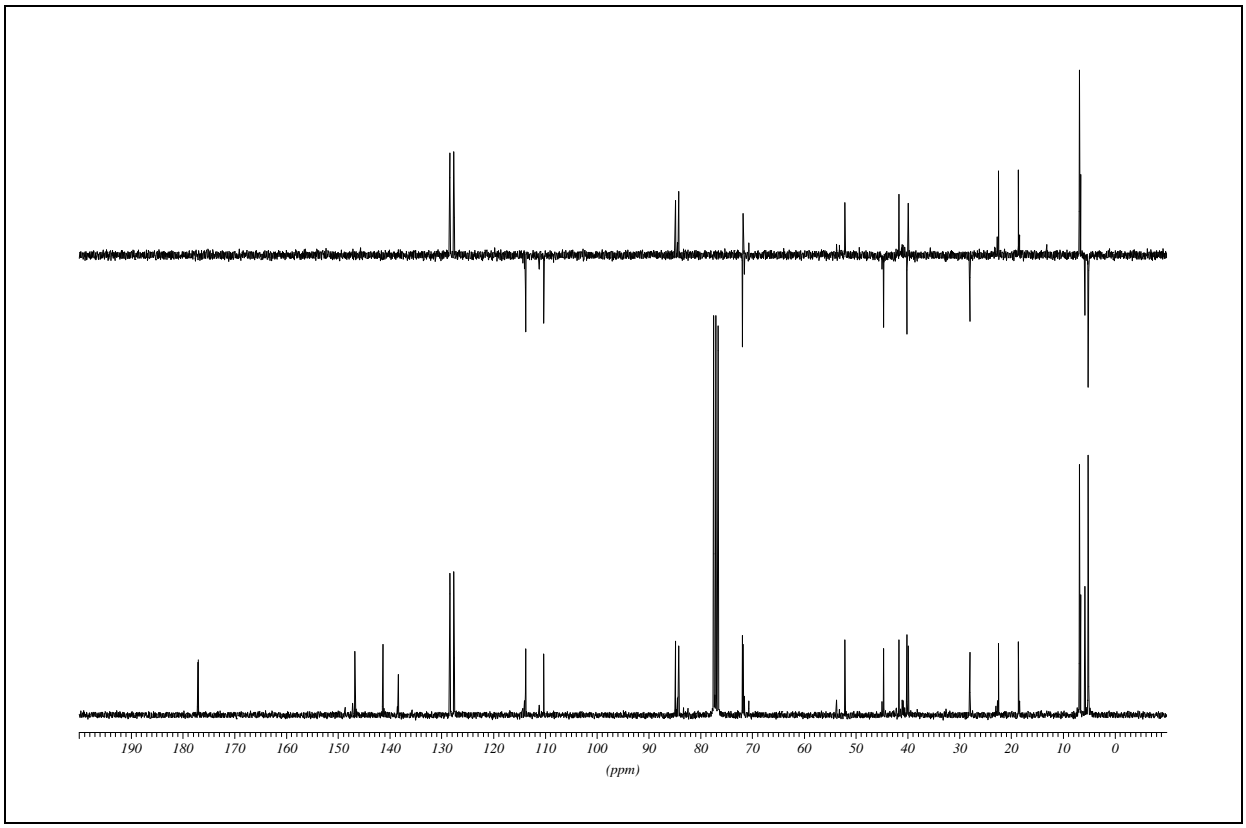
(4*S*,5*R*)-5-[(1'*S*,2'*S*,3'*S*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-{3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**236**)



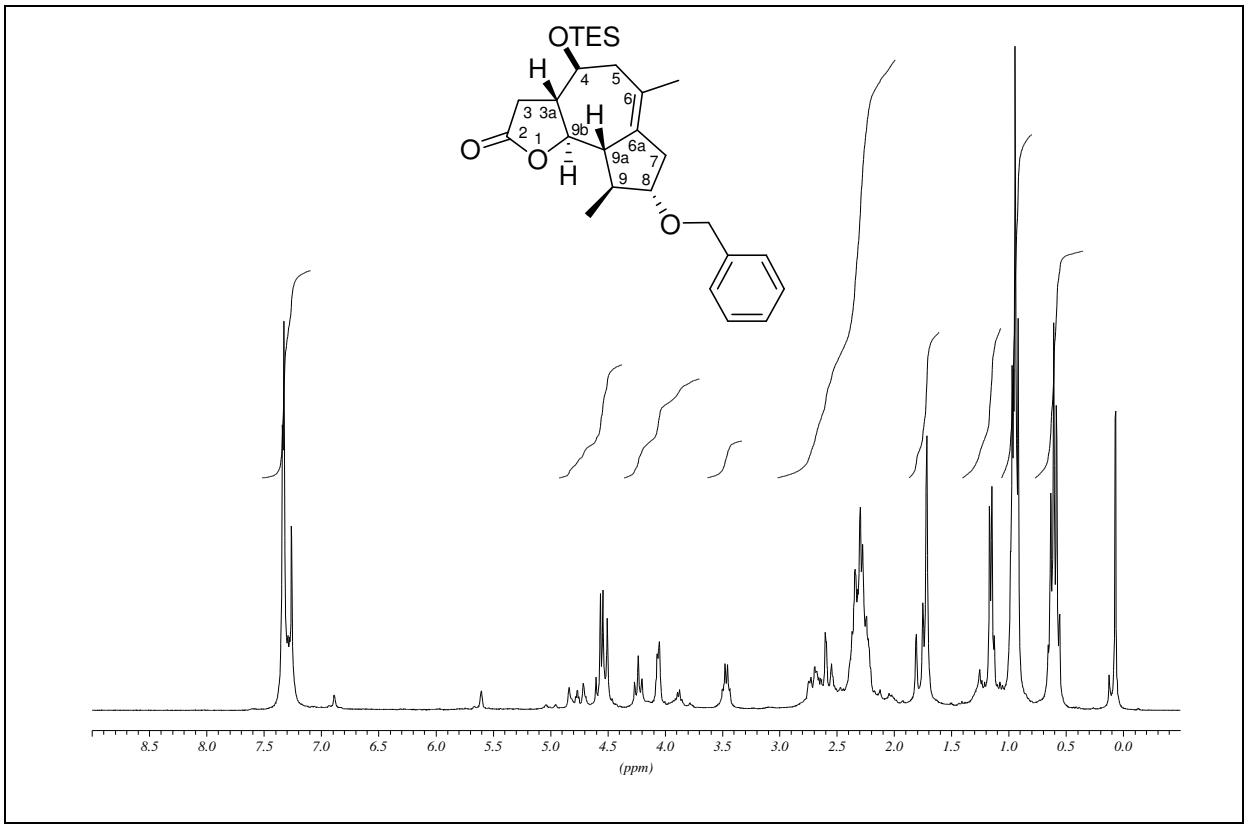


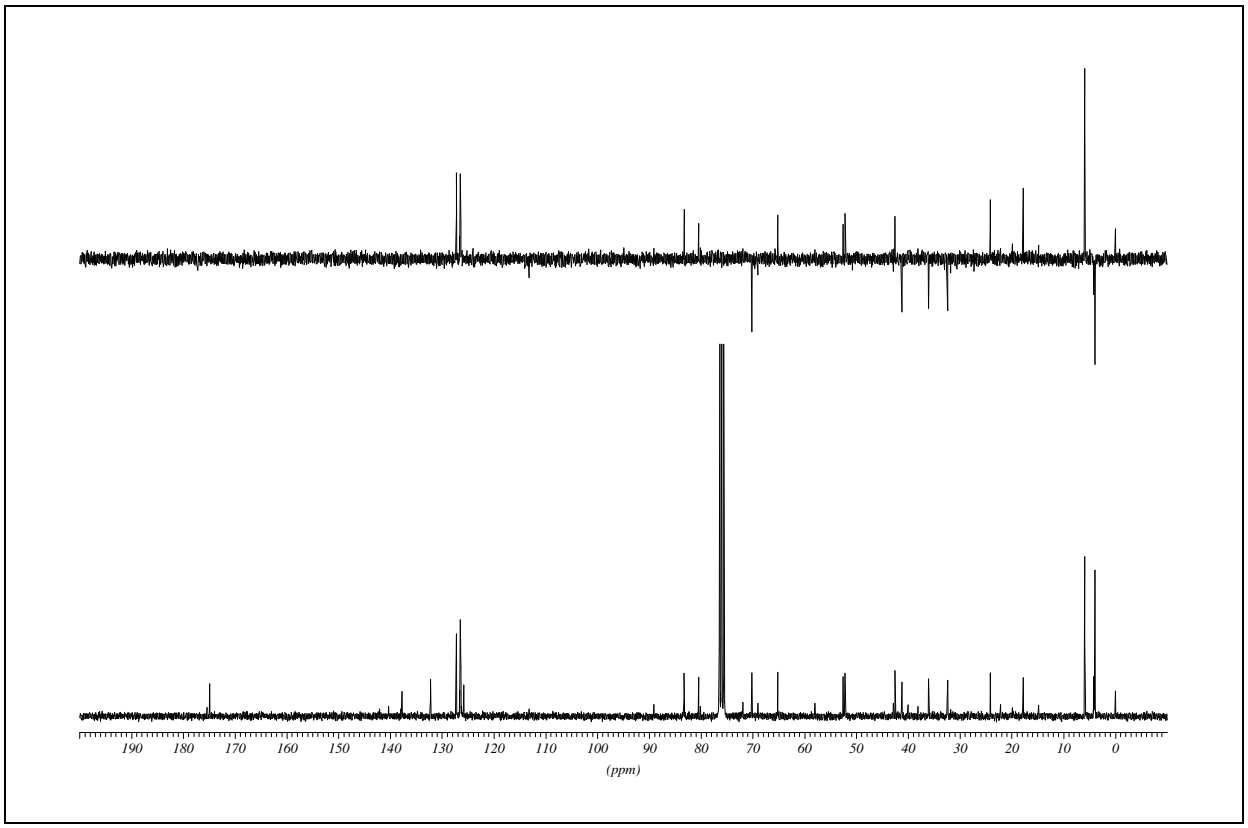
(4*S*,5*R*)-5-[(1'*R*,2'*R*,3'*R*)-3'-(benzyloxy)-2'-methyl-5'-methylenecyclopentyl]-4-{3"-methyl-1"-[(triethylsilyl)oxy]-3"-butenyl}dihydro-2(3*H*)-furanone (**238**)



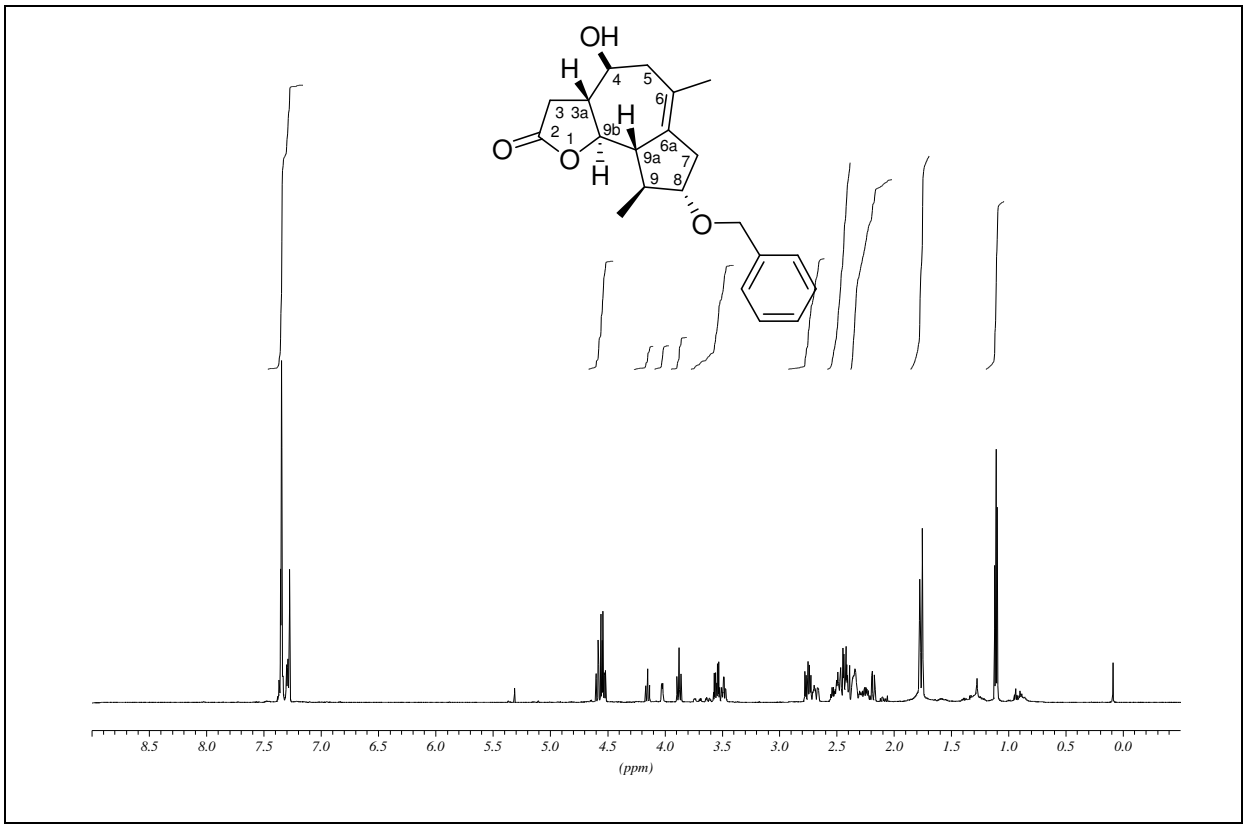


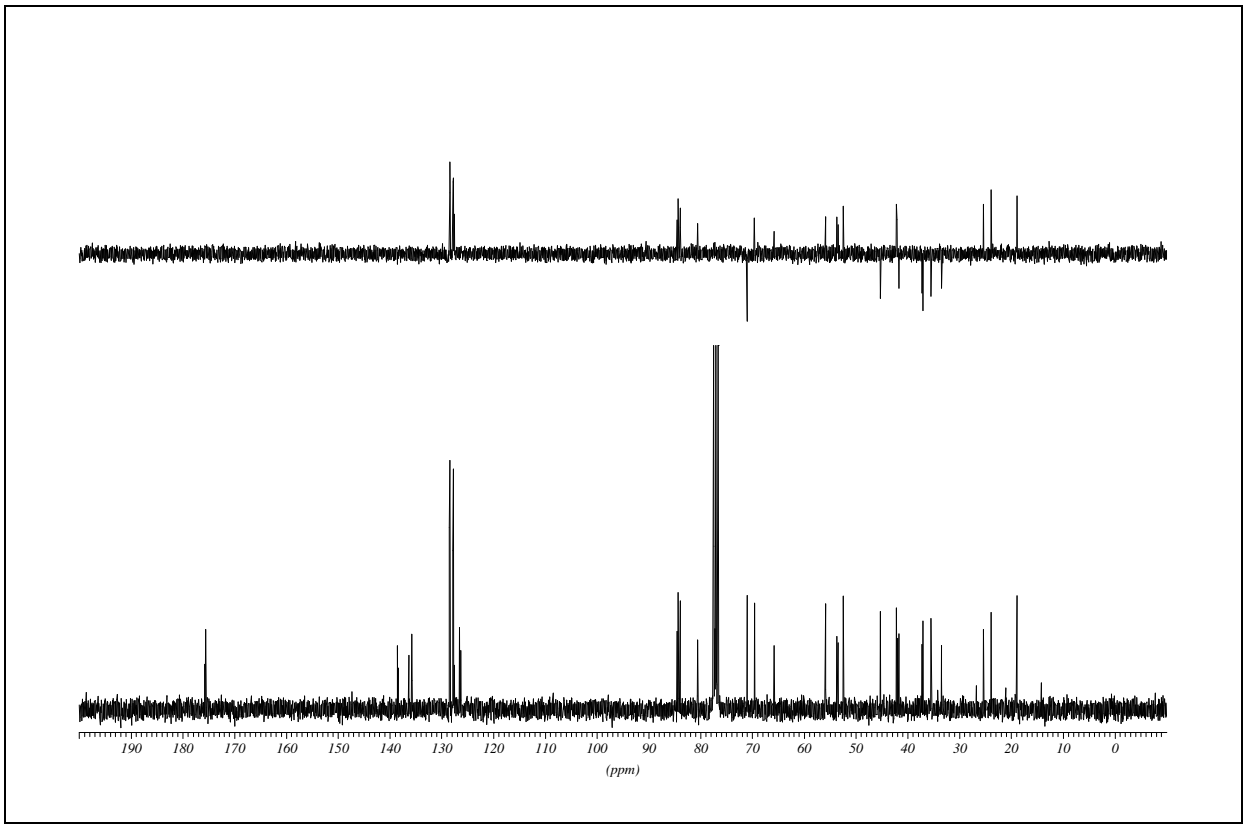
(3a*S*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-4-[(triethylsilyl)oxy]-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**239**)



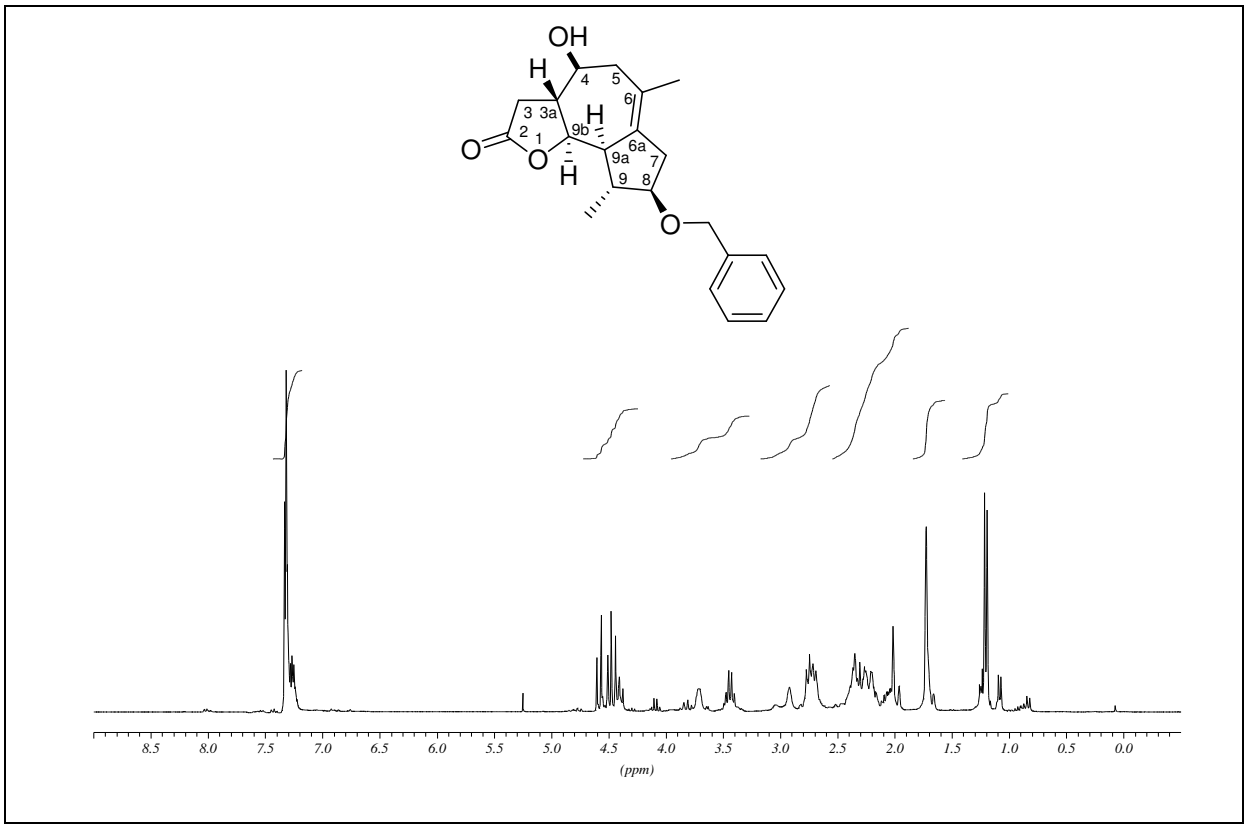


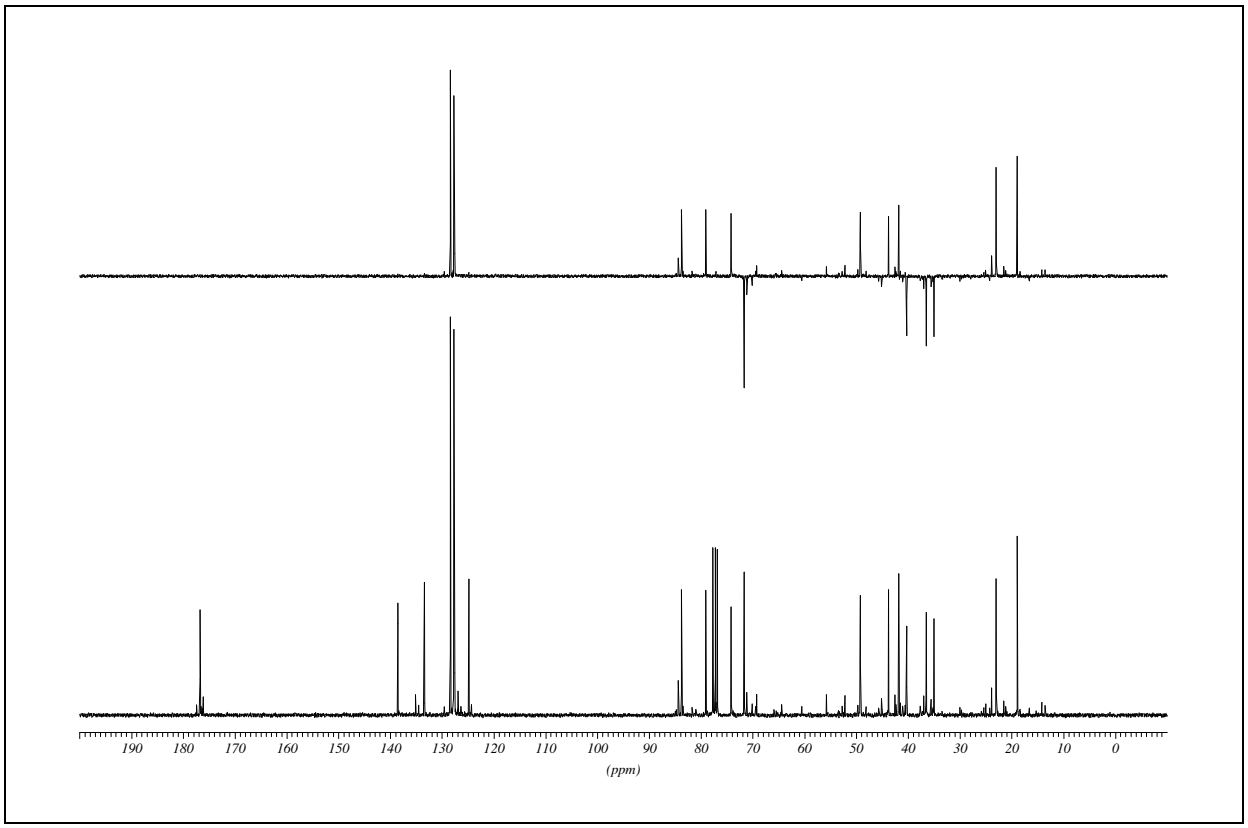
(3a*R*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-4-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**240**)



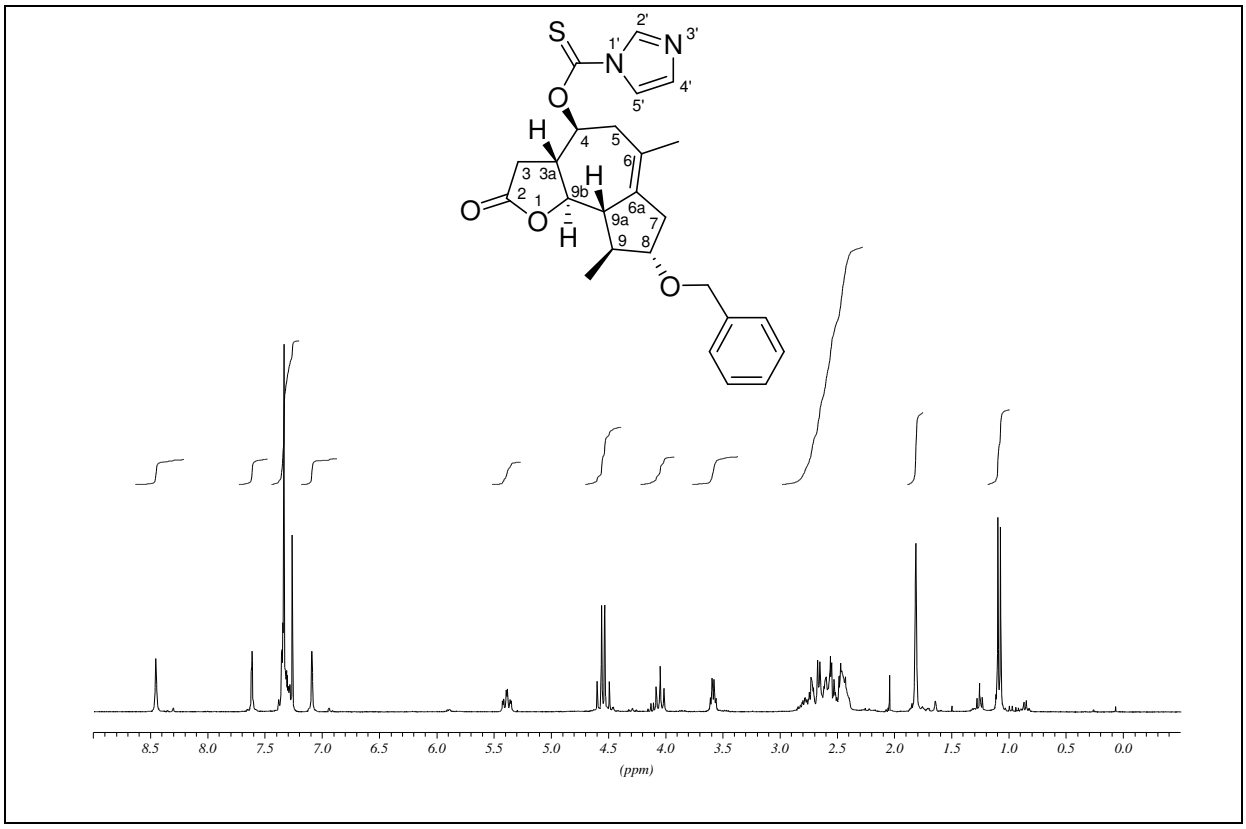


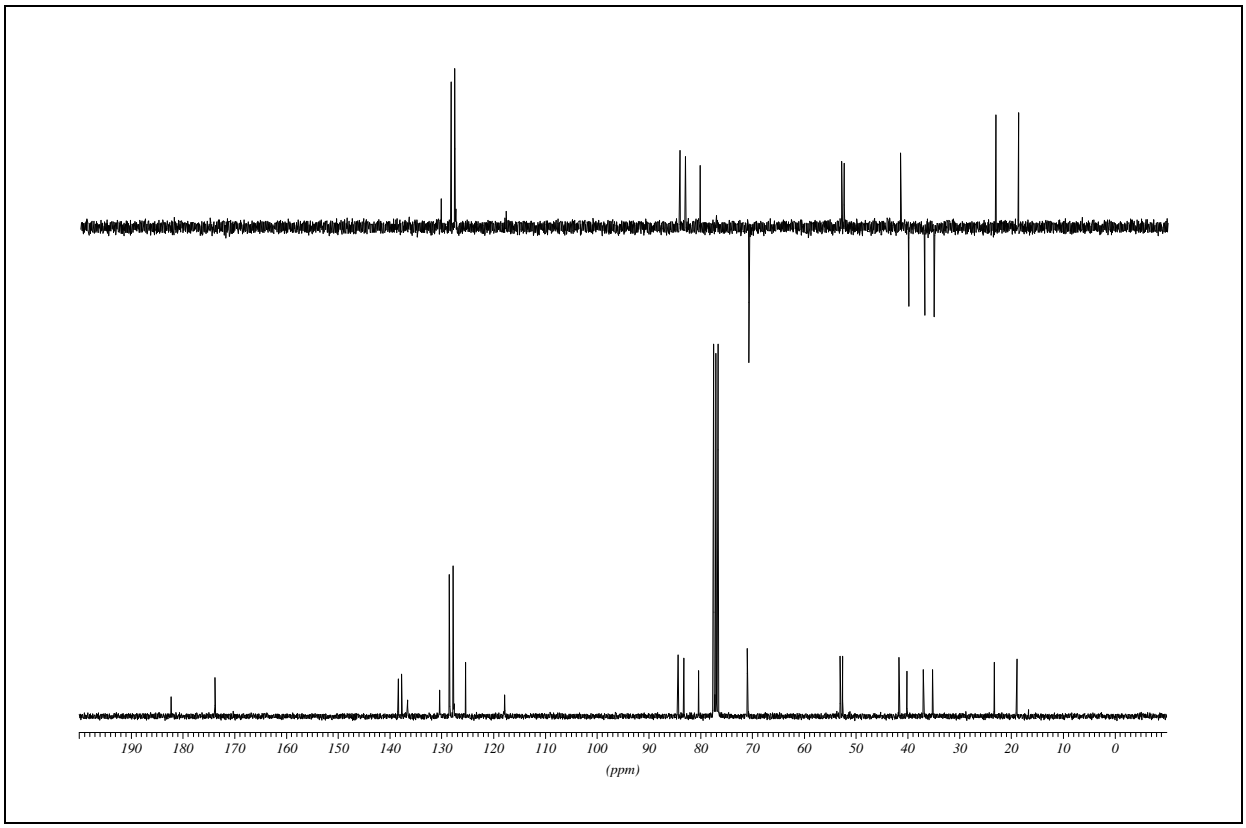
(3a*R*,4*S*,8*R*,9*R*,9a*R*,9b*R*)-8-(benzyloxy)-4-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**241**)



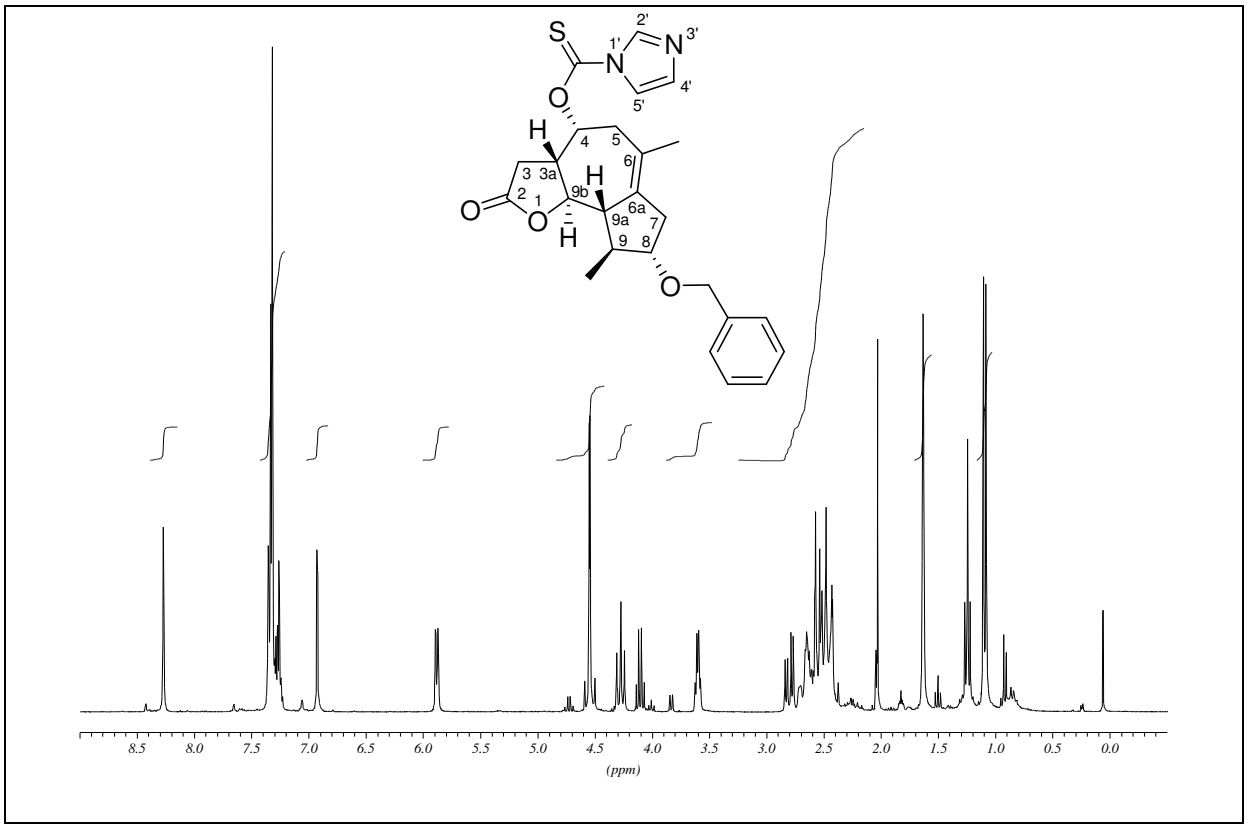


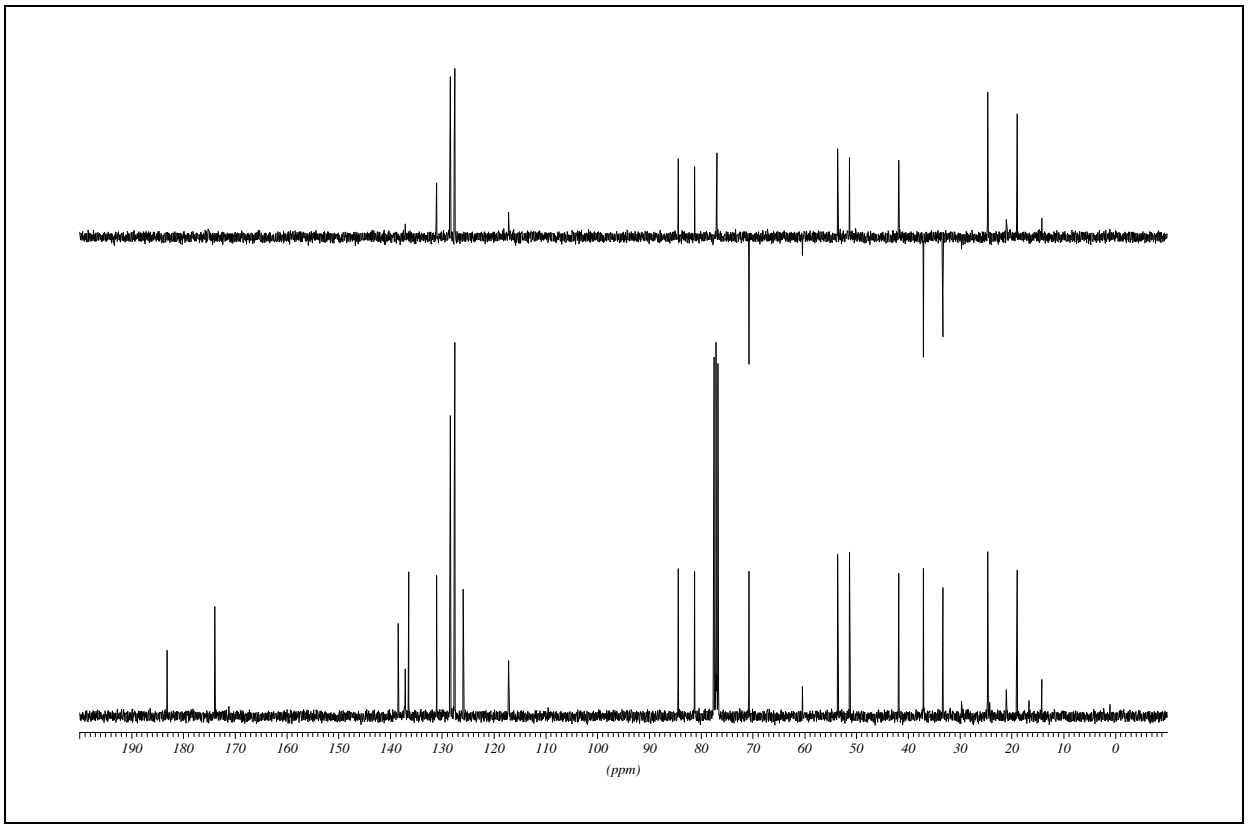
O-[(3a*S*,4*S*,8*S*,9*S*,9a*S*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-*b*]furan-4-yl] 1*H*-imidazole-1-carbothioate (**243**, major diastereomer)



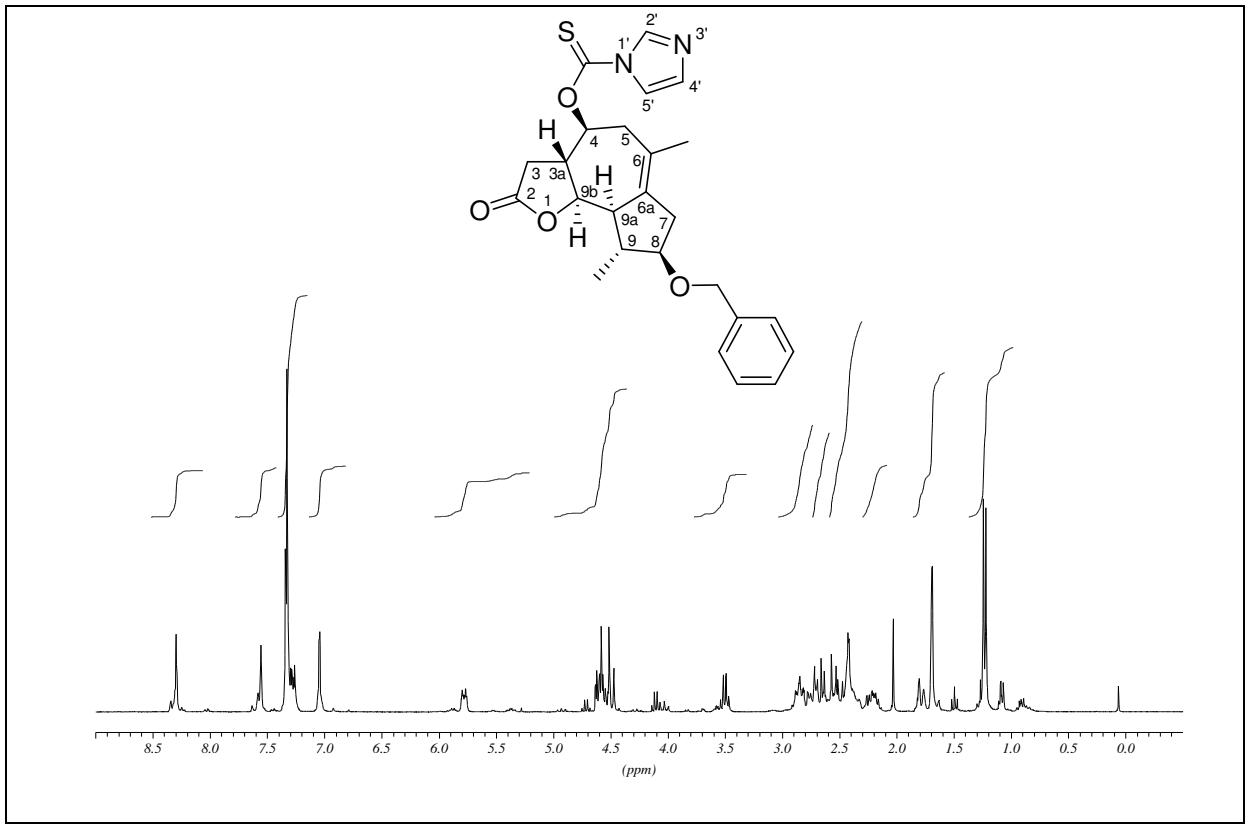


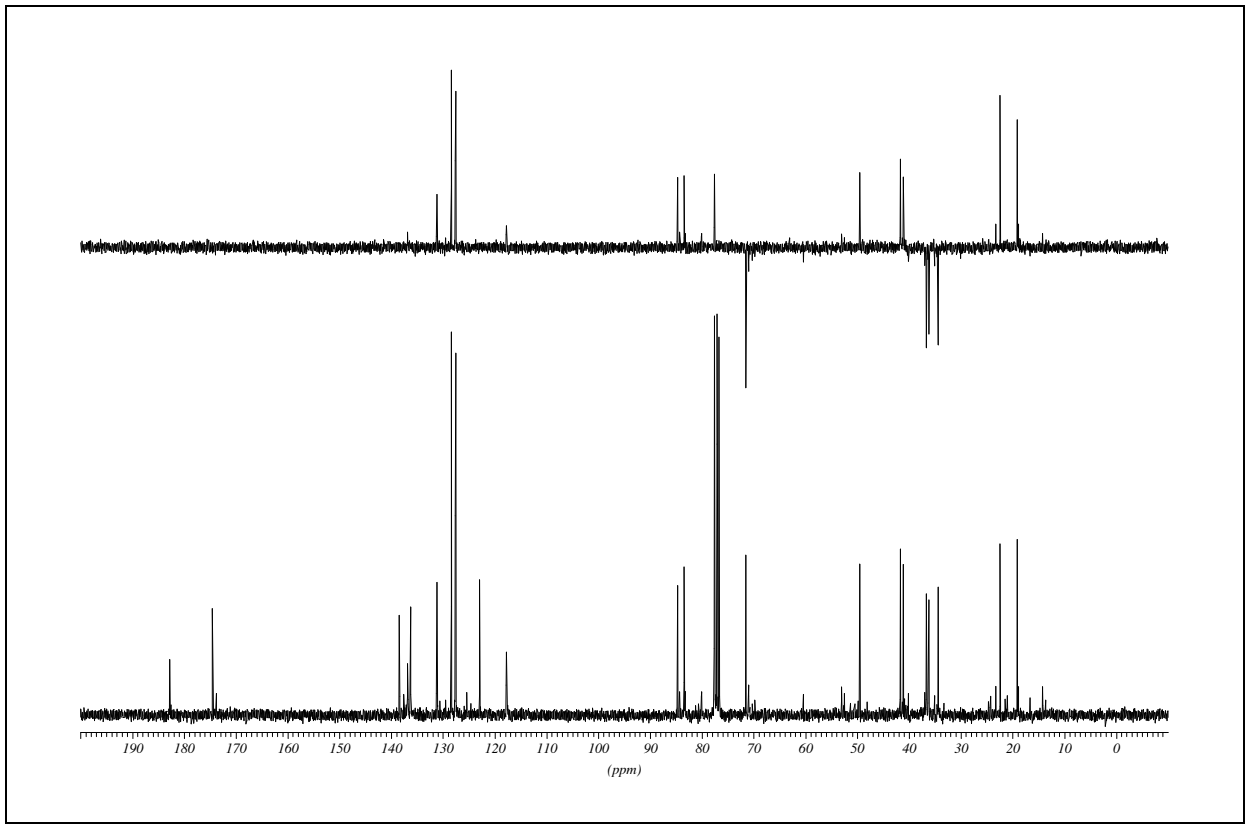
O-[(3aS,4R,8S,9S,9aS,9bR)-8-(benzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-b]furan-4-yl] 1H-imidazole-1-carbothioate (**243**, minor diastereomer)



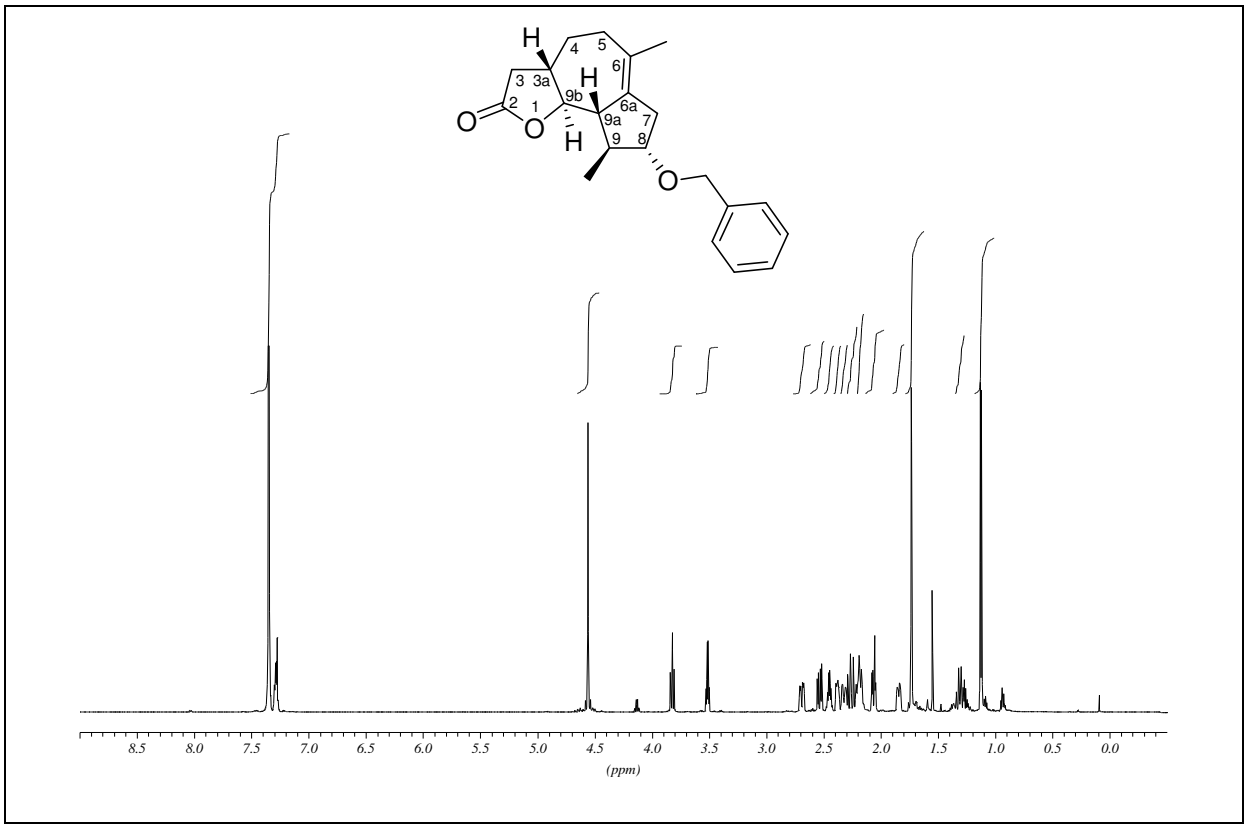


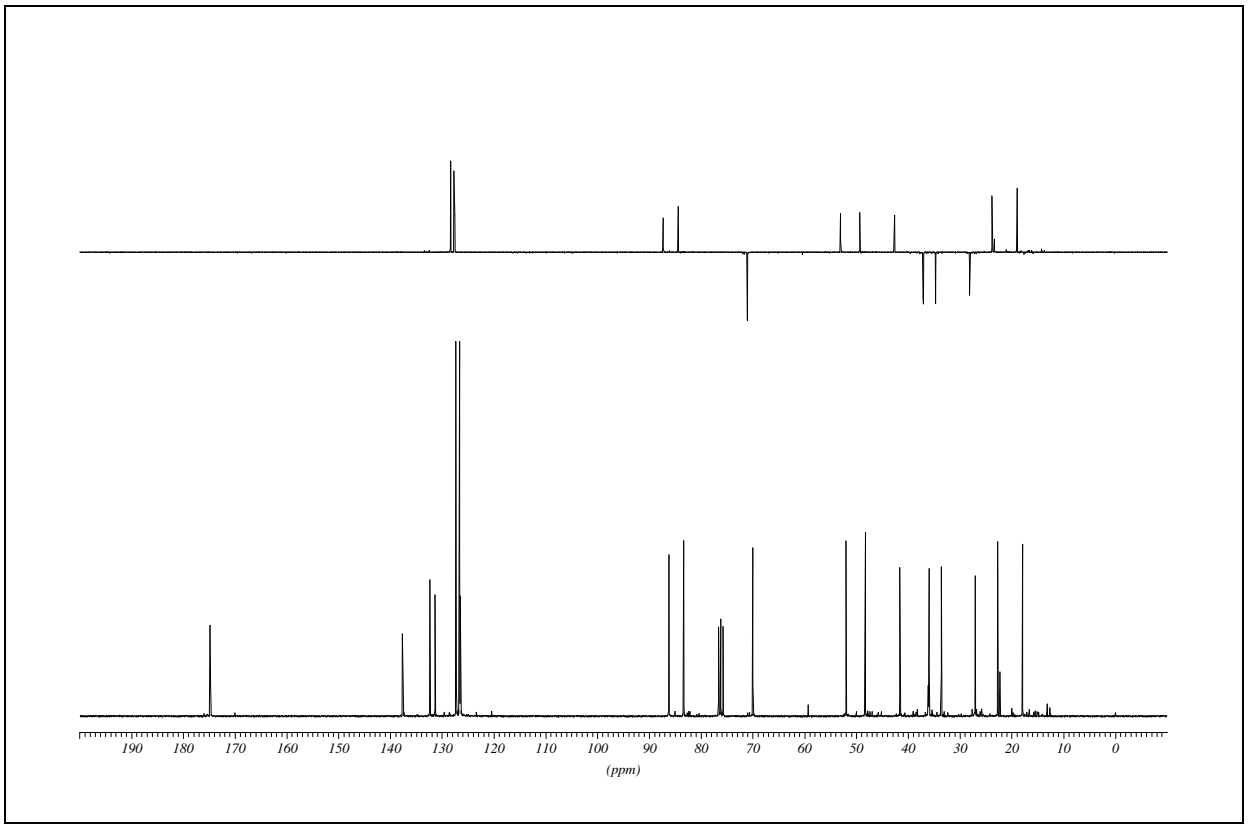
O-[(3a*S*,4*S*,8*R*,9*R*,9a*R*,9b*R*)-8-(benzyloxy)-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydroazuleno[4,5-*b*]furan-4-yl] 1*H*-imidazole-1-carbothioate (**245**)



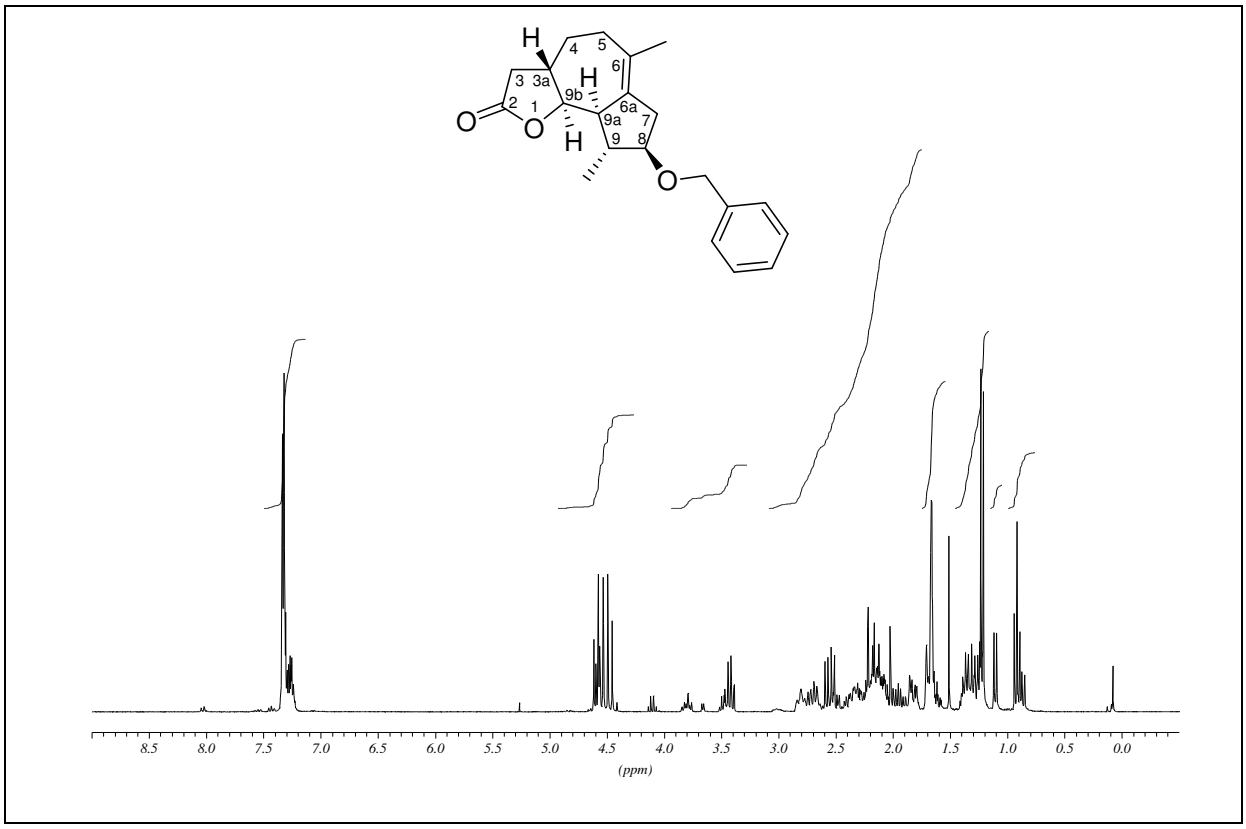


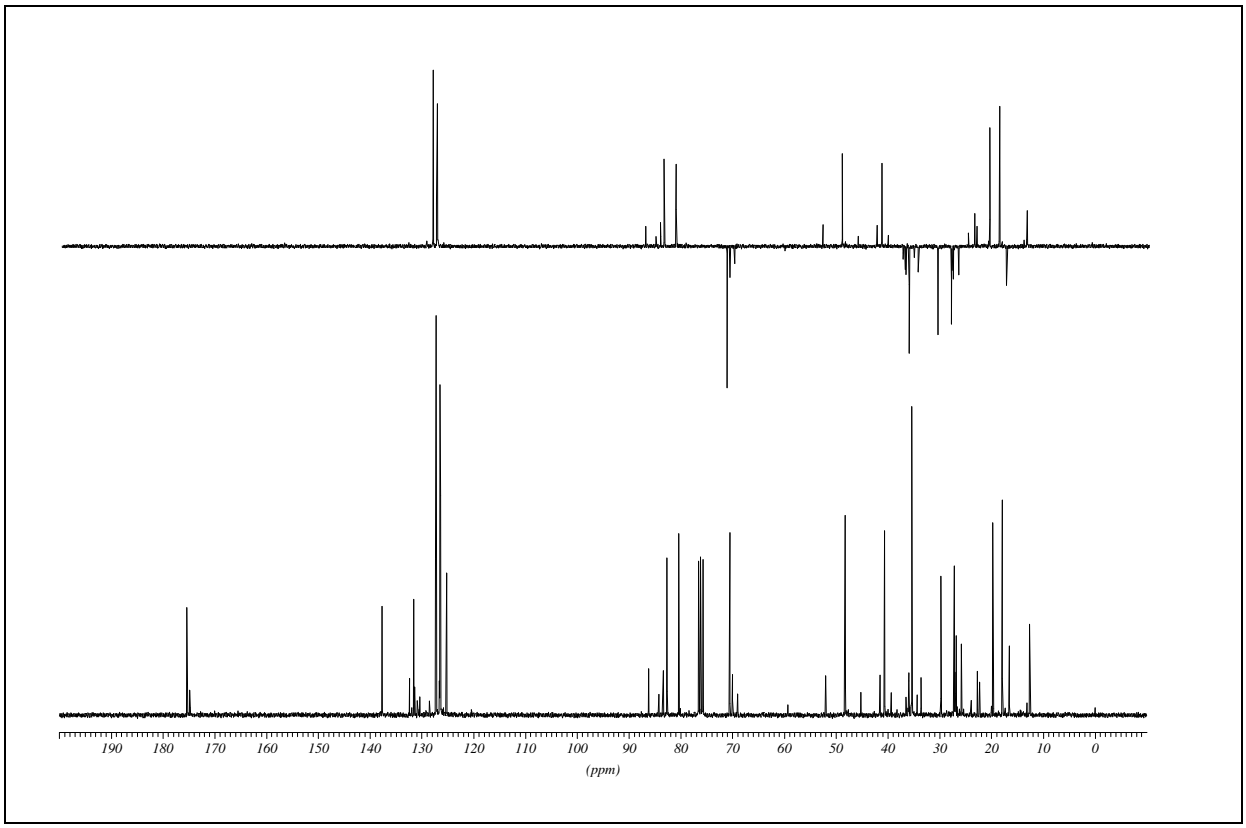
(3a*S*,8*S*,9*S*,9a*S*,9b*S*)-8-(benzyloxy)-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**244**)



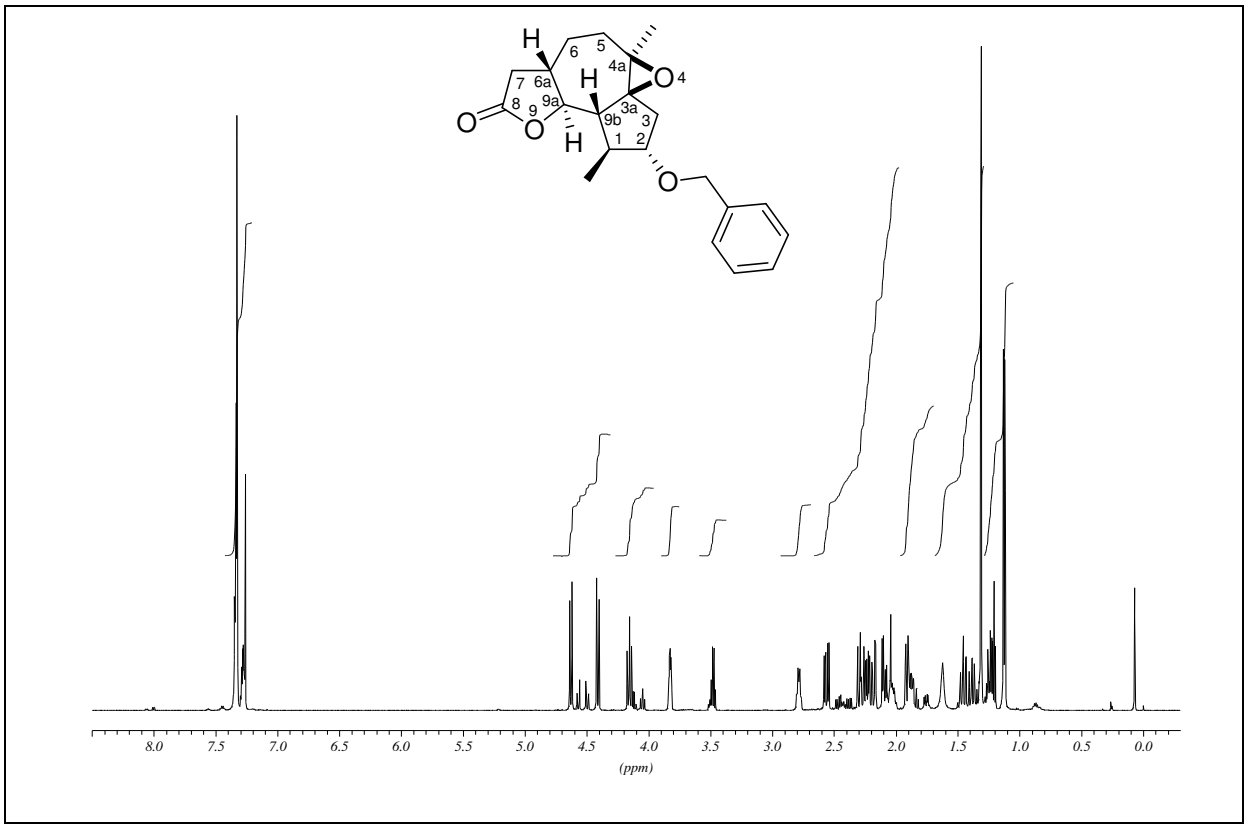


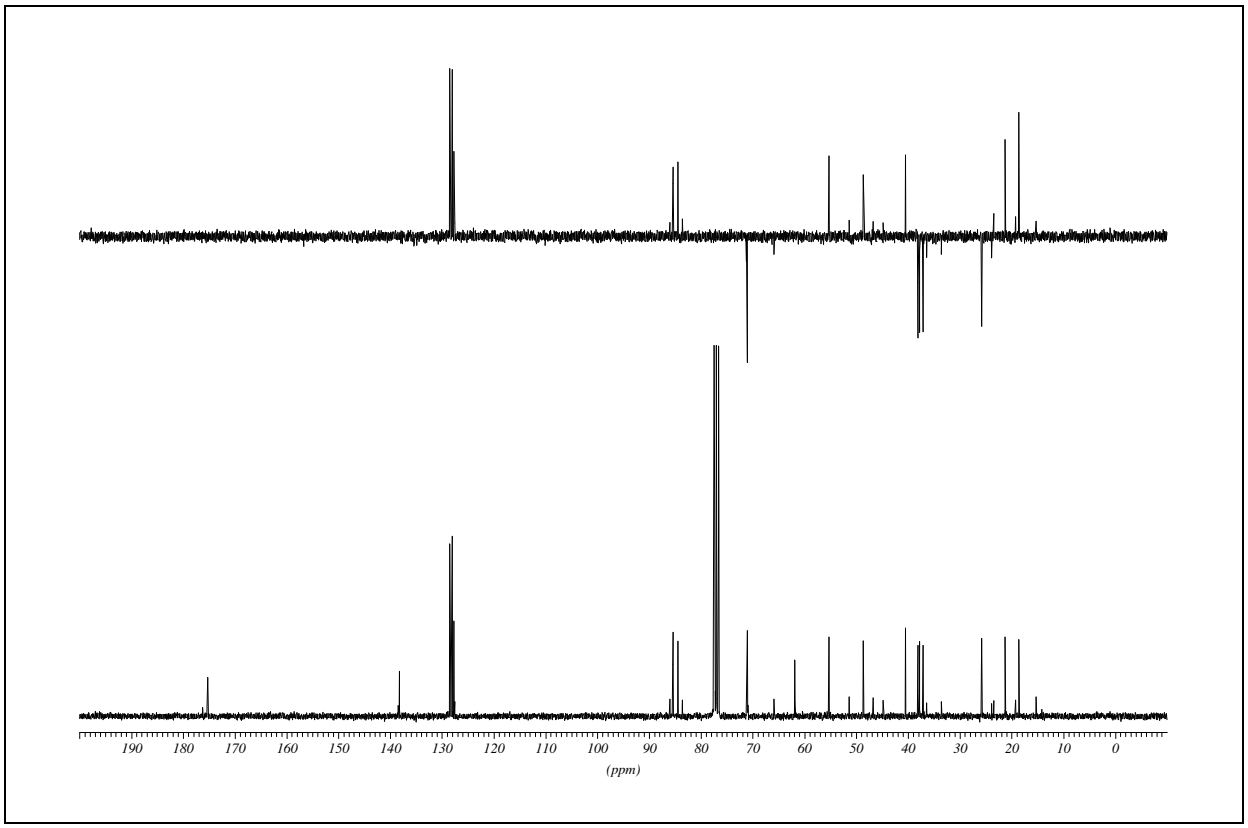
(3a*S*,8*R*,9*R*,9a*R*,9b*S*)-8-(benzyloxy)-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**246**)



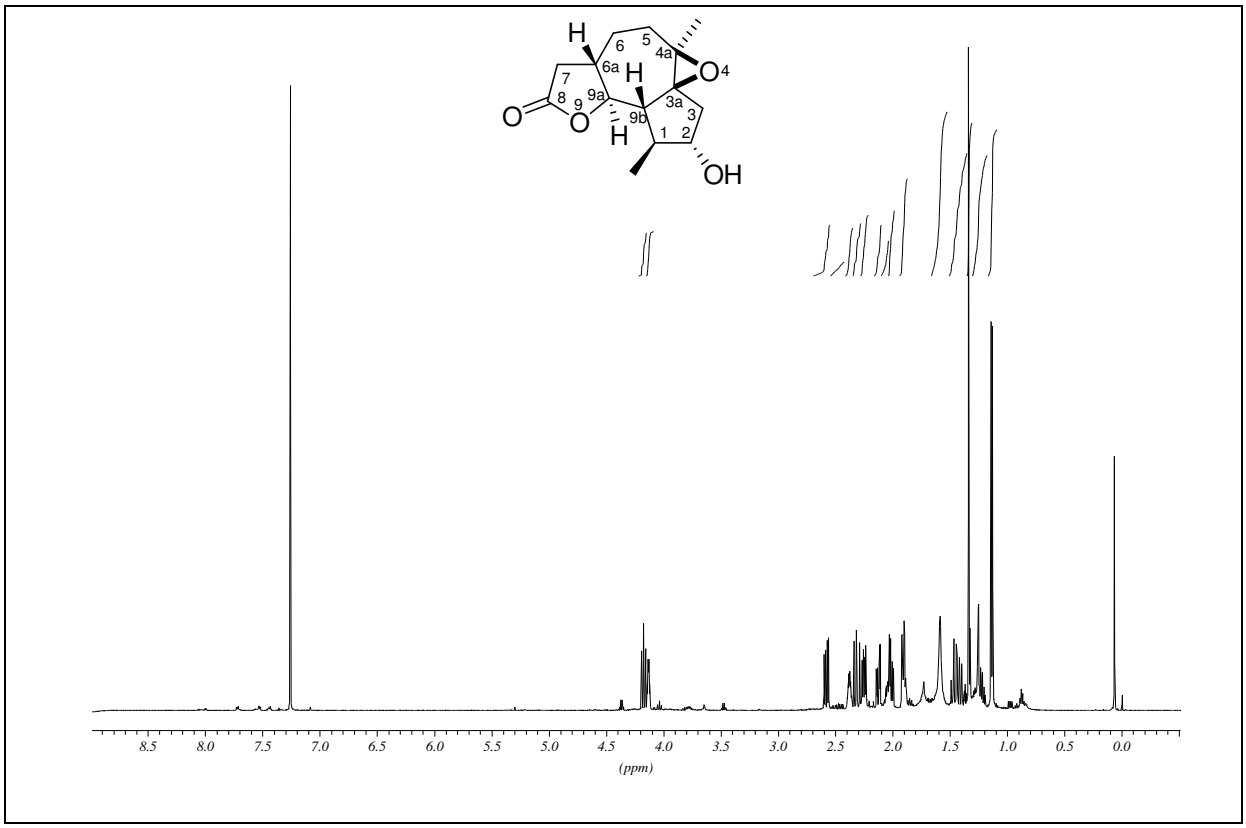


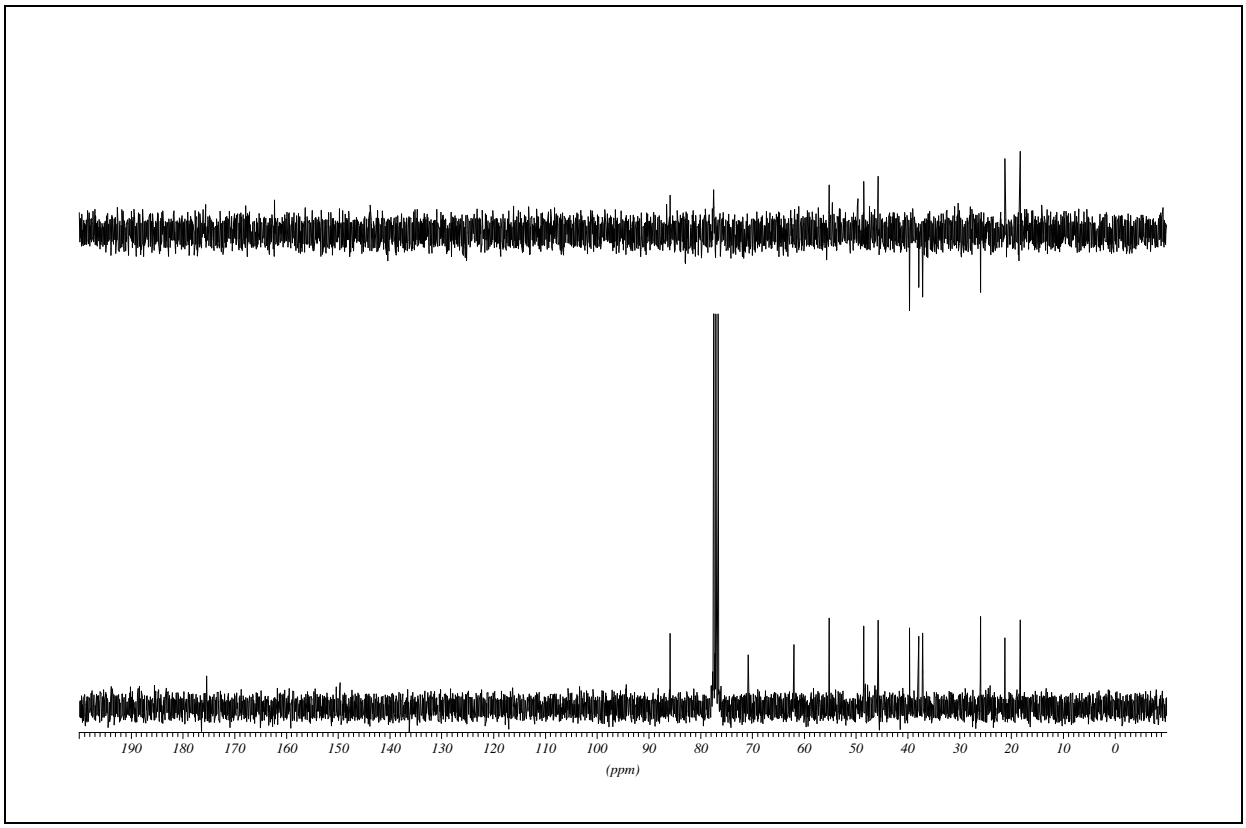
(1*S*,2*S*,3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-2-(benzyloxy)-1,4a-dimethyloctahydro-1*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (**248**)



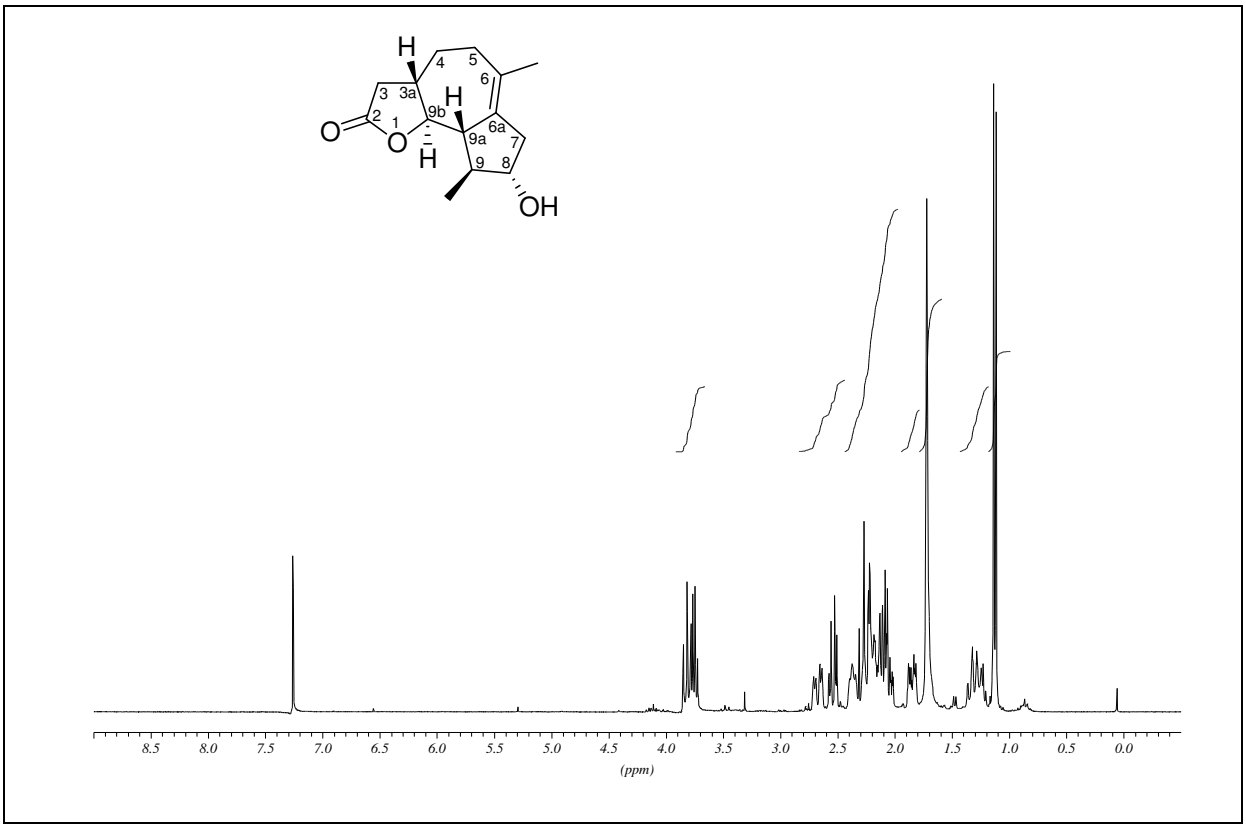


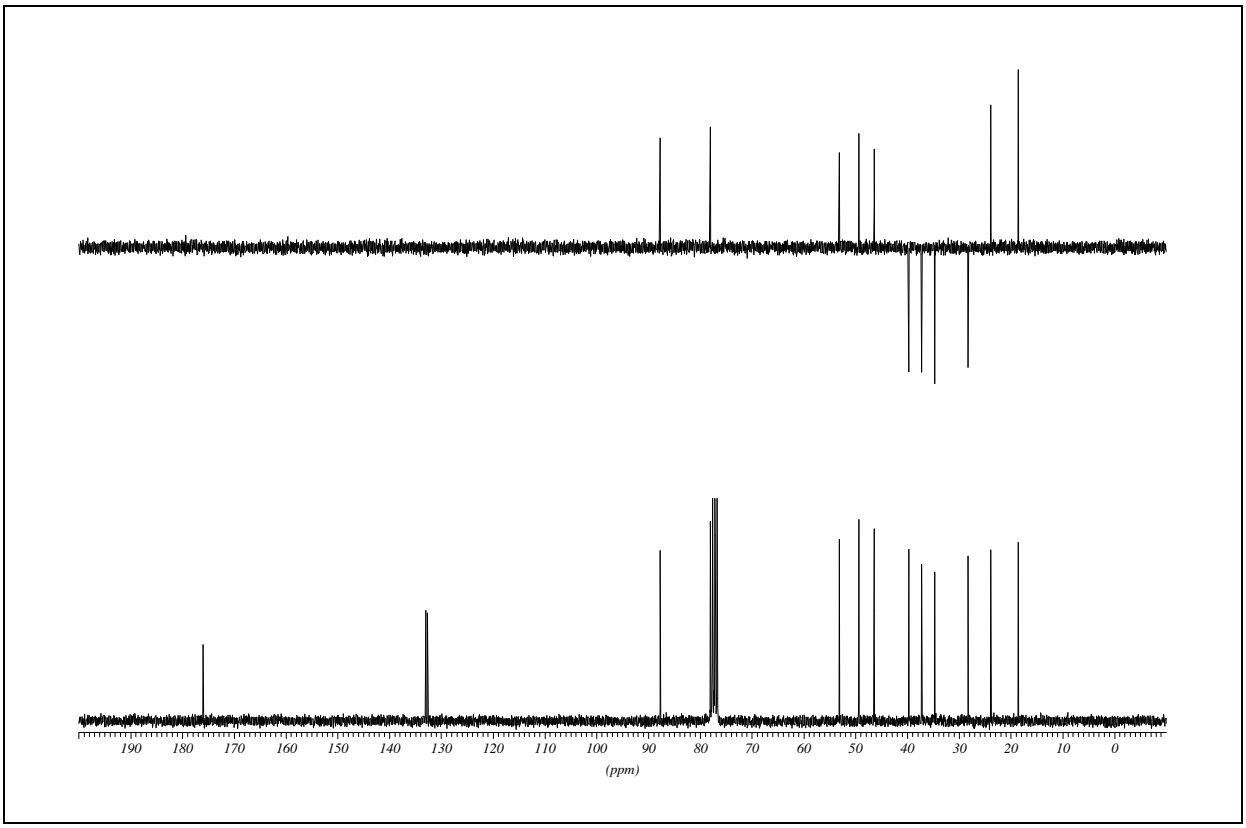
(1*S*,2*S*,3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-2-hydroxy-1,4a-dimethyloctahydro-1*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (**249**)



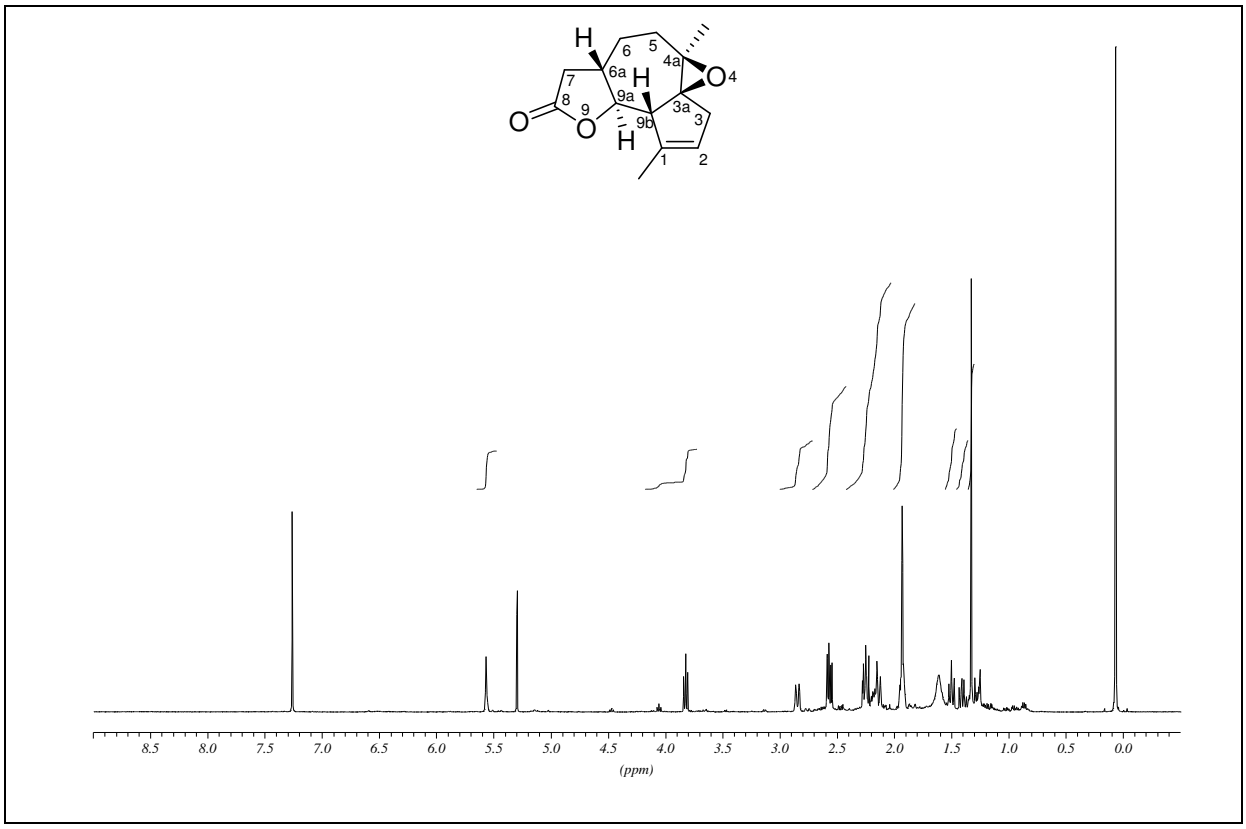


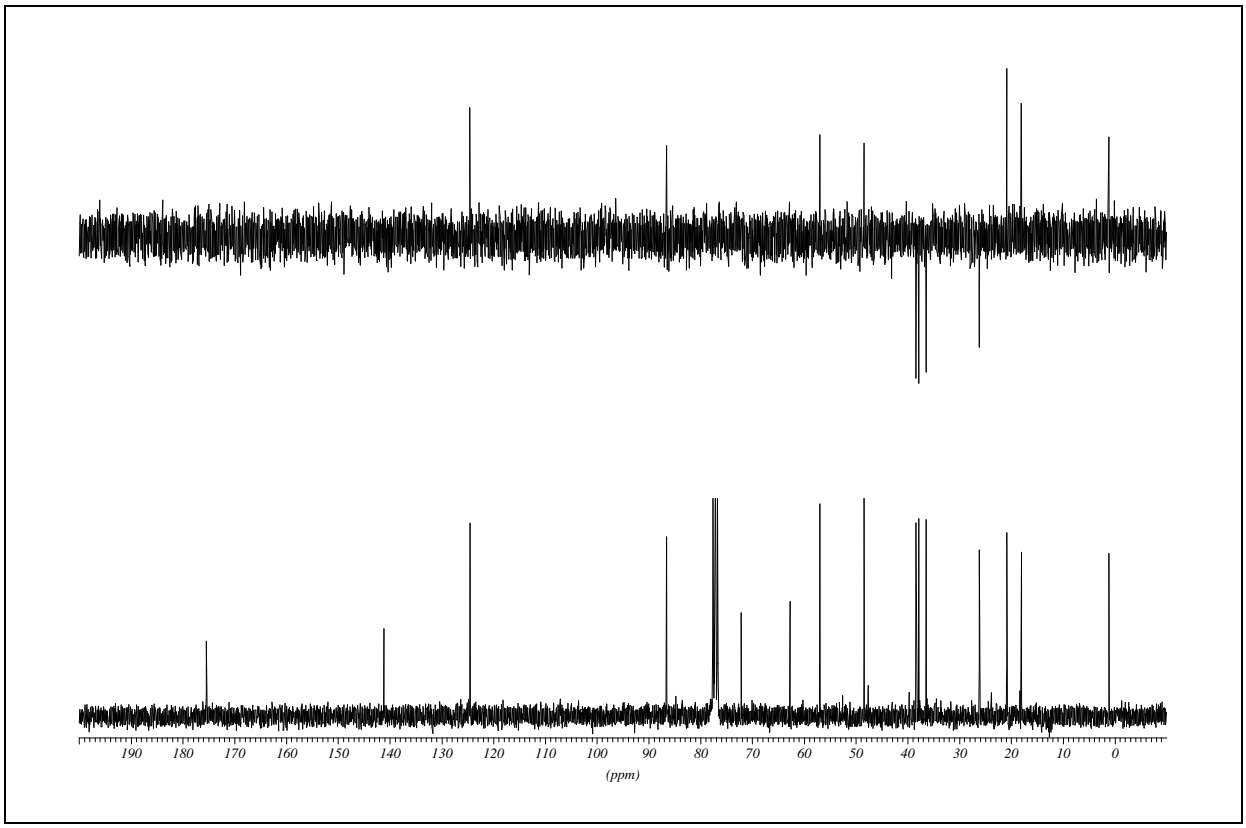
(3a*S*,8*S*,9*S*,9a*S*,9b*S*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydroazuleno[4,5-*b*]furan-2(3*H*)-one (**250**)



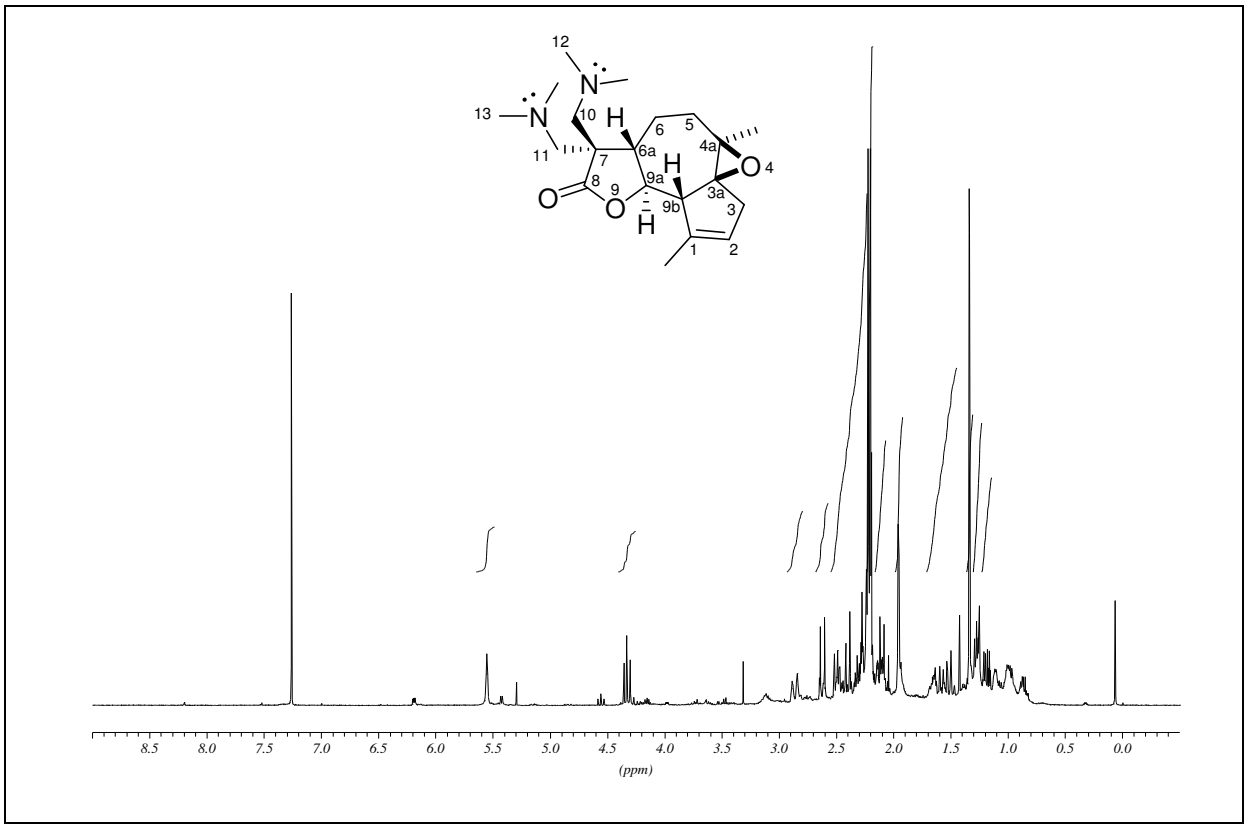


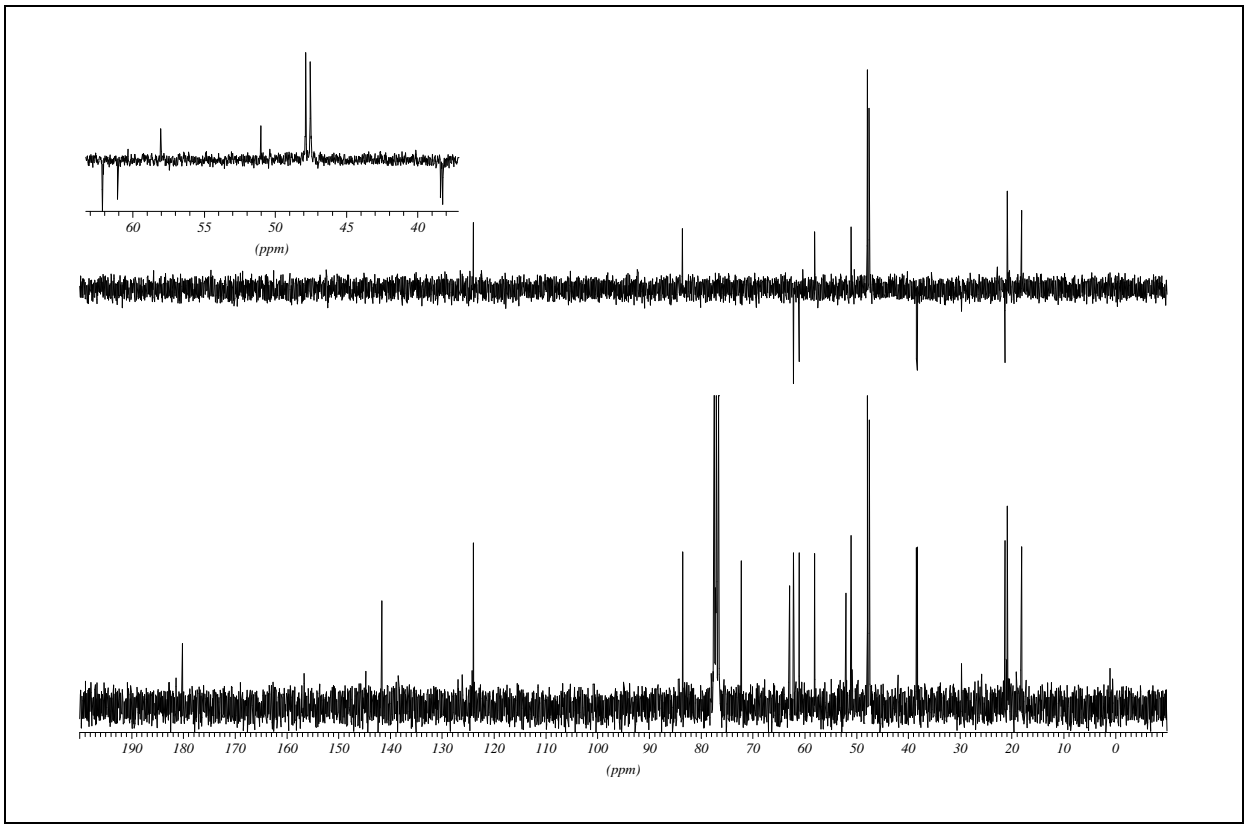
(3a*S*,4a*R*,6a*S*,9a*S*,9b*R*)-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (**251**)



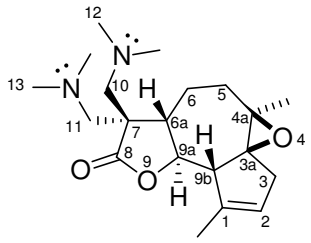


(3a*S*,4a*R*,6a*S*,9a*R*,9b*R*)-7,7-bis[(dimethylamino)methyl]-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (**263**)

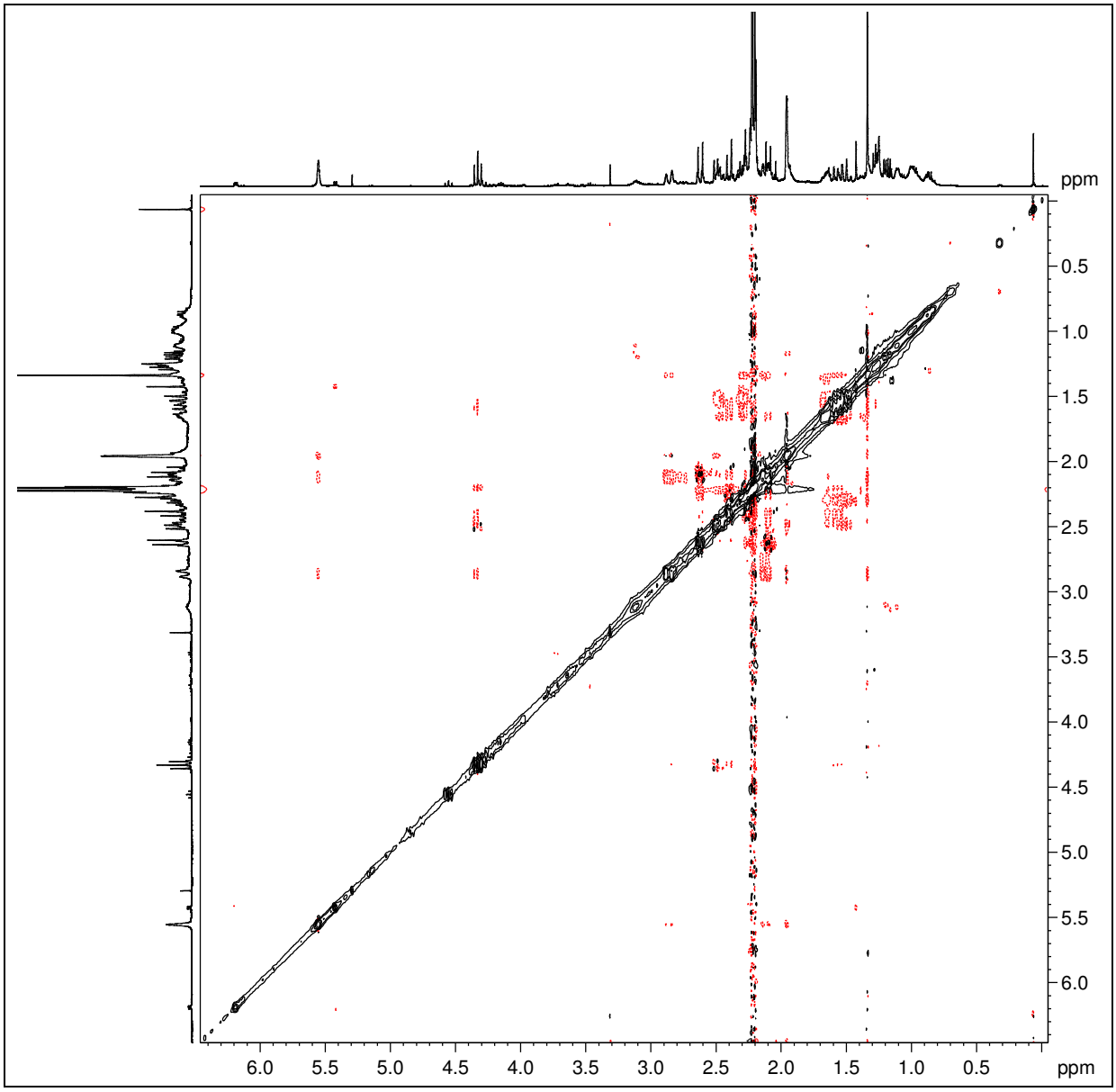




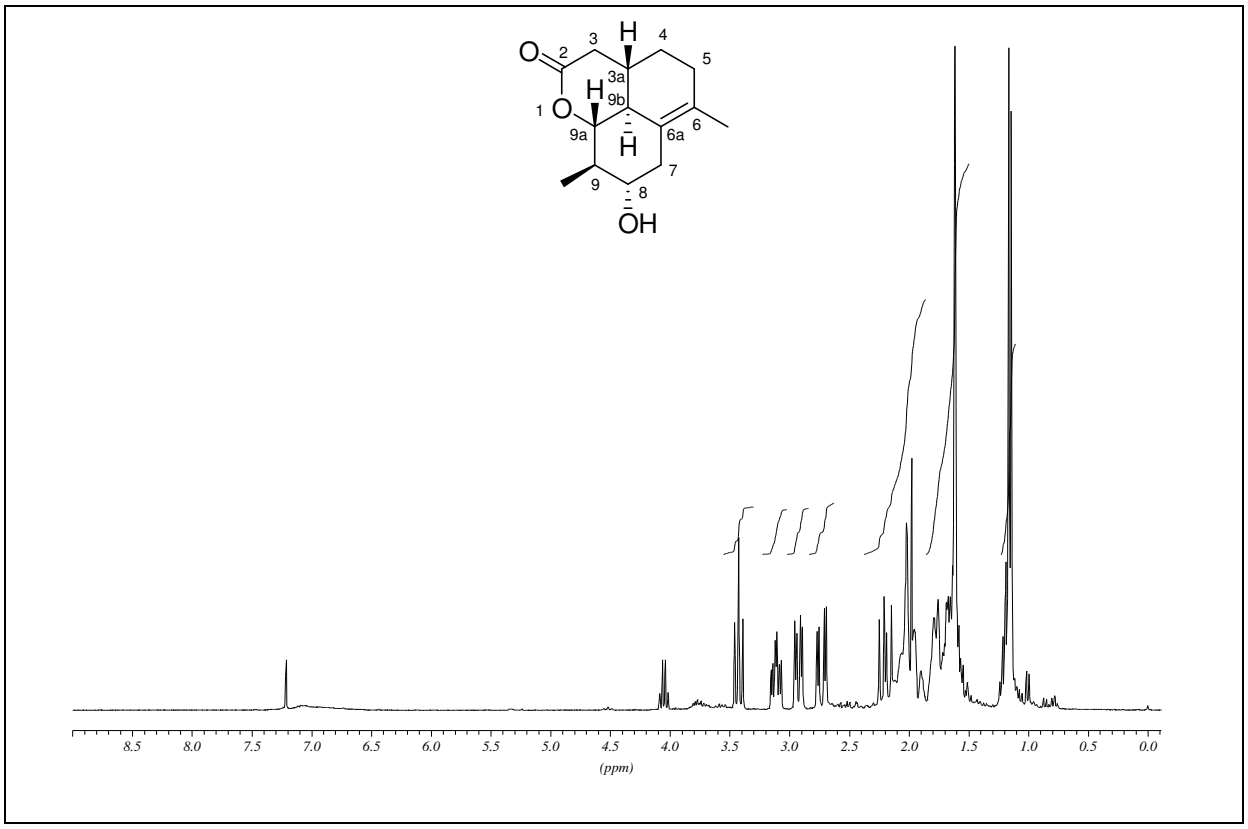
(3a*S*,4a*R*,6a*S*,9a*R*,9b*R*)-7,7-bis[(dimethylamino)methyl]-1,4a-dimethyl-5,6,6a,7,9a,9b-hexahydro-3*H*-oxireno[2',3':8,8a]azuleno[4,5-*b*]furan-8(4a*H*)-one (**263**) NOESY

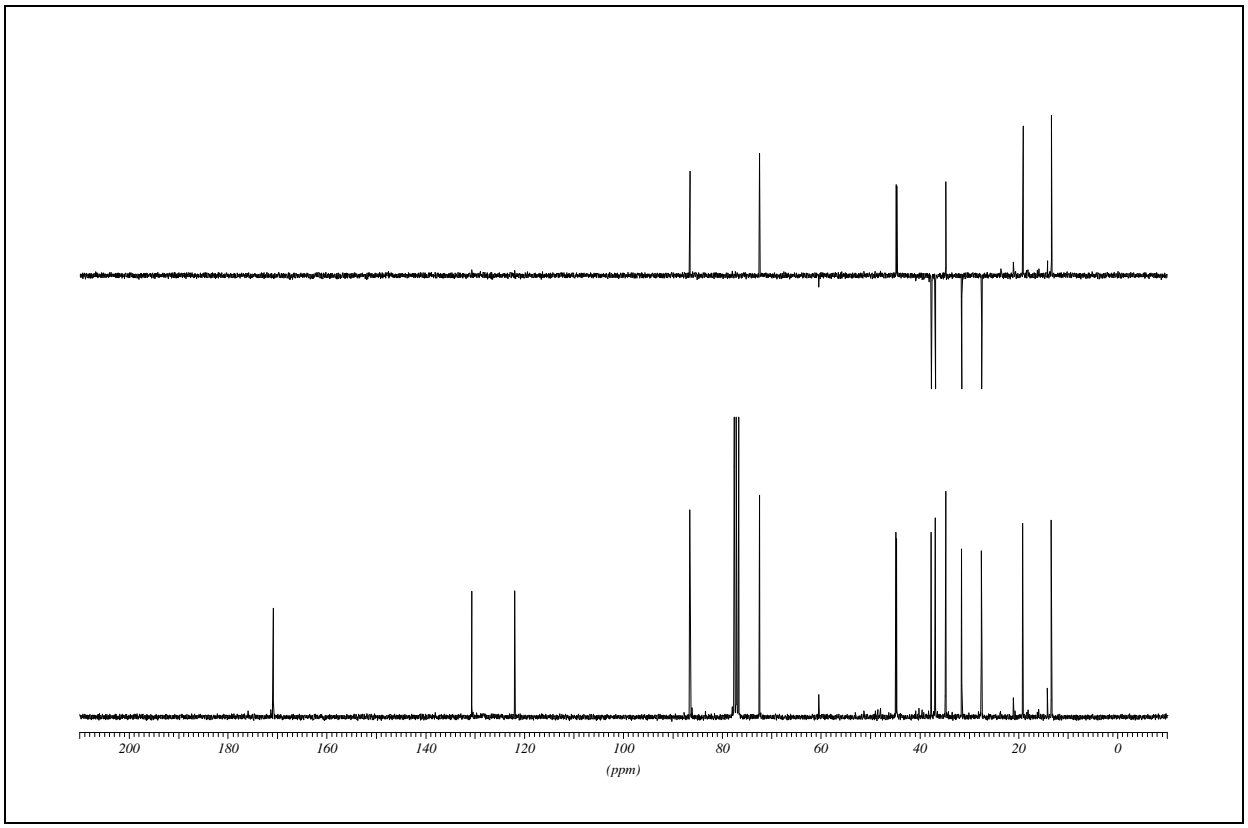


263

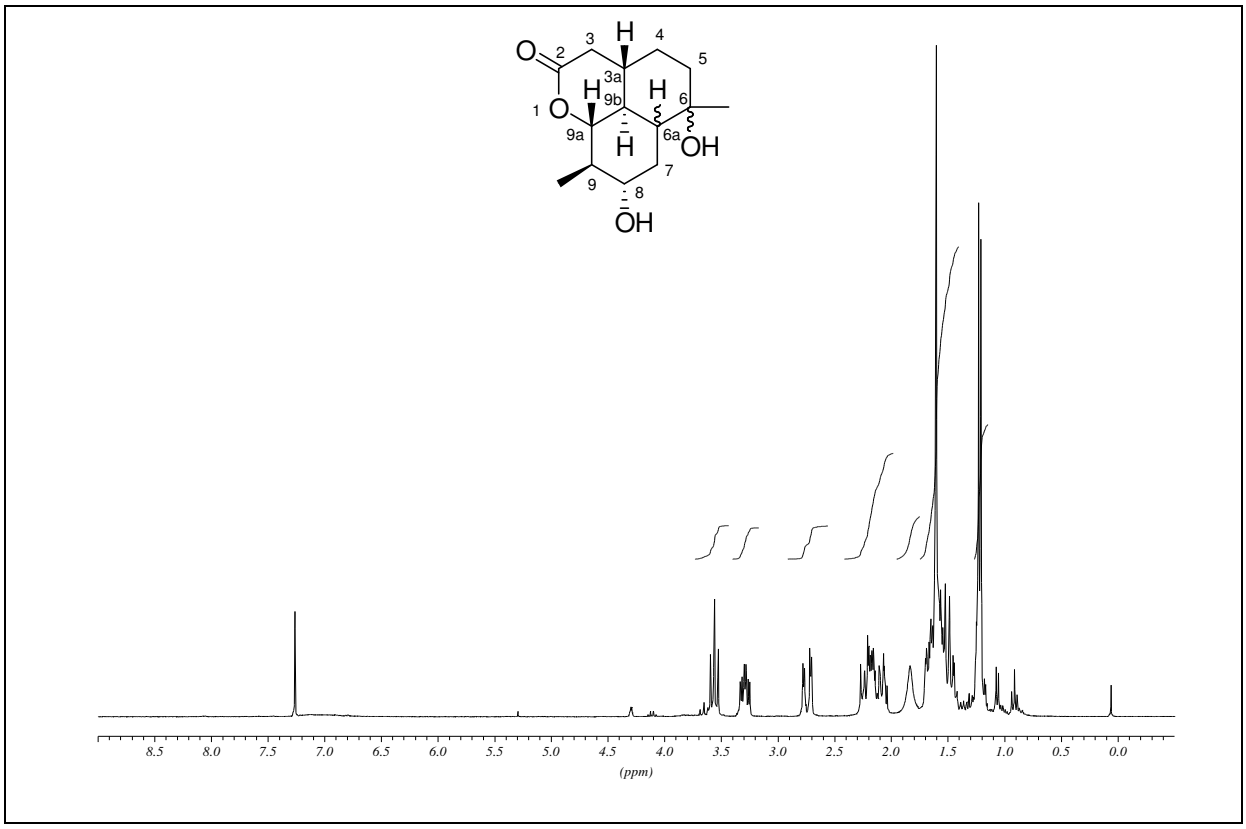


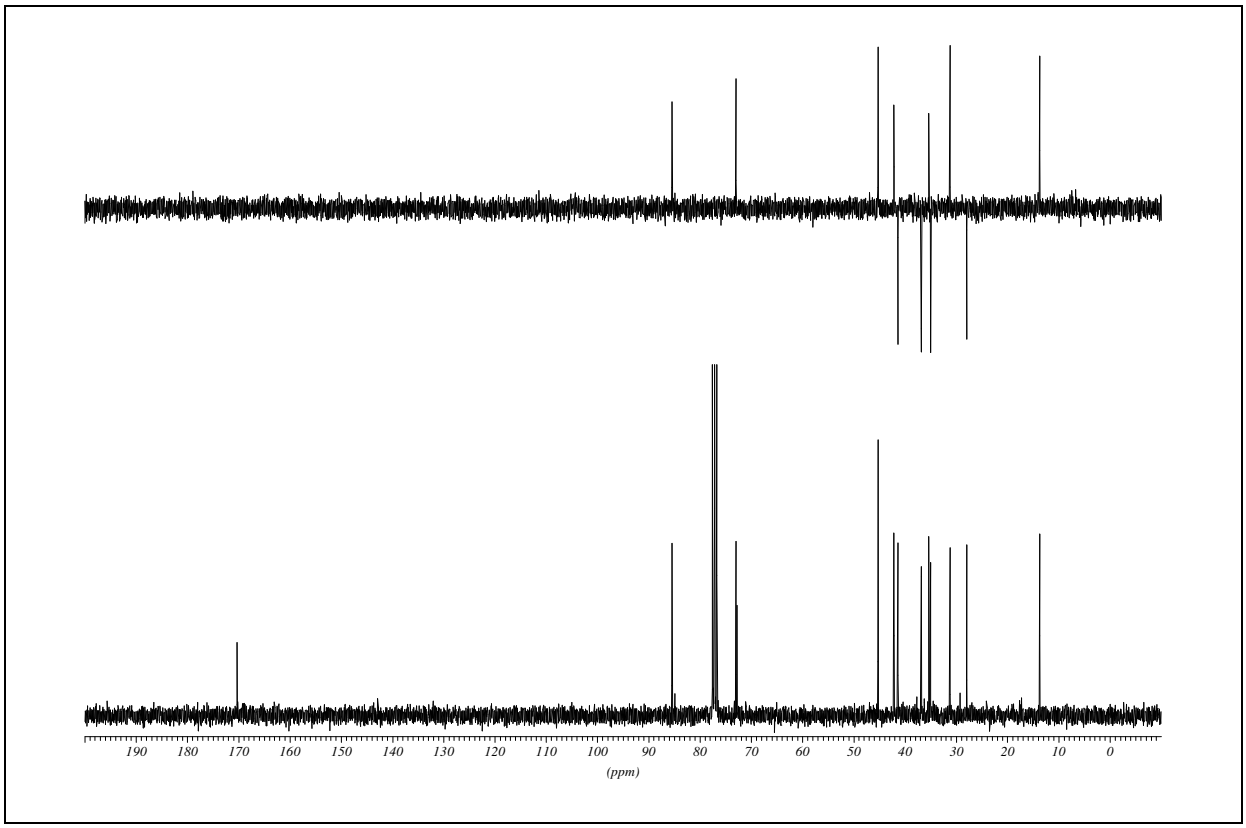
(3a*S*,8*R*,9*R*,9a*R*,9b*R*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (**247**)



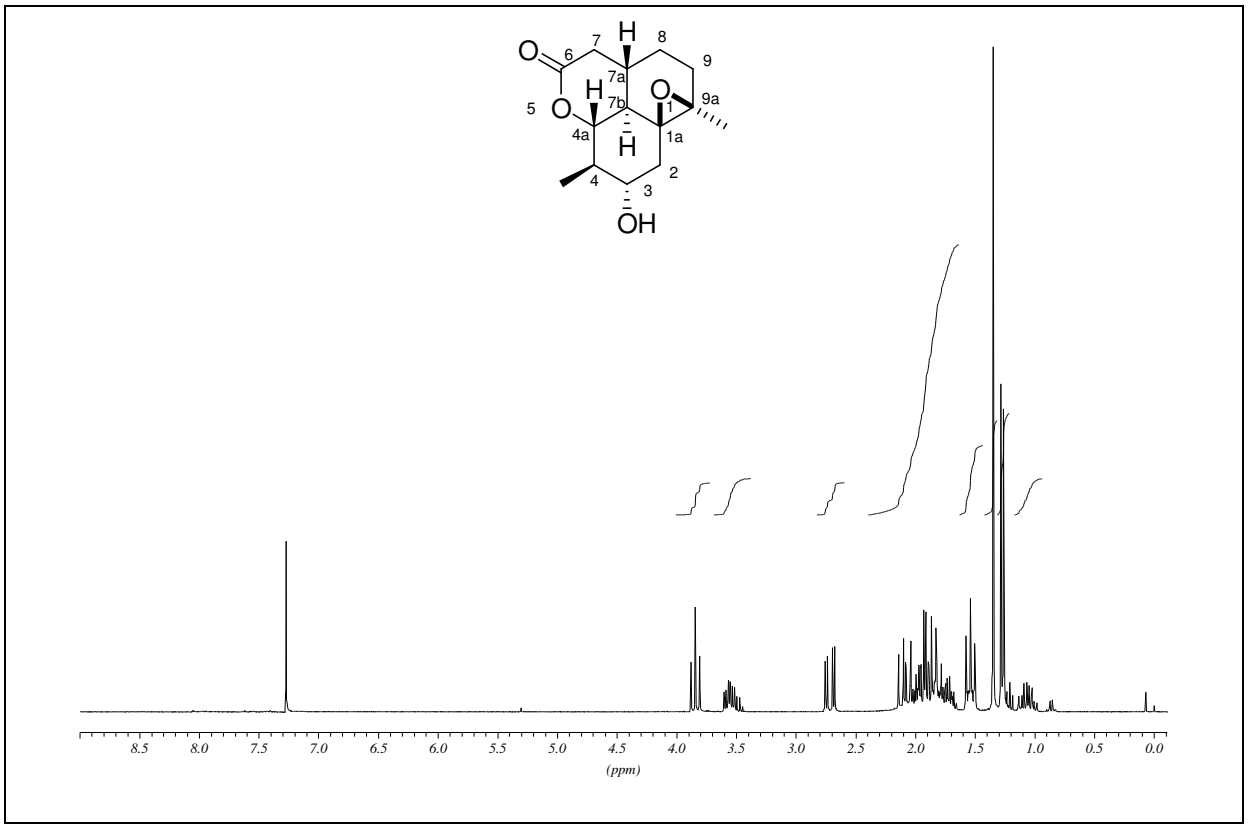


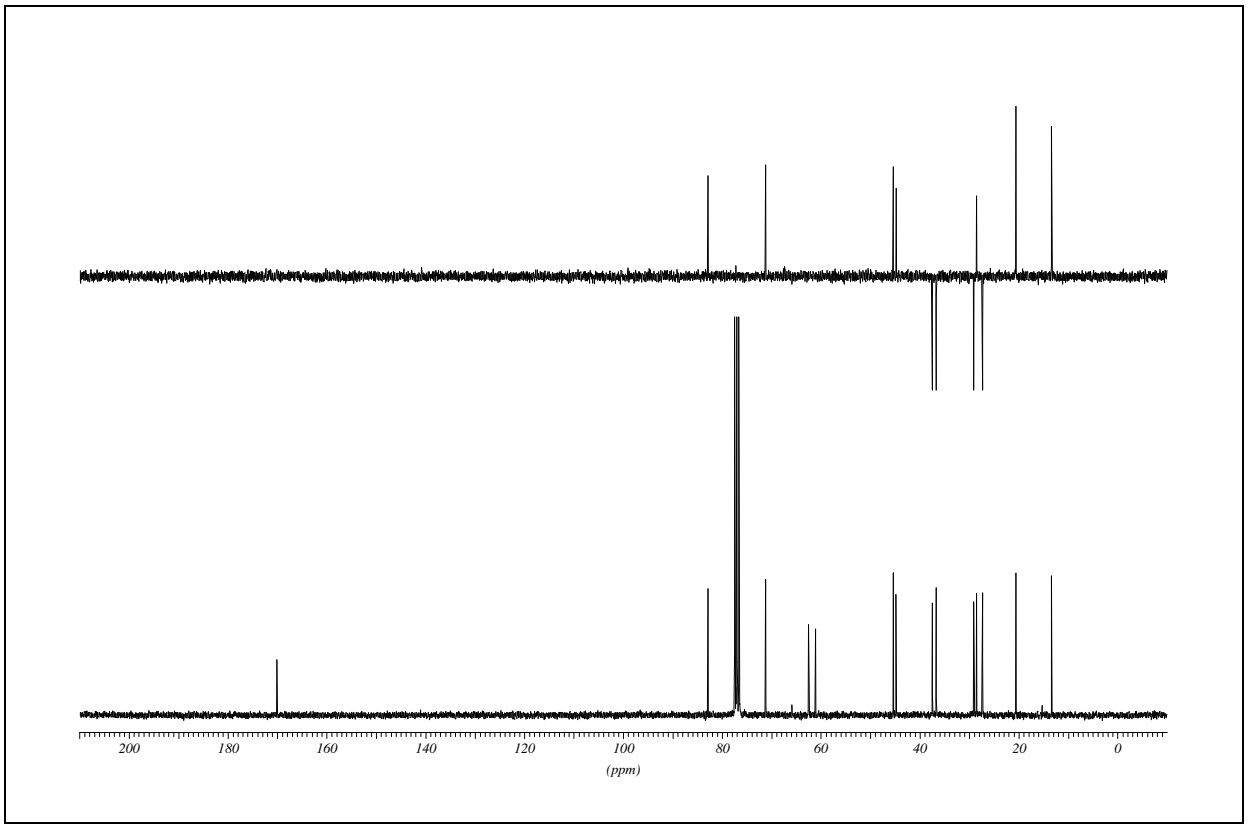
(3a*S*,8*R*,9*R*,9a*R*,9b*R*)-6,8-dihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (**279**)



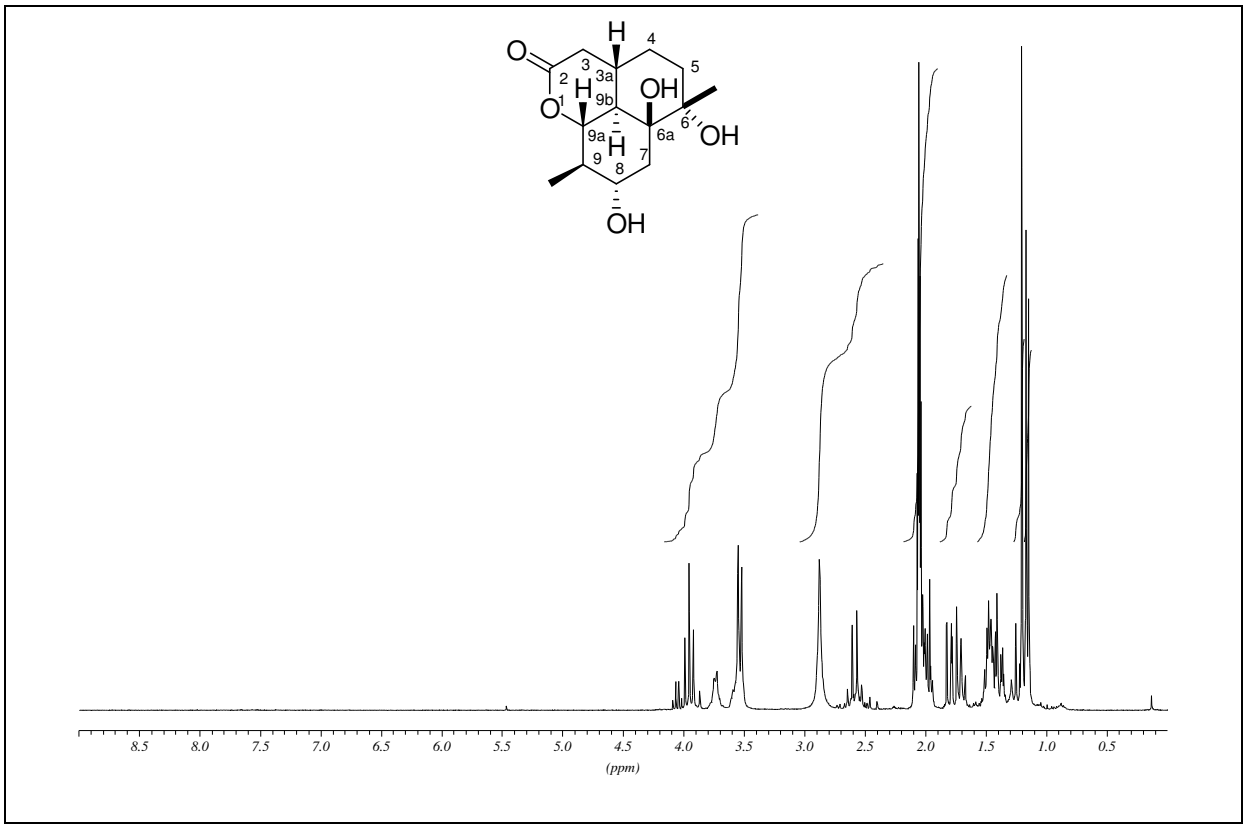


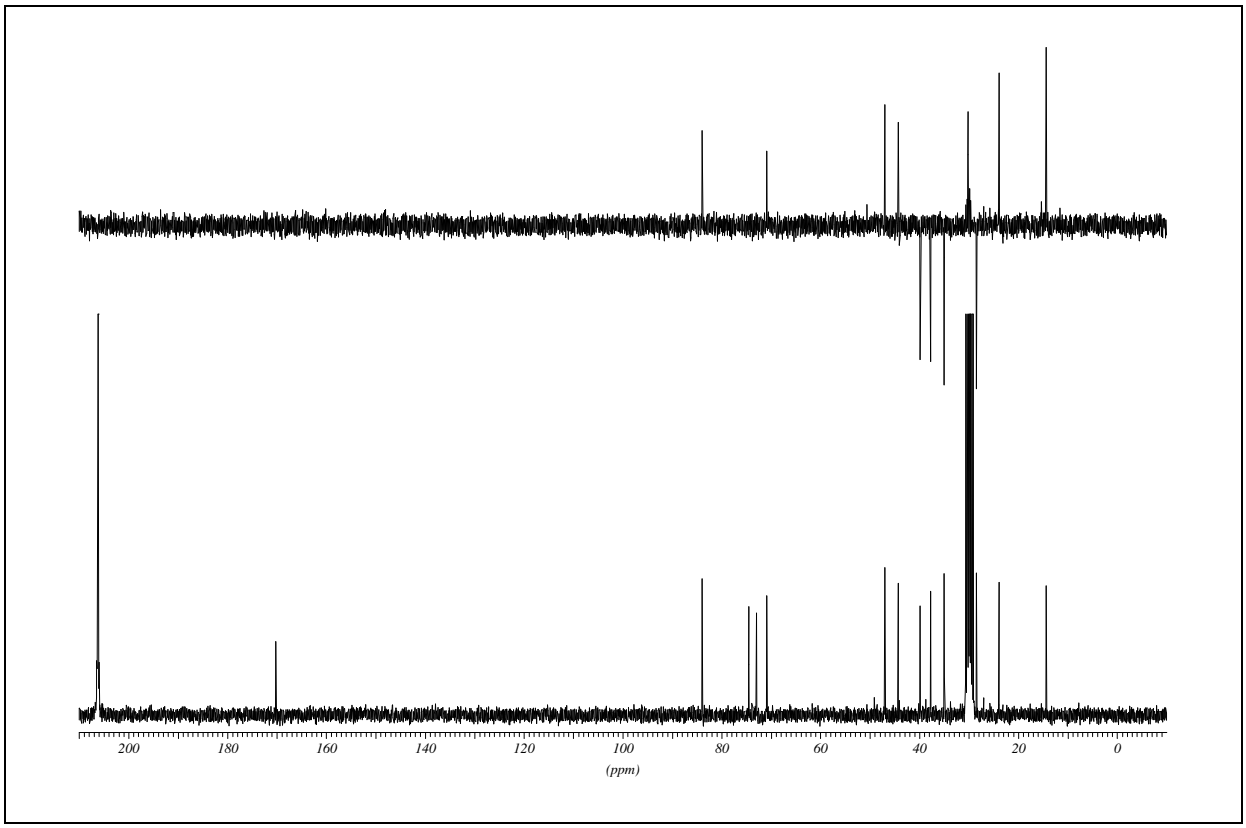
(1a*S*,3*R*,4*R*,4a*S*,7a*S*,7b*S*,9a*R*)-3-hydroxy-4,9a-dimethyloctahydro-2*H*-[1]benzoxireno[3,2,1a-*de*]chromen-6(7*H*)-one (**267**)





(3a*S*,6*R*,6a*S*,8*R*,9*R*,9a*S*,9b*S*)-6,6a,8-trihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (**268**, Acetone-d_6)

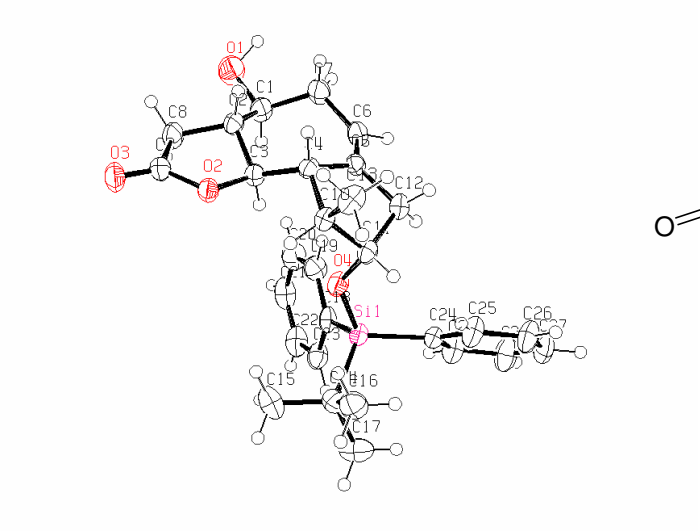




E. Appendix.

2. X-ray data

2.1 X-ray analysis of 228



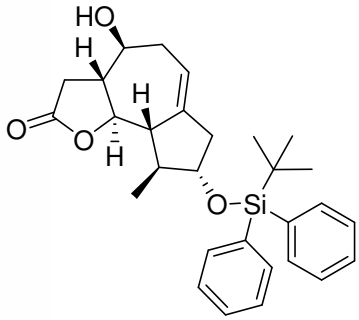


Table E.2.1.1 Crystal data and structure refinement for **228**.

Crystal Data ;

Empirical formula	C29 H36 O4 Si	
Formula weight	476.67	
Crystal size	0.36 x 0.24 x 0.24 mm	
Crystal description	prism	
Crystal colour	yellowish	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.8884(6) Å	α = 90 °
	b = 18.7322(10) Å	β = 112.046(8) °
	c = 9.4518(7) Å	γ = 90 °
Volume	1294.54(17) $Å^3$	
Z, Calculated density	2, 1.223 Mg/m^3	
Absorption coefficient	0.123 mm^{-1}	
F(000)	512	

Data Collection ;

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	173(1) K
Wavelength	0.71073 Å
Monochromator	graphite

Theta range for data collection	2.32 to 25.27 °
Index ranges	-9<=h<=9, -22<=k<=22, -11<=l<=11
Reflections collected / unique	9779 / 4655 [R(int) = 0.0350]
Reflections greater I>2\\s(I)	4106
Absorption correction	None

Refinement ;

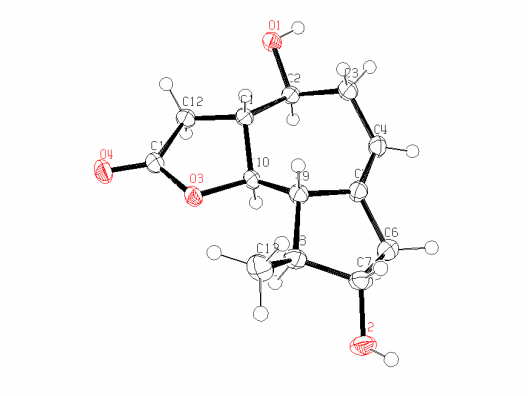
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	4655 / 1 / 315
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0963
R indices (all data)	R1 = 0.0461, wR2 = 0.0979
Absolute structure parameter	0.08(11)
Largest diff. peak and hole	0.527 and -0.177 e.$Å^{-3}$

Table E.2.1.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **228**. U(eq.) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si(1)	-4079(1)	-827(1)	-1671(1)	28(1)
O(1)	3289(3)	-2791(1)	4673(2)	55(1)
O(2)	-3039(2)	-2997(1)	2411(2)	32(1)
O(3)	-3321(2)	-3245(1)	4617(2)	44(1)
O(4)	-3696(2)	-1654(1)	-1038(2)	34(1)
C(1)	1901(3)	-2605(1)	3275(2)	35(1)
C(2)	159(3)	-2979(1)	3183(2)	30(1)
C(3)	-1592(3)	-2741(1)	1900(2)	28(1)
C(4)	-1880(3)	-3045(1)	333(2)	27(1)
C(5)	-619(3)	-2660(1)	-316(2)	28(1)
C(6)	1161(3)	-2538(1)	377(3)	34(1)
C(7)	2439(3)	-2796(2)	1918(3)	40(1)
C(8)	-356(3)	-2891(2)	4583(3)	38(1)
C(9)	-2373(3)	-3064(1)	3938(3)	34(1)
C(10)	-3835(3)	-2937(1)	-882(2)	29(1)
C(11)	-3663(3)	-2299(1)	-1838(2)	29(1)
C(12)	-1771(3)	-2396(1)	-1896(2)	32(1)
C(13)	-4515(4)	-3597(1)	-1886(3)	40(1)
C(14)	-6552(3)	-611(1)	-2025(3)	36(1)
C(15)	-6852(4)	-626(2)	-509(3)	52(1)
C(16)	-7781(4)	-1185(2)	-3083(3)	45(1)

C(17)	-7127(4)	122(2)	-2793(4)	57(1)
C(18)	-2369(3)	-291(1)	-79(2)	32(1)
C(19)	-777(3)	-637(2)	898(3)	39(1)
C(20)	536(4)	-278(2)	2095(3)	49(1)
C(21)	303(4)	437(2)	2347(3)	48(1)
C(22)	-1225(4)	785(2)	1405(3)	47(1)
C(23)	-2551(4)	431(1)	201(3)	40(1)
C(24)	-3650(3)	-675(1)	-3489(2)	31(1)
C(25)	-4252(4)	-1142(2)	-4738(3)	44(1)
C(26)	-3983(4)	-990(2)	-6078(3)	50(1)
C(27)	-3132(4)	-368(2)	-6220(3)	46(1)
C(28)	-2540(4)	99(2)	-5011(3)	53(1)
C(29)	-2785(4)	-51(2)	-3664(3)	43(1)

2.2 X-ray analysis of 232



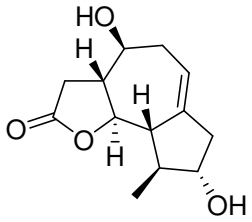


Table E.2.2.1 Crystal data and structure refinement for **232**.

Crystal Data ;

Empirical formula	C13 H18 O4	
Formula weight	238.27	
Crystal size	0.440 x 0.200 x 0.080 mm	
Crystal description	needle	
Crystal colour	colourless	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.0540(12) Å	α = 116.427(15) °
	b = 9.3834(13) Å	β = 94.776(18) °
	c = 9.8759(15) Å	γ = 110.882(16) °
Volume	597.8(2) $Å^3$	
Z, Calculated density	2, 1.324 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	

F(000)	256

Data Collection ;

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	123(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	2.41 to 26.85 °
Index ranges	-10<=h<=10, -11<=k<=11, -12<=l<=12
Reflections collected / unique	7493 / 2381 [R(int) = 0.0637]
Reflections greater I>2\s(I)	1534
Absorption correction	None
Max. and min. transmission	0.992 and 0.959

Refinement ;

Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	2381 / 0 / 224
Goodness-of-fit on F^2	0.895
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1003
R indices (all data)	R1 = 0.0753, wR2 = 0.1103
Absolute structure parameter	.
Largest diff. peak and hole	0.270 and -0.219 e.$Å^{-3}$

Table E.2.2.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **232**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	6571(2)	7338(2)	10106(2)	27(1)
O(2)	-2197(2)	898(2)	2303(2)	33(1)
O(3)	251(2)	5631(2)	8275(2)	23(1)
O(4)	188(2)	7749(2)	10507(2)	34(1)
C(1)	3334(2)	6083(3)	8961(2)	20(1)
C(2)	5195(2)	6369(3)	8591(2)	22(1)
C(3)	5249(3)	4619(3)	7521(2)	25(1)
C(4)	4108(3)	3649(3)	5814(2)	25(1)
C(5)	2289(3)	3094(3)	5291(2)	23(1)
C(6)	1178(3)	2182(3)	3581(3)	28(1)
C(7)	-817(3)	1246(3)	3567(2)	26(1)
C(8)	-952(3)	2497(3)	5159(2)	24(1)
C(9)	971(2)	3328(3)	6332(2)	21(1)

C(10)	1691(2)	5286(3)	7537(2)	21(1)
C(11)	1082(3)	7114(3)	9726(2)	25(1)
C(12)	3168(3)	7730(3)	10131(3)	25(1)
C(13)	-2593(3)	1589(3)	5622(3)	32(1)

2.3 X-ray analysis of 243.

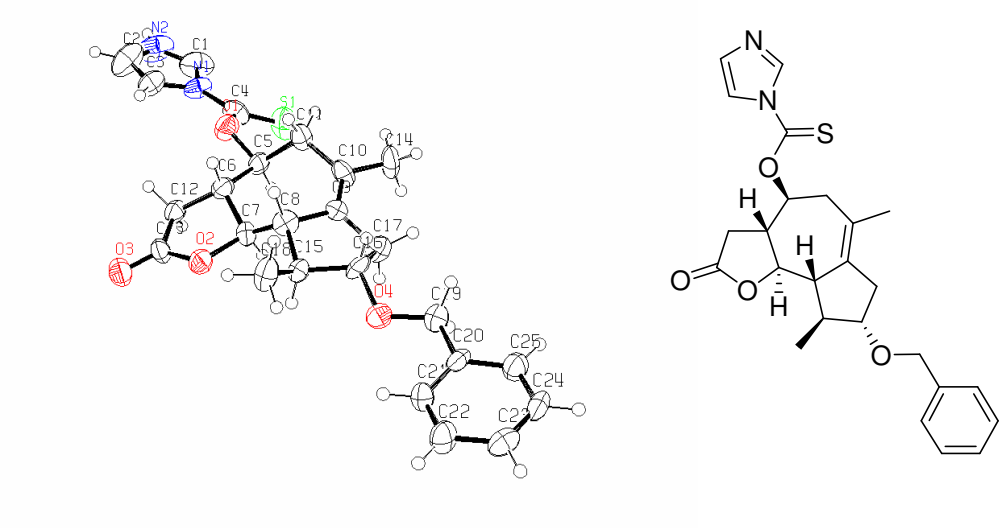


Table E.2.3.1 Crystal data and structure refinement for **243**.

Crystal Data ;

Empirical formula	C25 H28 N2 O4 S	
Formula weight	452.56	
Crystal size	0.080 x 0.060 x 0.060 mm	
Crystal description	prism	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.2765(9) Å	α = 90 °
	b = 8.8085(7) Å	β = 98.579(13) °
	c = 29.156(4) Å	γ = 90 °
Volume	2355.7(4) $Å^3$	
Z, Calculated density	4, 1.276 Mg/m^3	
Absorption coefficient	0.171 mm^{-1}	
F(000)	960	

Data Collection ;

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	173(1) K
Wavelength	0.71073 Å

Monochromator	graphite
Theta range for data collection	2.12 to 22.50 °
Index ranges	-9<=h<=9, -9<=k<=9, -31<=l<=31
Reflections collected / unique	12716 / 6082 [R(int) = 0.0712]
Reflections greater I>2\s(I)	3609
Absorption correction	None
Max. and min. transmission	0.990 and 0.987
Refinement ;	
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	6082 / 1 / 577
Goodness-of-fit on F^2	0.870
Final R indices [I>2sigma(I)]	R1 = 0.0636, wR2 = 0.1300
R indices (all data)	R1 = 0.1030, wR2 = 0.1416
Absolute structure parameter	-0.15(16)
Largest diff. peak and hole	0.358 and -0.251 e.$Å^{-3}$

Table E.2.3.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **243**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	544(2)	1634(3)	5229(1)	71(1)
O(1)	1852(5)	2522(6)	6063(2)	50(2)
O(2)	5011(5)	-169(6)	7144(2)	45(2)
O(3)	3485(5)	-201(6)	7668(2)	56(2)
O(4)	9564(5)	-1797(6)	6421(2)	46(2)
N(1)	-405(6)	3403(7)	5874(2)	45(2)
N(2)	-2527(8)	4535(9)	5857(3)	79(3)
C(1)	-1711(9)	3793(11)	5608(4)	72(4)
C(2)	-1723(9)	4651(12)	6303(4)	77(4)
C(3)	-439(8)	4002(9)	6326(3)	52(3)
C(4)	666(8)	2533(10)	5725(2)	51(3)
C(5)	3089(6)	1476(8)	6045(2)	38(2)
C(6)	3704(7)	1316(8)	6557(2)	39(2)
C(7)	4904(7)	130(9)	6638(2)	40(3)
C(8)	6344(7)	572(9)	6501(2)	40(3)
C(9)	6250(7)	365(8)	5970(2)	37(2)
C(10)	5321(8)	1054(9)	5648(2)	45(3)
C(11)	4198(7)	2206(9)	5773(2)	43(3)
C(12)	2685(7)	760(8)	6894(2)	39(2)

C(13)	3698(7)	81(9)	7278(2)	40(3)
C(14)	5301(8)	883(11)	5149(2)	64(3)
C(15)	7642(7)	-440(8)	6712(2)	38(3)
C(16)	8576(7)	-586(8)	6329(2)	41(3)
C(17)	7442(7)	-769(9)	5880(2)	44(3)
C(18)	8511(8)	162(10)	7170(3)	56(3)
C(19)	10373(7)	-2127(9)	6056(2)	45(3)
C(20)	11810(7)	-2873(8)	6234(2)	39(3)
C(21)	12211(7)	-3275(8)	6708(2)	42(3)
C(22)	13523(7)	-3929(9)	6860(3)	51(3)
C(23)	14515(8)	-4201(9)	6547(3)	50(3)
C(24)	14132(8)	-3836(9)	6090(3)	46(3)
C(25)	12807(7)	-3200(9)	5933(2)	47(3)
S(2)	4566(2)	7143(3)	210(1)	60(1)
O(5)	4051(5)	6117(5)	1032(2)	41(2)
O(6)	1868(5)	8639(5)	2151(2)	41(2)
O(7)	3861(6)	8552(6)	2685(2)	59(2)
O(8)	-3323(5)	10422(6)	1435(2)	45(2)
N(3)	6106(6)	5289(7)	824(2)	40(2)
N(4)	8249(7)	4128(8)	779(3)	60(3)
C(26)	7167(8)	4957(9)	554(3)	54(3)
C(27)	7854(8)	3932(9)	1223(3)	55(3)
C(28)	6567(8)	4619(10)	1259(3)	50(3)
C(29)	4874(8)	6183(9)	688(2)	44(3)
C(30)	2799(6)	7158(8)	1031(2)	35(2)
C(31)	2653(7)	7287(8)	1552(2)	35(2)
C(32)	1528(7)	8427(8)	1645(2)	36(3)
C(33)	-68(7)	8025(8)	1491(2)	36(2)
C(34)	-458(7)	8284(8)	966(2)	35(2)
C(35)	216(7)	7621(8)	640(2)	41(3)
C(36)	1443(6)	6468(9)	747(2)	43(3)
C(37)	3990(7)	7732(9)	1885(2)	41(3)
C(38)	3297(8)	8345(8)	2280(3)	41(3)
C(39)	-255(7)	7837(11)	137(2)	57(3)
C(40)	-1147(7)	9028(8)	1717(2)	38(2)
C(41)	-2423(7)	9204(8)	1326(2)	40(3)
C(42)	-1726(7)	9392(8)	885(2)	40(3)
C(43)	-1539(8)	8469(9)	2173(2)	49(3)
C(44)	-4506(7)	10758(9)	1074(2)	43(3)

C(45)	-5737(7)	11500(9)	1272(2)	42(3)
C(46)	-5657(8)	11890(8)	1749(2)	45(3)
C(47)	-6806(7)	12533(10)	1914(3)	51(3)
C(48)	-8082(8)	12824(9)	1618(3)	53(3)
C(49)	-8200(7)	12490(9)	1155(3)	45(3)
C(50)	-7055(7)	11838(8)	985(2)	40(2)

2.4 X-ray analysis of 241.

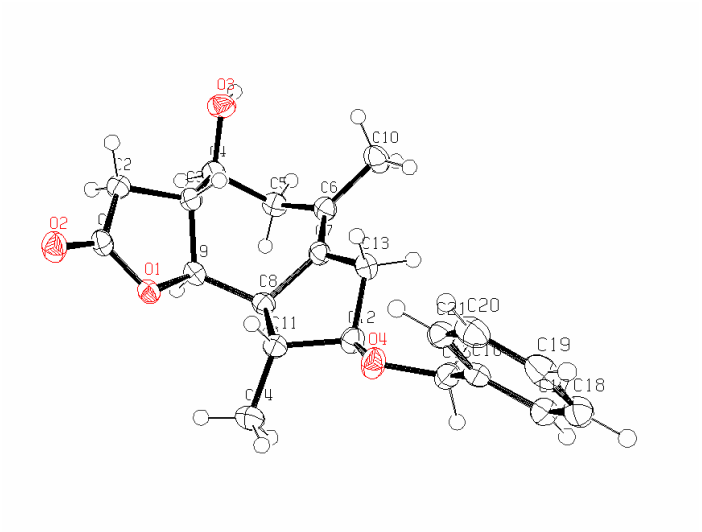


Table E.2.4.1 Crystal data and structure refinement for **241**.

Crystal Data ;

Empirical formula	C21 H26 O4	
Formula weight	342.42	
Crystal size	0.52	x 0.24 x 0.03 mm
Crystal description	plate	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.1820(11) Å	α = 90 °
	b = 5.7706(5) Å	β = 100.916(16) °
	c = 19.762(3) Å	γ = 90 °
Volume	916.2(2) $Å^3$	
Z, Calculated density	2, 1.241 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	368	

Data Collection ;

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation

Temperature	123(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	2.54 to 25.81 °
Index ranges	-9<=h<=9, -7<=k<=7, -24<=l<=24
Reflections collected / unique	8494 / 3436 [R(int) = 0.0412]
Reflections greater I>2\s(I)	3138
Absorption correction	None

Refinement ;

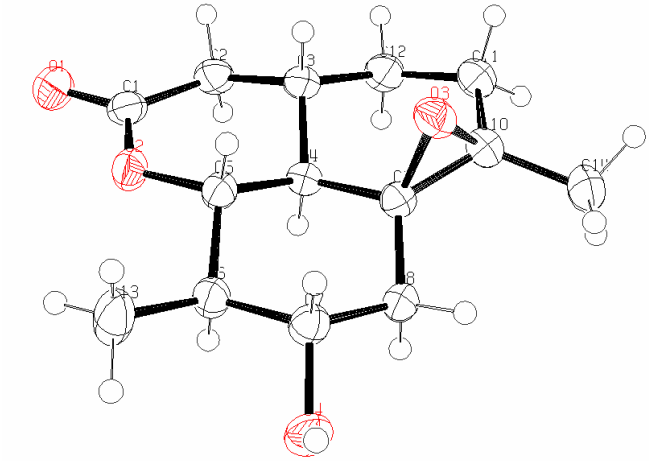
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	3436 / 1 / 226
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.0818
R indices (all data)	R1 = 0.0378, wR2 = 0.0833
Absolute structure parameter	0.3(8)
Largest diff. peak and hole	0.275 and -0.162 e.$Å^{-3}$

Table E.2.4.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **241**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4969(1)	3624(2)	1061(1)	26(1)
O(2)	6069(1)	978(2)	445(1)	32(1)
O(3)	-411(1)	396(2)	806(1)	32(1)
O(4)	6010(1)	4750(2)	3588(1)	30(1)
C(1)	4849(2)	1824(3)	616(1)	25(1)
C(2)	3056(2)	1096(3)	402(1)	25(1)
C(3)	2243(2)	2159(3)	971(1)	23(1)
C(4)	379(2)	2609(3)	796(1)	25(1)
C(5)	-181(2)	4318(3)	1314(1)	27(1)
C(6)	566(2)	3709(3)	2057(1)	25(1)
C(7)	2164(2)	4163(3)	2299(1)	23(1)
C(8)	3320(2)	5402(3)	1879(1)	23(1)
C(9)	3288(2)	4355(3)	1150(1)	23(1)
C(10)	-537(2)	2396(3)	2458(1)	33(1)
C(11)	5046(2)	5425(3)	2364(1)	25(1)
C(12)	4590(2)	5372(3)	3086(1)	26(1)
C(13)	3160(2)	3627(3)	3009(1)	26(1)
C(14)	6163(2)	7445(3)	2250(1)	35(1)

C(15)	5790(2)	5253(3)	4274(1)	27(1)
C(16)	6976(2)	3821(3)	4790(1)	25(1)
C(17)	7400(2)	4577(3)	5473(1)	28(1)
C(18)	8457(2)	3280(3)	5961(1)	33(1)
C(19)	9121(2)	1195(3)	5771(1)	35(1)
C(20)	8681(2)	416(3)	5097(1)	33(1)
C(21)	7610(2)	1713(3)	4608(1)	28(1)

2.5 X-ray analysis of 267.



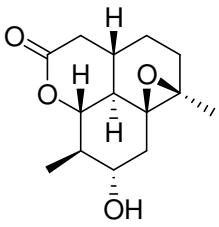


Table E.2.5.1 Crystal data and structure refinement for **267**.

Crystal Data ;

Empirical formula	C14 H20 O4	
Formula weight	252.30	
Crystal size	0.40 x 0.18 x 0.06 mm	
Crystal description	prism	
Crystal colour	colourless	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 9.9932(11) Å	α = 74.093(12) °
	b = 10.7513(11) Å	β= 64.581(12) °
	c = 11.5297(13) Å	γ = 63.542(11) °
Volume	996.4(2) $Å^3$	
Z, Calculated density	3, 1.261 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	408	

Data Collection ;

Measurement device type	STOE-IPDS diffractometer

Measuremnet method	rotation
Temperature	173(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	3.79 to 28.02 °
Index ranges	-13<=h<=13, -14<=k<=14, -15<=l<=15
Reflections collected / unique	10802 / 8398 [R(int) = 0.0325]
Reflections greater I>2\s(I)	7161
Absorption correction	None

Refinement ;

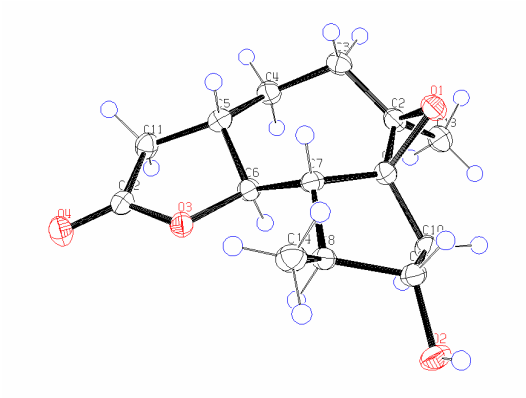
Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	:
Data / restraints / parameters	8398 / 3 / 497
Goodness-of-fit on F^2	0.963
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.0966
R indices (all data)	R1 = 0.0479, wR2 = 0.0989
Absolute structure parameter	0.0(5)
Largest diff. peak and hole	0.258 and -0.239 e.$Å^{-3}$

Table E.2.5.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **267**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	6291(2)	6410(2)	4168(1)	46(1)
O(2)	5533(2)	7934(1)	2643(1)	37(1)
O(3)	8439(2)	9754(1)	-943(1)	36(1)
O(4)	3037(2)	11860(2)	-4(1)	37(1)
C(1)	6554(2)	7298(2)	3303(2)	34(1)
C(2)	7892(2)	7789(2)	2992(2)	35(1)
C(3)	8381(2)	8567(2)	1649(2)	30(1)
C(4)	6846(2)	9628(2)	1419(2)	26(1)
C(5)	5855(2)	8866(2)	1451(2)	29(1)
C(6)	4234(2)	9881(2)	1341(2)	33(1)
C(7)	4543(2)	10814(2)	56(2)	32(1)
C(8)	5628(2)	11552(2)	-92(2)	30(1)
C(9)	7160(2)	10534(2)	135(2)	28(1)
C(10)	8674(2)	10768(2)	-480(2)	35(1)
C(11)	9920(2)	10119(2)	170(2)	39(1)
C(12)	9425(2)	9339(2)	1514(2)	37(1)
C(13)	3191(3)	9123(3)	1444(3)	54(1)

C(14)	8807(2)	12035(2)	-1445(2)	46(1)
O(5)	4284(2)	7872(2)	6929(1)	39(1)
O(6)	5255(2)	9451(2)	5684(2)	50(1)
O(7)	1622(2)	5980(2)	6143(1)	36(1)
O(8)	1973(2)	4689(2)	10101(1)	41(1)
C(15)	4261(2)	8946(2)	5989(2)	39(1)
C(16)	2955(3)	9547(2)	5434(2)	41(1)
C(17)	2168(2)	8554(2)	5541(2)	34(1)
C(18)	1844(2)	7817(2)	6913(2)	29(1)
C(19)	3426(2)	6975(2)	7133(2)	30(1)
C(20)	3226(2)	6233(2)	8502(2)	32(1)
C(21)	2307(2)	5284(2)	8777(2)	31(1)
C(22)	728(2)	6076(2)	8525(2)	33(1)
C(23)	985(2)	6842(2)	7183(2)	30(1)
C(24)	5(2)	7082(2)	6414(2)	41(1)
C(25)	-130(3)	8290(3)	5343(2)	48(1)
C(26)	586(3)	9317(2)	5298(2)	45(1)
C(27)	4859(3)	5383(2)	8661(2)	46(1)
C(28)	-1331(3)	6541(3)	6914(2)	57(1)
O(9)	2739(1)	2607(1)	5855(1)	34(1)
O(10)	2749(2)	1780(2)	7798(1)	51(1)
O(11)	6609(2)	2794(1)	2084(1)	35(1)
O(12)	1743(2)	5751(2)	2152(2)	50(1)
C(29)	3481(2)	2140(2)	6702(2)	35(1)
C(30)	5161(2)	2115(2)	6315(2)	35(1)
C(31)	6036(2)	2357(2)	4862(2)	29(1)
C(32)	4818(2)	3510(2)	4299(2)	27(1)
C(33)	3516(2)	3014(2)	4486(2)	28(1)
C(34)	2182(2)	4136(2)	4007(2)	33(1)
C(35)	2955(2)	4624(2)	2577(2)	37(1)
C(36)	4269(2)	5112(2)	2375(2)	38(1)
C(37)	5533(2)	3959(2)	2873(2)	31(1)
C(38)	7270(2)	3669(2)	2275(2)	36(1)
C(39)	8338(2)	2934(2)	3083(2)	40(1)
C(40)	7431(2)	2797(2)	4549(2)	35(1)
C(41)	913(3)	3585(2)	4197(2)	46(1)
C(42)	7962(3)	4515(3)	1050(2)	51(1)

2.6 X-ray analysis of 249.



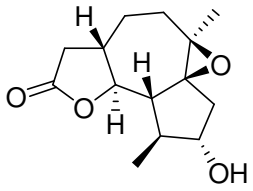


Table E.2.6.1 Crystal data and structure refinement for **249**.

Crystal Data ;

Empirical formula	C14 H20 O4	
Formula weight	252.30	
Crystal size	0.40 x 0.16 x 0.08 mm	
Crystal description	rod	
Crystal colour	colourless	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.3991(4) Å	α = 90 °
	b = 16.8591(12) Å	β = 90 °
	c = 28.082(2) Å	γ = 90 °
Volume	2556.1(3) $Å^3$	
Z, Calculated density	8, 1.311 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	1088	

Data Collection ;

Measurement device type	STOE-IPDS diffractometer
Measuremnet method	rotation
Temperature	123(1) K
Wavelength	0.71073 Å
Monochromator	graphite
Theta range for data collection	2.42 to 25.89 °
Index ranges	-6<=h<=6, -20<=k<=20, -34<=l<=34
Reflections collected / unique	22645 / 4938 [R(int) = 0.0498]
Reflections greater I>2\s(I)	4472
Absorption correction	None

Refinement ;

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

Hydrogen treatment	:
Data / restraints / parameters	4938 / 0 / 445
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0769
R indices (all data)	R1 = 0.0361, wR2 = 0.0780
Absolute structure parameter	0.6(6)
Largest diff. peak and hole	0.270 and -0.148 e.Å^{-3}

Table E.2.6.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **249**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4363(2)	99(1)	5756(1)	23(1)
O(2)	5741(2)	-2228(1)	5009(1)	25(1)
O(3)	8385(2)	300(1)	4193(1)	20(1)
O(4)	10297(2)	920(1)	3597(1)	25(1)
C(1)	6260(3)	-183(1)	5432(1)	18(1)
C(2)	6878(3)	432(1)	5785(1)	21(1)
C(3)	6989(3)	1307(1)	5649(1)	23(1)
C(4)	9039(3)	1527(1)	5293(1)	22(1)
C(5)	8344(3)	1292(1)	4785(1)	20(1)
C(6)	8193(3)	393(1)	4708(1)	18(1)
C(7)	5908(3)	-35(1)	4893(1)	18(1)
C(8)	5623(3)	-876(1)	4668(1)	18(1)
C(9)	5185(3)	-1414(1)	5101(1)	20(1)
C(10)	6854(3)	-1060(1)	5481(1)	20(1)
C(11)	10150(3)	1528(1)	4391(1)	22(1)
C(12)	9677(3)	917(1)	4009(1)	19(1)
C(13)	8369(3)	212(1)	6221(1)	26(1)
C(14)	3653(3)	-942(1)	4281(1)	23(1)
O(5)	10927(2)	7372(1)	3353(1)	23(1)
O(6)	9106(3)	9879(1)	2824(1)	33(1)
O(7)	6622(2)	7587(1)	1813(1)	21(1)
O(8)	4790(2)	7076(1)	1167(1)	27(1)
C(15)	8953(3)	7745(1)	3077(1)	19(1)
C(16)	8413(3)	7036(1)	3367(1)	21(1)
C(17)	8226(3)	6212(1)	3149(1)	22(1)
C(18)	6048(3)	6110(1)	2804(1)	21(1)
C(19)	6660(3)	6474(1)	2322(1)	19(1)
C(20)	6839(3)	7383(1)	2319(1)	18(1)

C(21)	9171(3)	7755(1)	2529(1)	18(1)
C(22)	9410(3)	8648(1)	2394(1)	20(1)
C(23)	9850(3)	9073(1)	2868(1)	23(1)
C(24)	8350(3)	8589(1)	3225(1)	23(1)
C(25)	4805(3)	6337(1)	1921(1)	21(1)
C(26)	5337(3)	7011(1)	1579(1)	20(1)
C(27)	6994(3)	7140(1)	3827(1)	27(1)
C(28)	11343(3)	8825(1)	2012(1)	25(1)

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1. Nosse, B.; Schall, A.; Jeong, W. B. *Adv. Synth. Catal.* **2005**, *347*, 1869-1874. „Optimization of Ring-Closing Metathesis: Inert Gas Sparging and Microwave Irradiation".

2. Nosse, B.; B. Chhor, R.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett*. **2003**, *5*, 941-944.
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Poster presentation

1. Jeong, W. B.; Chhor, R. B.; Nosse, B.; Reiser, O.
   Summer School 2005, Shanghai, China, 25th–28th September **2005**: *Asymmetric Total Synthesis towards Arglabin.*

2. Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O.
   GDCh Jahrestagung, München, Deutschland, 6th-11th October **2003**: *Studies directed to Total Synthesis of γ-butyrolactone derived Natural Products.*

Patent

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