Total Synthesis Studies on a novel neurotrophic Drimane-Type Sesquiterpenoid from Thai *Basidiomycota*

Dissertation

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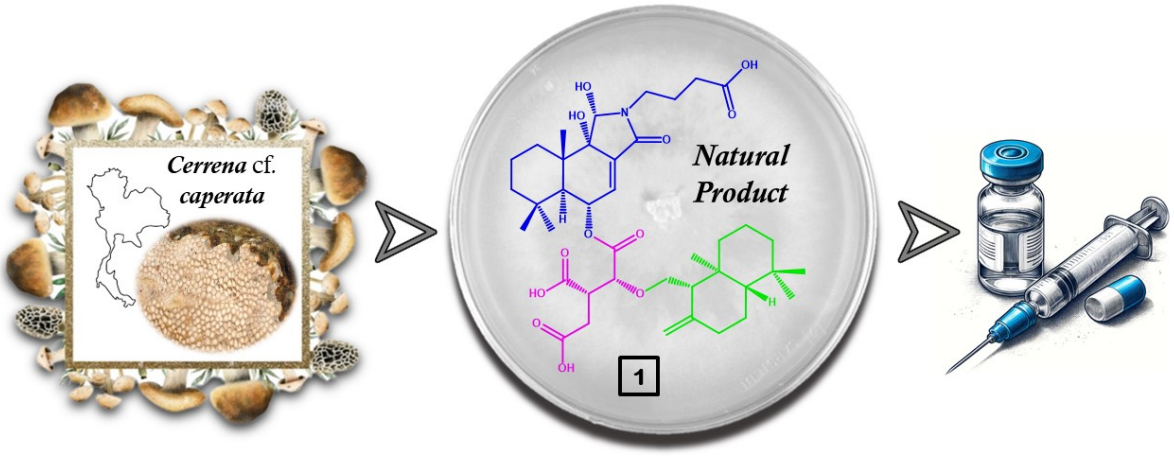
Abstract

Drimane-type sesquiterpenoids (STs), celebrated for their structural diversity and bioactive properties, have attracted significant attention for their potential therapeutic applications, as they exhibit promising pharmacological activities.

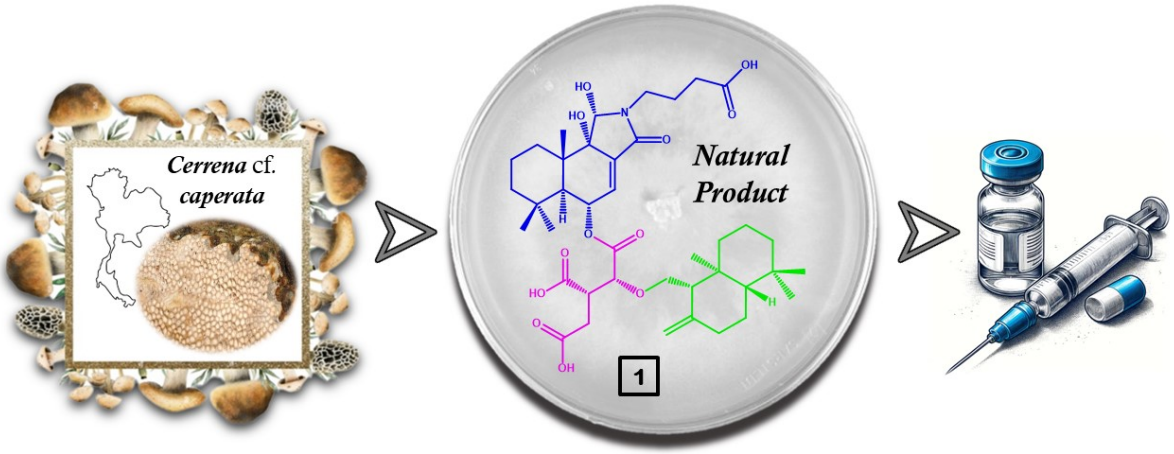
Compound ***1***, a dimeric meroterpenoid with a sesquiterpene component and a lactam nucleus, has been studied not only for its specific activity but also for its complex and unique structure. This remarkable natural product, isolated from cultures of the tropical white-rot Basidiomycete Cerrena sp. caperata originating from Thailand, further underscores the novelty of the findings, as it has yet to be formally named.



Researchers at the Helmholtz Center for Infection Research (HZI) in Braunschweig have identified neurotrophic modulatory properties in this *Cerrena* metabolite, representing a promising therapeutic strategy for the treatment of neurodegenerative diseases (NDDs). Compound ***1*** has emerged as a key structure in this context, further intensifying interest in its synthesis and therapeutic potential. The primary objective of this work was the total synthesis of compound ***1***. The rarity of sesquiterpenoids with a lactam nucleus found in Basidiomycetes presented an intriguing synthetic challenge. Due to this unusual structural feature, the strategy employed enabled significant progress toward the synthesis of this complex sesquiterpenoid, suggesting valuable solutions for the development of similar dimeric terpenoid structures.

Zusammenfassung

Driman-Typ Sesquiterpenoide (STs), die für ihre strukturelle Vielfalt und bioaktiven Eigenschaften bekannt sind, haben aufgrund ihres potenziellen therapeutischen Nutzens große Aufmerksamkeit erregt, die vielversprechende pharmakologische Aktivitäten zeigen. Verbindung ***1***, ein dimeres Meroterpenoid mit einer Sesquiterpen-Komponente und einem Lactam-Ring, wurde nicht nur aufgrund seiner spezifischen Aktivität, sondern auch wegen seiner komplexen und einzigartigen Struktur untersucht. Diese faszinierende Verbindung ist ein Naturprodukt, das aus Kulturen eines tropischen Weißfäulepilzes, Basidiomyceten, isoliert wurde, der aus Thailand stammt und als *Cerrena* sp. *Caperata* identifiziert wurde. Die Neuheit der präsentieren Ergebnisse wird noch zusätzlich unterstrichen, da Verbindung ***1*** bis lang noch kein Name hat.



Forscher des Helmholtz-Zentrums für Infektionsforschung (HZI) in Braunschweig haben neurotrophe modulierende Eigenschaften in diesem *Cerrena*-Metaboliten identifiziert, was eine vielversprechende therapeutische Strategie für die Behandlung neurodegenerativer Erkrankungen (NDDs) darstellt. Verbindung ***1*** hat sich in diesem Zusammenhang als Schlüsselstruktur erwiesen, was das Interesse an ihrer Synthese und ihrem therapeutischen Potenzial weiter verstärkt. Das Hauptziel dieser Arbeit war die Totalsynthese von Verbindung ***1***. Die Seltenheit von Sesquiterpenoiden mit einem Lactam-Ring, die in Basidiomyceten gefunden werden, stellte eine interessante synthetische Herausforderung dar. Aufgrund dieser ungewöhnlichen strukturellen Eigenschaft ermöglichte die angewandte Strategie bedeutende Fortschritte bei der Synthese dieses komplexen Sesquiterpenoids und schlägt wertvolle Lösungen für die Entwicklung ähnlicher dimerer Terpenstrukturen vor.

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List of Abbreviations

1321N1	*Human astrocytoma cell line*
2,2-DMP	*2,2-Dimethoxypropane*
3,5-DNB-Cl	*3,5-Dinitrobenzoyl chloride*
Ac_2O	*Acetic anhidride*
AIBN	*Azobisisobutyronitrile*
AIP	*Aluminium Isopropoxide*
AKT	*Protein kinase B*
ALS	*Amyotrophic lateral sclerosis*
BAIB	*(Diacetoxyiodo)benzene*
BDNF	*Brain-derived neurotrophic factor*
BH_3·THF	*Borane-tetrahydrofuran complex*
BnBr	*Benzyl bromide*
Boc_2O	*Di-tert-butyl pyrocarbonate*
Boc-Pro-OH	*Boc-L-prolin*
Bu_3SnH	*Tributyltin hydride*
CBS	*Corey-Bakshi-Shibata reagent*
$CDCl_3$	*Chloroform*
$CeCl_3·7H_2O$	*Cerium(III) chloride heptahydrate*
CH_2Cl_2	*Dichloromethane*
CH_2N_2	*diazomethane*
CH_3CN	*Acetonitrile*
C-JUN	*Transcription factor*
Co	*Cobalt*
$CoBr_2$	*Cobalt (II) bromide*
COX2	*Cyclooxygenase 2*
Cp_2TiCl_2	*Bis(cyclopentadienyl) titanium (IV) dichloride*
CREB	*cAMP response element-binding protein*
CrO_3	*Chromium trioxide*
CSA	*Camphorsulfonic acid*
D_2O	*Deuterium oxide*
DA	*Diels-Alder*

DBU	*1,8-diazabiciclo [5.4.0] undec-7-ene*
DEG (or EG)	*Diethylene glycol*
DIBAL-H	*Diisobutylaluminium hydride*
DIPEA	*N-etildiisopropilammina*
DMAD	*Dimethyl acetylenedicarboxylate*
DMAP	*4-Dimethylaminopyridine*
DMF	*N,N-Dimethylformamide*
DMP	*Dess–Martin periodinane*
DTS	*Drimane-type sesquiterpenoid*
EDC·HCl or EDCl	*1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide*
ERK1/2	*Extracellular signal-regulated kinase*
Et_2O	*Diethylether*
EtOCOCl	*Ethyl chloroformate*
EtOH	*Ethanol*
EtONa	*Sodium ethoxide*
FDA	*Food and Drug Administration*
H_2O	*Water*
H_2O_2	*Hydrogen peroxide*
H_2SO_4	*Sulfuric acid*
HATU	*Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium*
HCl	*Hydrogen chloride*
HF	*Hydrogen fluoride*
HF·Py	*Hydrogen fluoride pyridine*
HMBC	*Heteronuclear Multiple Bond Correlation*
***i*-PrOH**	*Isopropanol*
IKK	*IkappaB kinase*
JNK	*Stress-activated phospho-kinases*
K_2CO_3	*Potassium carbonate*
$KHCO_3$	*Potassium bicarbonate*
KOH	*Potassium hydroxide*
L-Selectride	*Lithium tri-sec-butylborohydride*
LC-MS	*Liquid Chromatography Mass Spectrometry*

LDA	*Lithium diisopropylamide*
$LiOH \cdot H_2O$	*Lithium hydroxide monohydrate*
MAPK	*Mitogen-activated protein kinase*
m-CPBA	*meta-chloroperoxybenzoic acid*
MEK1/2	*Dual-specificity threonine/tyrosine kinases*
MeOH	*Methanol*
Mn	*Manganese*
MnO_2	*Manganese oxide*
$Na_2S_2O_3$	*Sodium thiosulfate*
Na_2SO_4	*Sodium sulfate*
NaBARF	*Sodium tetrakis[3,5-bis(trifluoromethyl) phenyl] borate*
$NaBH_4$	*Sodium borohydride*
N-Boc-L-Pro	*N-alpha-t-Butyloxycarbonyl-L-proline*
NaCl	*Sodium chloride*
$NaClO_2$	*Sodium chlorite*
NaH	*Sodium hydride*
NaH_2PO_4	*Monosodium phosphate*
$NaHCO_3$	*Sodium bicarbonate*
$NaHPO_4$	*Sodium phosphate*
NaOH	*Sodium hydroxide*
NDDs	*Neurodegenerative diseases*
NEt_3	*Triethylamine*
NF-Kb	*Nuclear factor kappa-light-chain-enhancer of activated B cells*
NGF	*Nerve growth factor*
NH_4Cl	*Ammonium chloride*
NH_4OH	*Ammonium hydroxide*
NOESY	*Nuclear Overhauser Effect Spectroscopy*
NSAIDs	*Nonsteroidal anti-inflammatory drugs*
NT	*Neurotrophins*
ON	*overnight*
p53	*Tumor protein P53*
$p75^{NTR}$	*p75 neurotrophin receptor*

PBr_3	*Phosphorus tribromide*
PC-12	*Cell line from a pheochromocytoma of the rat adrenal medulla*
PD	*Parkinson's disease*
Pd/C	*Palladium on carbon*
$PhI(OAc)_2$	*(Diacetoxyiodo)benzene*
PI3K	*Phosphatidylinositol 3-kinase*
PivCl	*Trimethylacetyl chloride*
PKC	*Proteinkinase C*
PKS	*Polyketide synthases*
PPTS	*Pyridinium p-toluenesulfonate*
PTSA	*p-Toluene sulfonic acid monohydrate*
Py	*Pyridine*
Pyr·TsOH	*Pyridinium p-toluenesulfonate*
RAS	*Small guanosine triphosphatases (GTPases)*
[(R,R) BenzP*]	*1,2-Bis(t-butylmethylphosphino) benzene*
SOD1	*Superoxide dismutase type 1*
STAB	*Sodium triacetoxyborohydride*
TBAF	*Tetra-n-butylammonium fluoride*
TBD	*Triaza-bicyclo-decene*
TBSCl	*Tert-Butyl dimethyl lsilyl chloride*
TBSOTf	*Trimethylsilyl trifluoromethanesulfonate*
***t*-BuOH**	*Tert-butyl alcohol*
***t*-BuOK**	*Potassium tert-butoxide*
TCBC	*2,4,6-Trichlorobenzoyl chloride*
TCDI	*1,1'-Thiocarbonyldiimidazole*
TDP-43	*Transactive response DNA binding protein of 43 kDa*
TEMPO	*(2,2,6,6-Tetramethylpiperidin-1-yl) oxyl*
TESCl	*Chlorotriethylsilane*
TLC	*Thin-layer chromatography*
TFA	*Trifluoroacetic acid*
THF	*Tetrahydrofuran*
TRAF6	*TRAF (TNF receptor associated factor) human protein*

Trk	*Tropomyosin receptor kinase A*
WHO	*World Health Organization*
Zn	*Zinc*

1. Introduction

1.1. NDDs: causes, symptoms, and treatments

Neurodegenerative disorders (NDDs) represent a significant global concern, corresponding to a massive health burden and costing healthcare systems billions annually. According to the World Health Organization (WHO, 2016), these disorders impact up to one billion people worldwide each year and contribute to an estimated 6.8 million deaths[1]. NDDs are a range of disorders of the nervous system characterized by progressive degradation of neuronal structures and their function in the brain and spinal cord, resulting in neuronal damage and death. Alterations in the generation and death of neurons are often the cause of NDDs, as neurons are critical in brain development and preservation[2]. The apoptosis of many neurons, resulting in progressive neurodegeneration, can be initiated by several aberrant mechanisms, including toxic protein aggregation, mis-localization and degradation of essential proteins[3]. In addition, many neurodegenerative diseases involve the misfolding of normal or mutant versions of natural proteins triggered by genetic mutations. Intracellular degradation processes that could be altered by NDDs usually remove these proteins, thus, as consequence of this breakdown, they form insoluble aggregates provided with hydrophobic surface residues that lead them to interact with membranes. Those residues, by accumulating in and out of cells, form stable microscopic deposits (resistant to proteolysis) that cause damage to neurons. Depending on the specific area of the brain where the progressive and irreversible loss of neurons occurs, different type of disorders may result:

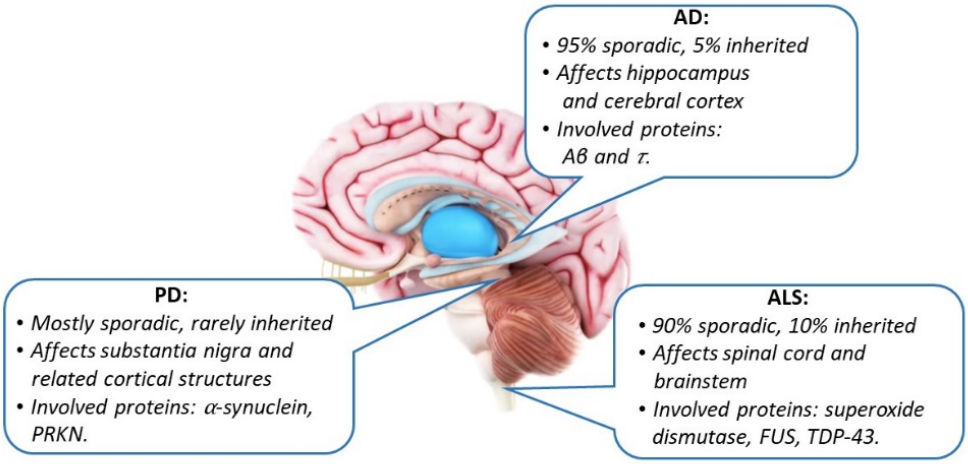


Figure 1.1.1. *Summary of NDDs*
(AD= Alzheimer's disease; PD= Parkinson's disease; ALS= Amyotrophic lateral sclerosis).

Affected Brain Area	*Main Symptoms*	*Associated Disease*
• *Basal ganglia*	abnormalities in movement control	Parkinson's disease
• *Hippocampus and cerebral cortex*	loss of memory and cognitive abilities	Alzheimer's disease
• *Spinal, cortical, and bulbar neurons*	muscles weakness	Amyotrophic lateral sclerosis[4]

The main diseases just mentioned are the most prevalent and exhibit the following characteristics, which are associated with the corresponding symptoms:

- Dementia: The progressive damage in various brain regions leads to neuron death and a range of symptoms, such as confusion, memory loss, difficulty in concentrating, and behavioral changes. Conditions in this category encompass *Alzheimer's disease*.
- Demyelinating: The damage and loss of myelin impact the transmission and relay of nerve signals, leading to symptoms like tingling or numbness, pain, muscle spasms, weakness, and paralysis, as well as coordination issues and fatigue. Examples include multiple *sclerosis*.
- Damage or death of specific neurons in the brain responsible for motor control: Parkinsonian-type diseases focus on movement disorders because of specific brain damage, and symptoms include slowed movements, tremors, balance problems, shuffling steps, and a hunched posture; examples of Parkinsonian-type diseases include *Parkinson's disease* and other forms of *parkinsonism*. Motor neuron diseases involve the death of neurons controlling movement, leading to progressive muscle weakness and paralysis; examples of motor neuron diseases include *amyotrophic lateral sclerosis* (ALS), also known as "Lou Gehrig's disease"[5].

With the rise in life expectancy, coupled with the fact that these disorders typically present themselves in advanced age (after 60 years), it is evident that their prevalence is on the incline. The rationale behind the manifestation of these disorders in later life stems from the susceptibility of the nervous system to age-related degenerative changes[6]. The cellular abnormalities and disease mechanisms involved in neurodegenerative diseases often overlap,

complicating the understanding of disease progression. The symptoms can vary widely among individuals with the same condition due to the unique diversity of each person's brain.

As neurodegenerative diseases can be attributed to either a singular identifiable cause or the convergence of multiple contributing factors, experts have delineated various elements contributing to these conditions, systematically categorized into specific groups:

Age: The most significant factor, with a strong correlation between aging and the development of these diseases[7].

Genetics: Familial components and inherited mutations play a crucial role, alongside spontaneous mutations, and gene combinations[7].

Environmental factors: Pollution, chemicals, toxins, infections, and geographical location can significantly contribute. For instance, lower vitamin D levels in areas farther from the equator are linked to dementia-type diseases[7].

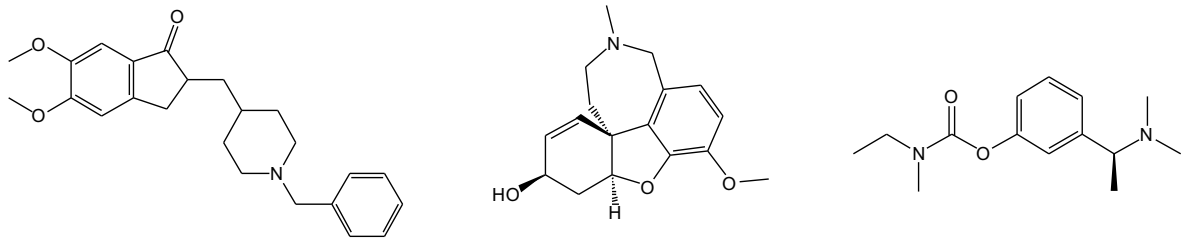
Medical history and past health events: Certain medical events such as cancer, infections, and head injuries can impact the development or progression of neurodegenerative conditions[7].

Habits, routines, and choices: Lifestyle factors also contribute to the development of these diseases[7]. Although, as anticipated, neurodegenerative disorders are primarily recognized for motor and cognitive alterations, they affect a variety of physical processes; indeed, a range of psychiatric problems such as depression, schizophrenia, and behavioral changes is also observed. For these disorders, there are drugs capable of mitigating symptoms to some extent, although they cannot be considered an effective and permanent means of treatment[8,9]. Currently, there is no definitive cure for NDDs, but treatments can help manage symptoms and slow down their progression. For example, in Alzheimer's disease, available drugs can temporarily improve cognitive symptoms. In Parkinson's disease, the use of dopaminergic drugs can help control motor symptoms. However, following is a list of the most prescribed drugs currently by neurologists and approved by the FDA for the treatment of those diseases.

Alzheimer's disease (AD)

Although for AD there are several hypotheses of pathological pathways, the cholinergic is the oldest and most widely accepted hypothesis followed later by the other two, the amyloid-ß, and the τ protein hypotheses[10]. The most prescribed drugs by neurologists for Alzheimer's

disease to improve cognitive (decreased memory and attention) and behavioral symptoms (agitation, apathy, hallucinations) are acetylcholinesterase inhibitors: *Donepezil* ***(2)***, *Galantamine* ***(3)*** and *Rivastigmine* ***(4)*** *in* ***Fig.1.1.2.*** Acetylcholinesterase (AChE) is an enzyme that destroys acetylcholine so that it does not accumulate between cells. Since the cholinergic hypothesis holds that in Alzheimer's disease there is a deficiency of acetylcholine in the brain, it goes without saying that the use of these inhibitors concurs to increase the availability of acetylcholine in the brain and more specifically in the synaptic space. By crossing the blood-brain barrier, those drugs can reach the central nervous system exerting their therapeutic activity.



DONEPEZIL ***(2)*** *GALANTAMINE* ***(3)*** *RIVASTIGMINE* ***(4)***

Figure 1.1.2. *Inhibitors of AChE for treatment of AD.*

Amyotrophic lateral sclerosis (ALS) also called Lou Gehrig's disease after the baseball player who was diagnosed with it, means "a-" *no*, "myo-" *muscle*, "trophic" *nourishment*. Thus, amyotrophic means "*no muscle nourishment*," and when a muscle has no nourishment, it "atrophies" or wastes away; "*Lateral*" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area degenerates, it leads to scarring or hardening ("sclerosis") in the region. The death of motor neurons, extending from the brain to the spinal cord, leads to progressive impairment of voluntary muscle action, resulting in potential loss of speech, eating, movement, and breathing abilities in individuals with ALS. Recent scientific advancements have enriched our understanding of ALS physiology. Currently, four drugs are approved by the FDA to treat ALS and its symptoms[11], yet the cause remains unknown in most cases. In other cases, causes may include family history and people with familial ALS only need to inherit it from one parent to develop symptoms. In their case, the disease is caused by an inherited mutation in a dominant gene, SOD1 (superoxide dismutase), a gene that encodes for a protein called SOD1, which is deputed to the disposal of toxic byproducts produced during normal cellular processes that would otherwise damage cells. Mutations in SOD1 may cause misfolding and aggregation

within motor neurons and astrocytes, the types of cells involved in ALS development and progression. These clumps (aggregates) may interfere with healthy cell functions or may cause other necessary proteins to misfold and lose their function, damaging the nervous system and leading to the development of ALS. Researchers have identified the gene mutation and developed *Tofersen* *in* ***Fig.1.1.3.***, an antisense oligonucleotide *(ASO)* designed to inhibit the production of toxic SOD1 proteins by binding to the mutated SOD1 gene's RNA.

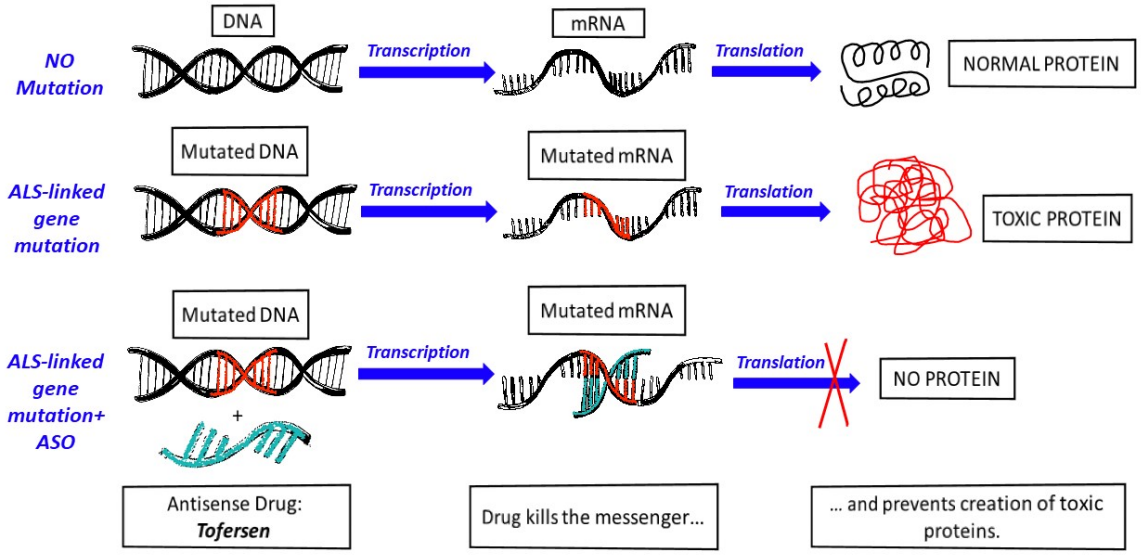


Figure 1.1.3. *Mechanism of action of Tofersen.*

Relyvrio ***(5)*** in ***Fig.1.1.4.*** is a fixed-dose combination of two compounds: *tauroursodeoxycholic acid* and *sodium phenylbutyrate*. These compounds act synergistically to prevent nerve cell death by blocking stress signals within two specific cellular compartments, namely mitochondria and the endoplasmic reticulum. As previously mentioned, in most ALS cases, certain proteins fail to fold correctly and accumulate in abnormal aggregates, which can induce stress signals ultimately leading to cell death. This drug is designed not only to enhance the energy production of mitochondria but also to assist proteins in acquiring their normal shape, thereby preventing the formation of protein aggregates that cause nerve cell death. Since the oxidative stress (resulting from an imbalance between the production of reactive oxygen species (ROS) and the biological system's ability to detoxify the reactive intermediates) plays a critical role in ALS. FDA approved for the treatment of ALS a potent pyrazolone-based free radical scavenger and antioxidant, *Edaravone* ***(6)*** ***(Fig.1.1.4.)***. It is theorized to be effective because it reduces the effects of oxidative stress in ALS. Among the likely causes of ALS, it is believed that the excessive release of glutamate causes damage to nerve cells, as it leads to

an overactivation of the cells, triggering a cascade of events that culminates in the death of nerve cells. The result is an ongoing and unrestrained cycle of cell death, as dying cells release glutamate, contributing to the death of neighboring cells. It is thought that <u>*Riluzole*</u> ***(7)*** ***(Fig.1.1.4.)*** can block glutamate signaling, slowing the deterioration and progression of symptoms. Recent studies suggest *Riluzole* can reduce the toxic accumulation of TDP-43[12] protein clumps, which occurs in about 97% of ALS cases and is thought to contribute to nerve cell dysfunction. This is the first drug having prolonged the survival of people with ALS.

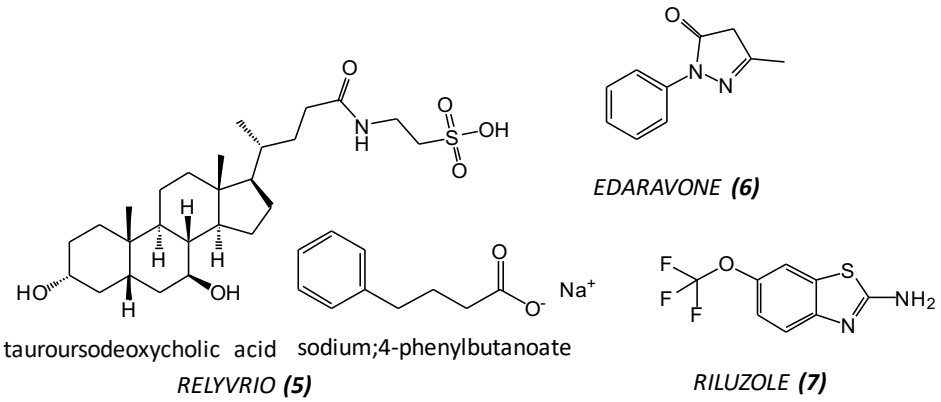


Figure 1.1.4. *Drugs approved for treatment of ALS.*

<u>*Parkinson's disease (PD)*</u>

Parkinson's disease is a chronic neurodegenerative disorder caused by the selective and progressive destruction of neurons located in the substantia nigra of the midbrain. These neurons, responsible for the production and release of dopamine, degrade, disrupting the balance among various neurotransmitter systems (cholinergic system, GABAergic system, glutamatergic system, ***Fig.1.1.5.***) and triggering a series of effects responsible for the complexity of symptoms in Parkinson's disease. Eventually influencing the regulation of neural pathways involved in motor control and cognitive functions[13].

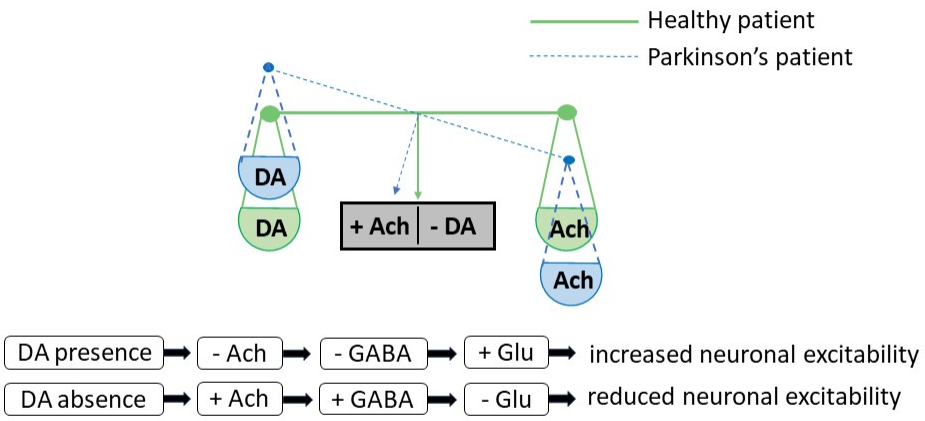
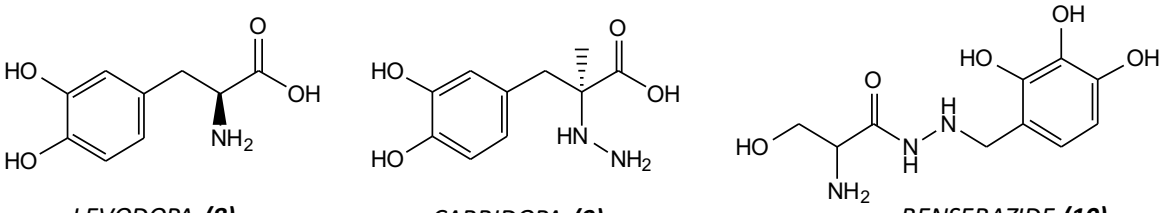


Figure 1.1.5. *Alteration of neurotransmitter systems in Parkinson's disease (**DA**: Dopamine; **GABA**: Gamma-Aminobutyric Acid; **Ach**: Acetylcholine; **Glu**: Glutamate).*

It is evident that the dopaminergic therapy is the therapy of choice, and this includes:

- *Drugs that increase dopamine synthesis in the Central Nervous System (CNS)*. This category includes *L-Dopa* ***(8)*** ***(Fig.1.1.6.)***, the immediate precursor of biogenic amine (dopamine), the most widely used drug for over 50 years. Despite prolonged use, it is not without issues such as desensitization of the aromatic amino acid transporter (allowing L-Dopa to cross the Blood-Brain Barrier and intestinal barrier), nausea, vomiting, and psychosis – symptoms related to peripheral activation of L-Dopa by ubiquitous decarboxylases transforming the drug into dopamine. To mitigate these side effects, L-Dopa is administered with peripheral decarboxylase inhibitors, *Carbidopa* ***(9)*** or *Benserazide* ***(10)*** ***(Fig.1.1.6.)***, compartmentalizing L- Dopa in the CNS and avoiding peripheral effects.

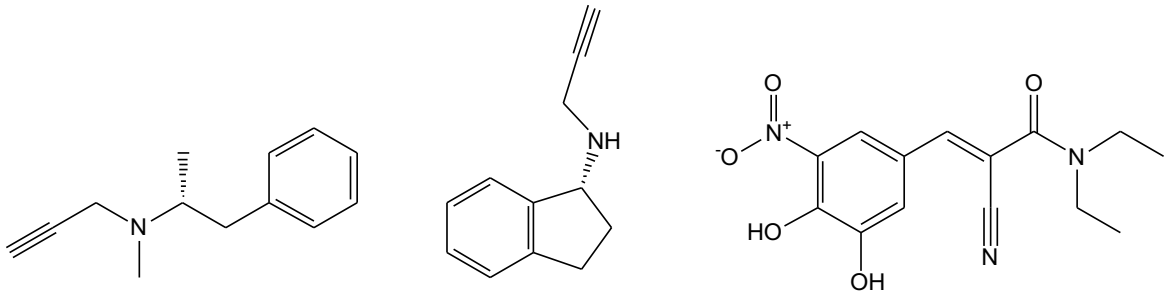


LEVODOPA ***(8)*** *CARBIDOPA* ***(9)*** *BENSERAZIDE* ***(10)***

Figure 1.1.6. *Drugs that increase synthesis of dopamine.*

- *Drugs that decrease dopamine metabolism.* This category includes drugs inhibiting enzymes responsible for dopamine degradation, such as irreversible and selective monoamine oxidase inhibitors (MAO-B, more selective and specific for dopamine),

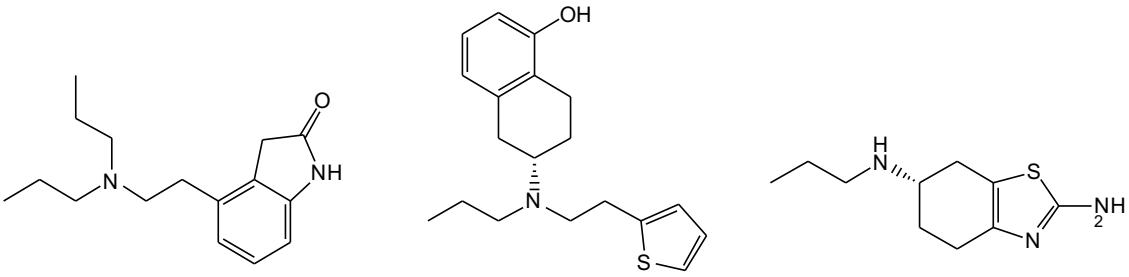
such as *Selegiline* ***(11)*** and *Rasagiline* ***(12)*** *(**Fig.1.1.7.**)*. Inhibitors of these isoforms act on a 10% neurotransmitter quota, achieving an increase in dopaminergic firing sufficient for antiparkinsonian activity. In addition to MAO-B inhibitors, there are also catechol-O-methyltransferase inhibitors (COMT), like *Entacapone* ***(13),*** which, in combination with L-Dopa, reduce its metabolic degradation.



SELEGILINE ***(11)*** *RASAGILINE* ***(12)*** *ENTACAPONE* ***(13)***

Figure 1.1.7. *Drugs that decrease dopamine.*

- *Dopaminergic agonist drugs*. *Ropinirole* ***(14)***, *Rotigotine* ***(15)***, and *Pramipexole* ***(16)*** *(**Fig.1.1.8.**)*, act as agonists of dopamine receptors and are used to compensate for dopamine deficiency in the brains of Parkinson's patients.



ROPINIROLE ***(14)*** *ROTIGOTINE* ***(15)*** *PRAMIPEXOLE* ***(16)***

Figure 1.1.8. *Drugs that act as dopamine agonist.*

In conclusion, neurodegenerative diseases pose a significant challenge to human health, with a major impact on the quality of life of patients. Research continues to seek a deeper understanding of the causes and mechanisms of these diseases, as well as new therapies to slow down their progression and improve symptom management. Increasing public awareness, supporting research organizations, and promoting healthy lifestyles can help control these diseases and improve the lives of those affected. Since current therapies for NDDs mainly aim to relieve symptoms and control damage, it would be advantageous to design

drugs that can promote the regeneration of neural axons, dendrites, and synapses within the adult nervous system[4]. Scientific research is currently focused on the neuroprotective factors such as antioxidants (vitamins E and C)[14], NSAIDs (COX2-selective inhibitors)[15], Coenzyme Q[16], anti-apoptotic agents (caspase inhibitors)[17], and on the development of neurotrophic compounds, very similar in the activity to endogenous neurotrophic factors. The use of neurotrophic factors represents the most promising approach for repairing the neurodegenerative damage[18], but presents also cons: they are high-molecular weight proteins; they are not able to cross the blood-brain barrier; they are easily degraded by peptidase under physiological conditions. Thus, most of these compounds are peptides that are challenging to synthesize and exhibit a poor pharmacokinetic profile (such as poor serum stability, low oral bioavailability, and limited penetration of the blood-brain barrier). This suggests that scientific research is also directed towards molecules endowed with neurotrophic activity. These molecules should be capable of mimicking neurotrophins, possessing an improved pharmacokinetic profile, and promoting the survival and differentiation of neurons. They should also circumvent the limitations of protein-based therapeutics in order to be utilized in future clinical applications[4].

1.2. Neurotrophic Activity

1.2.1. Neurotrophins and Cell Signaling

Understanding the mechanism of the endogenous molecules (the *neurotrophins)* responsible for the neurotrophic activity can shed light on potentially active molecules. The *neurotrophins* belong to a group of proteins that, acting on cell membrane receptors, induce survival, development, and function of neurons. There are four structurally related neurotrophins:

- nerve growth factor (NGF, discovered by Rita Levi-Montalcini in the early 1950's for its effect on growth and differentiation of specific populations of neurons of the peripheral nervous system[19], discovery that would earn her the 1986 Nobel Prize in Physiology or Medicine);
- brain-derived neurotrophic factor (BDNF);
- neurotrophin-3 (NT-3);
- neurotrophin-4/5 (NT-4/5).

For the activation of neuronal signal transduction, each neurotrophin binds selectively to its tyrosine kinase receptor family (TrkA, TrkB, and TrkC) and binds non-selectively to the p75 neurotrophin receptor ($p75^{NTR}$). For instance, NGF binds to TrkA, BDNF and NT-4 to TrkB and NT-3 mainly to TrkC[20]. Trk signaling occurs through two pathways (***Fig. 1.2.1.1.***):

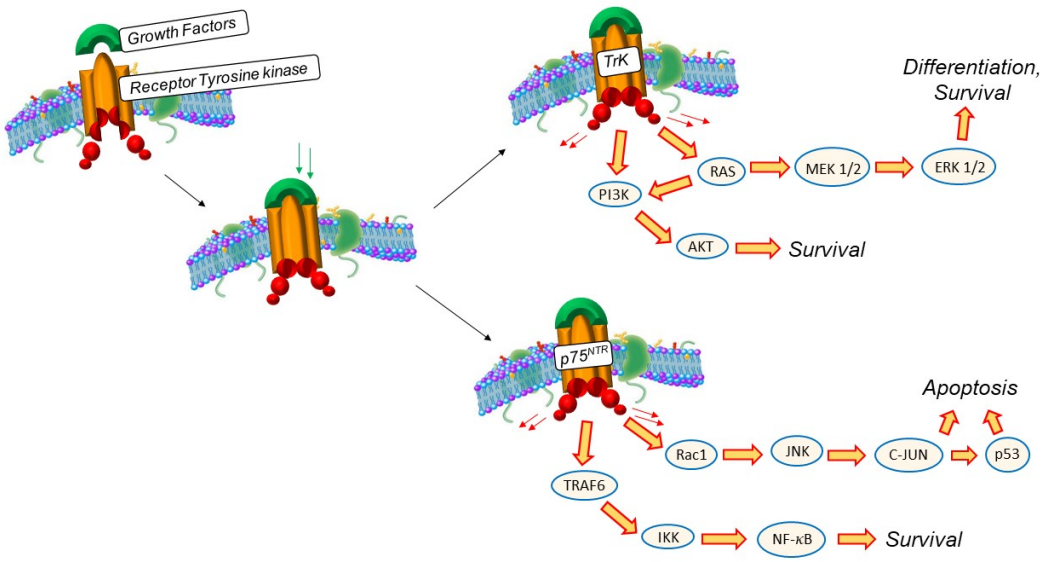


Figure 1.2.1.1. *Neurotrophin signaling pathways.*

- MAPK (mitogen-activated protein kinase) and PI3 (phosphoinositide 3-kinase) control the fate of neurotrophin signaling in terms of cell survival and cell differentiation.
- Binding of neurotrophins to $p75^{NTR}$ can also trigger neuron apoptosis[4].

The ultimate signal of activation of these pathways is a process characterized by developing neurons that produce new projections in response to driving stimuli represented by neurotrophins that thus regulate the growth of neurites. The dynamic growth of neurites during development results in the formation of a complex neuronal architecture, which leads to the creation of the fully functional nervous system (***Fig. 1.2.1.2.***).

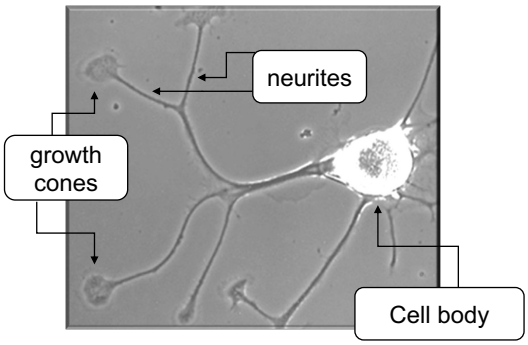


***Figure* 1.2.1.2.** *Regenerated neurites emerging from the cell body; growth cones can be observed at the tips of these regenerating neurite processes.*

Over the decades, researchers encountered many families of neurotrophic natural products in their quest to discover new compounds that promote neurite outgrowth, especially those that have NGF-potentiating activity with low molecular weight or those that modulate neural cellular signaling and could be an alternative solution for the treatment of neurodegenerative disease[21]. Many metabolites from mushrooms have shown NGF-like neuritogenic effects, therefore, it is of utmost importance to elucidate the molecular mechanism responsible for the activity, although it is not always straightforward to understand how it evolves. For example, cell growth and differentiation are not always regulated by the involvement of the Trk family of receptor tyrosine kinase (TrkA); in some cases, there may not be a direct involvement of the Trk family of receptor tyrosine kinase (TrkA), thus the activation of TrkA may not be necessary[22] (see ***Fig.1.2.1.3.***).

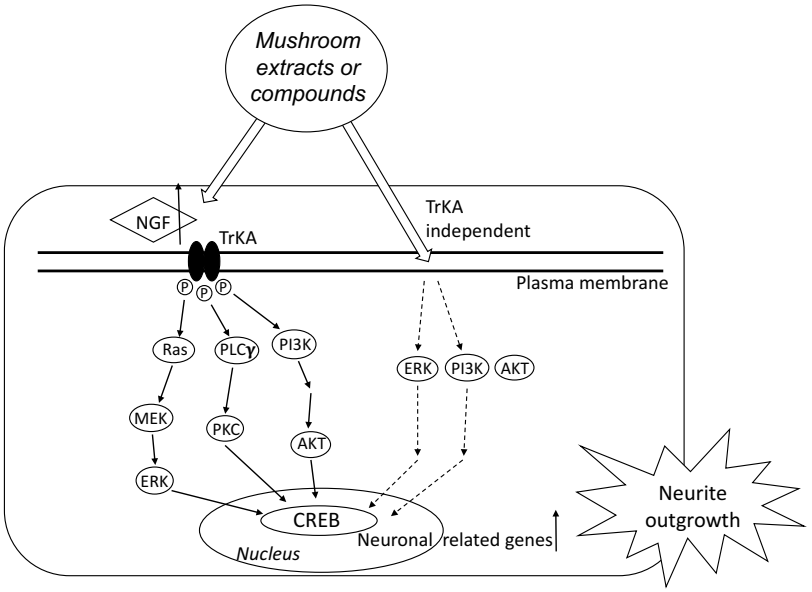


Figure 1.2.1.3. *Schematic model of neurite outgrowth of mushroom extracts/compounds*[22]*.*

It has been known that the MAPK signal cascade is involved. In detail, three mitogen-activated protein kinases' families (MAPK) have been characterized, namely extracellular signal-regulated kinase (ERK), C-Jun N-terminal kinase/ stress-activated protein kinase (JNK/SAPK), and p38 kinase. NGF induces the activation of MEK and phosphorylation of ERK1/2, therefore, the mushroom extracts (as well as NGF) induced the activation of MEK1/2, resulting in neurite outgrowth. It is widely accepted that PI3K/AKT regulates neuritogenesis. AKT is a serine/threonine kinase essential for neurotrophin-induced cell survival and the activation of AKT by neurotrophins is mediated by phosphatidylinositol-3 kinase (PI3K): inhibition of PI3K/AKT negatively affected neurite outgrowth of PC-12 cells. For some categories of fungi that will be mentioned below, the mechanism by which they act is already known, e.g.:

- *Lanostanoids* from *G. lucidum* enhance the neurite outgrowth of PC-12 cells via activation of CREB transcription.
- *Cyrneine A* from the mushroom *Sarcodon cyrneus* enhances the activation of nuclear factor-kB and ERK1/2 is required for Cyrneine A-induced neuritogenesis.
- *Scabronine G* induces neuritogenesis through PKC-cascade[23].

Others from the fungal kingdom whose activity is known, but whose mechanism is unknown, are discussed in the next chapter.

1.3. Neurotrophic Drug Leads from Basidiomycota Natural Products

Here, the neurotrophic natural products (isolated from fungi) will be elucidated that have been shown to enhance neurite outgrowth. In detail, division Basidiomycota represent an amazing reservoir for such incredible molecules provided with the most diverse activities, and in particular neurotrophic activity. From a wide range of *Basidiomycota*, researchers found some interesting hits. Below is a compilation of compounds that displayed this uncommon activity along the last two decades.

- *Cyathane diterpenoids isolated from different cultured mycelia:*

<u>*Cyathane xylosides*</u> ***(Fig.1.3.1.)*** *from H. erinacium*[24] promote the neurite outgrowth of PC12 cells, enhance NGF mRNA expression, and the secretion of NGF from 1321N1 human astrocytoma cells[25]. Further, in vivo tests suggest that compounds extracted from H. erinaceus could promote the regeneration of nerve injury in the early stage of recovery[26].

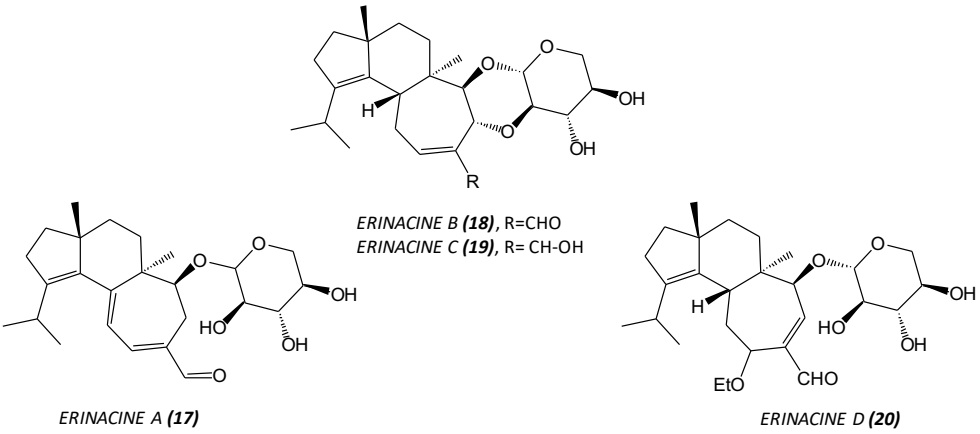
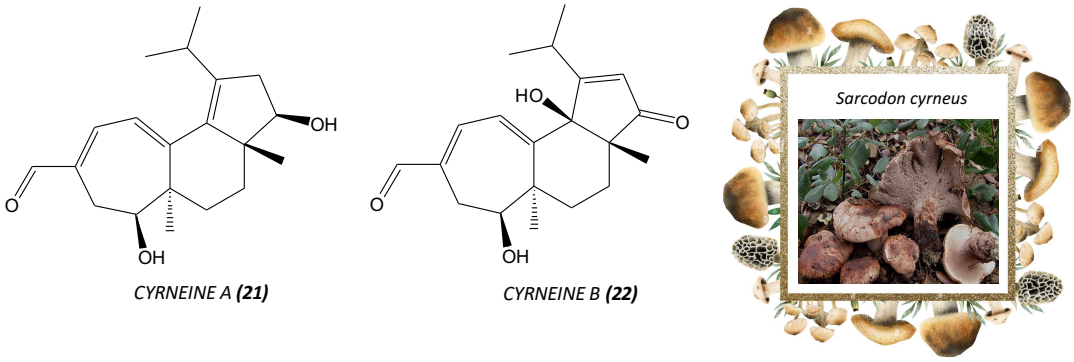


Figure 1.3.1. *Cyathane diterpenoids from H. erinacium.*

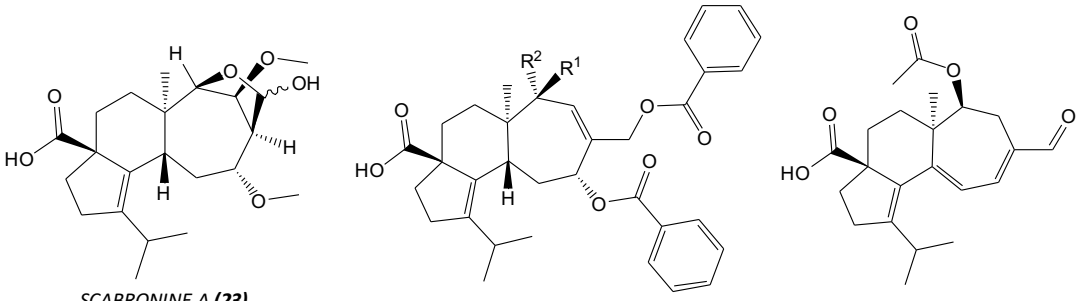
<u>*Cyrneine*</u> <u>*A*</u> ***(21)*** and <u>*Cyrneine*</u> <u>*B*</u> ***(22)*** in ***Fig.1.3.2.*** from *S. Cyrneus*[27] stimulated neurite outgrowth in PC-12 at 100 mM with no cytotoxicity and both cyrneines promote NGF production in 1321N1 cells[22].



CYRNEINE A ***(21)*** *CYRNEINE B* ***(22)***

Figure 1.3.2. *Cyathane diterpenoids from S. Cyrneus.*

Among Cyathane diterpenoids named *Scabronines* (***Fig.1.3.3.***) isolated from the fruit body of mushroom *S. scabrosus*[28], *Scabronine A* ***(23)*** showed potent inductive activity of NGF synthesis in 1321N1 human astrocytoma cells[29]. Further investigation led to the isolation of novel cyathane diterpenoids named *Scabronine B* ***(24)***, *C* ***(25)***, and *D* ***(26)*** which show NGF-synthesis stimulating activity[22].



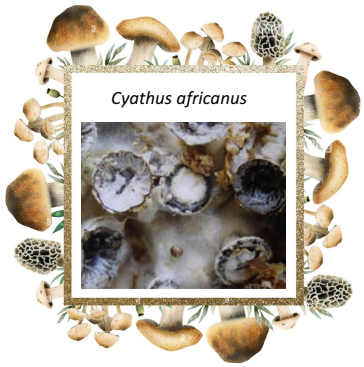
SCABRONINE A ***(23)***

SCABRONINE B ***(24)***, R^1=OH, R^2=H
SCABRONINE C ***(25)***, R^1/R^2=O

SCABRONINE D ***(26)***

Figure 1.3.3. *Cyathane diterpenoids from S. scabrosus.*

From the investigation on solid cultures of *Cyathus africanus*[30] two new cyathane diterpenoids, *Neocyathin S* ***(27)*** and *Neocyathin T* ***(28)*** in ***Fig.1.3.4.***, were isolated and were found to exert neurite outgrowth-promoting activity in NGF-mediated PC-12 cells[28].



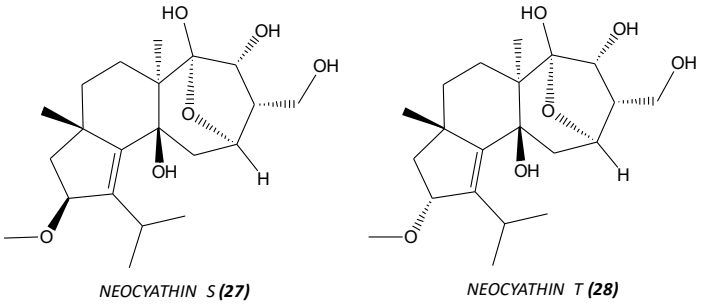
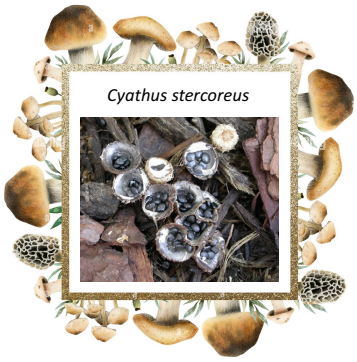


Figure 1.3.4. *Cyathane diterpenoids from Cyathus africanus.*

Three novel cyathanes, ***(29), (30)*** *and* ***(31)*** in ***Fig.1.3.5.***, isolated from *Cyathus stercoreus*[31], displayed good neurotrophic activity in PC-12 cells[32].



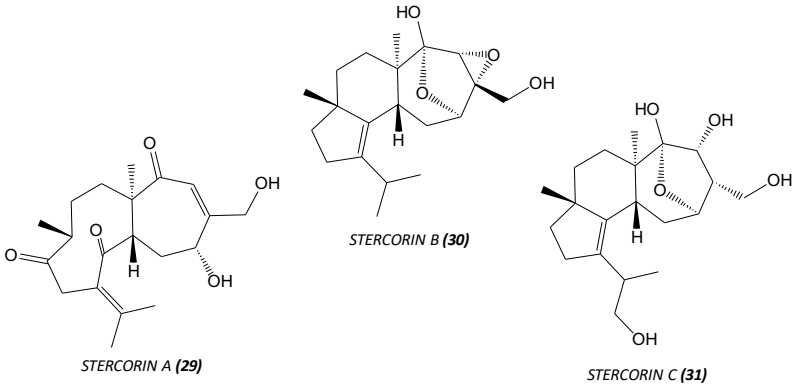
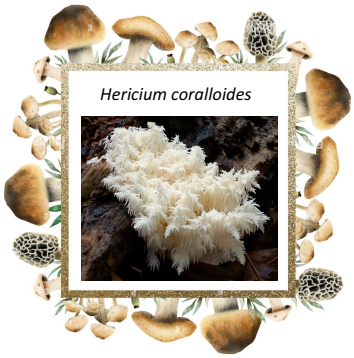


Figure 1.3.5. *Novel cyathane diterpenoids from C. stercoreus.*

- Various isoindolinone derivatives, <u>*Corallocins A-C*</u> (***Fig.1.3.6.***) isolated from fruiting bodies of *H. coralloides*[33], exhibited NGF and BDNF expression in human 1321N1 astrocytes at different concentrations[33]. For the first time it was observed a promoting effect of fungal isoindolinone derivatives not just on NGF, but also on BDNF expression[33].



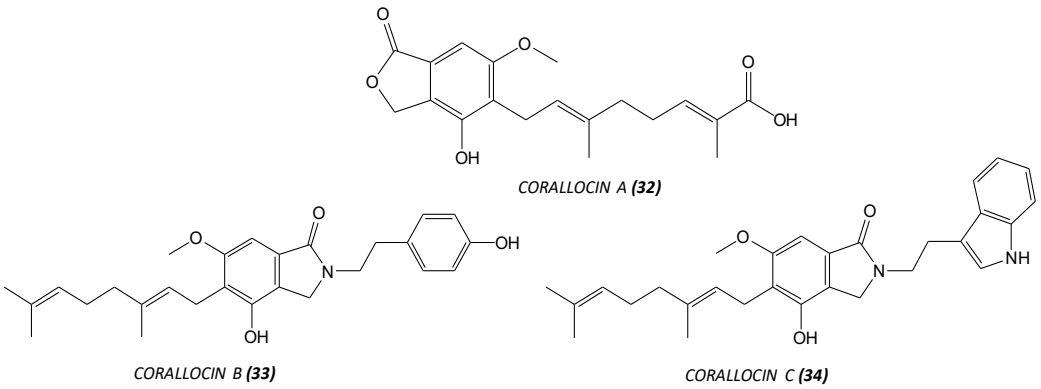
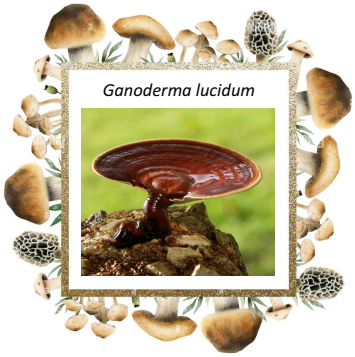


***Figure 1.3.6**. Isoindolinone derivatives from H. coralloides.*

- <u>*Lanostanoids*</u> (***Fig.1.3.7.***) from dried fruiting bodies of *Ganoderma lucidum*[34] especially *compound **(35)** and **(39)*** show nerve growth factor-like neuronal survival-promoting effects, triterpenoids ***(35)*** and ***(38)-(41)*** have BDNF-like neuronal-survival-promoting activities[35].



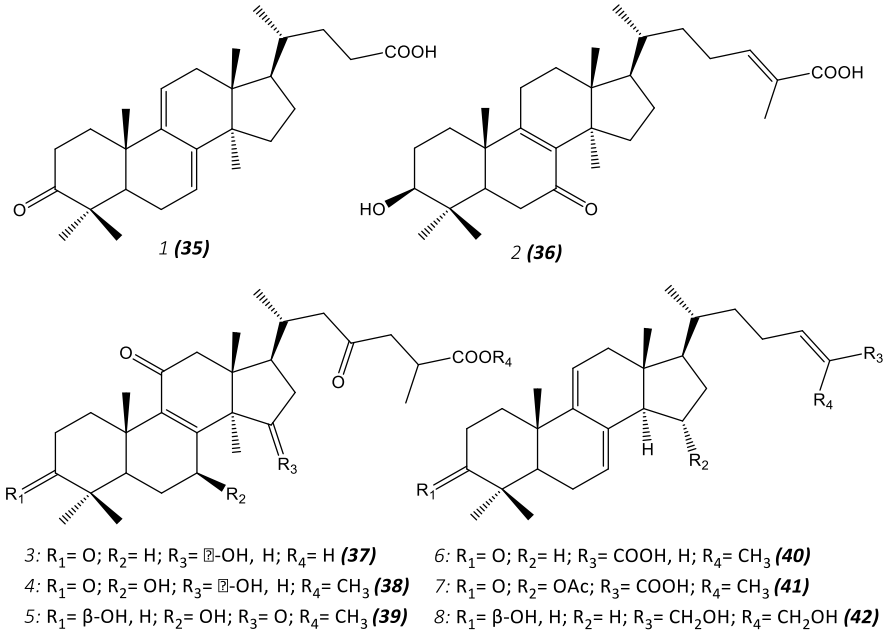
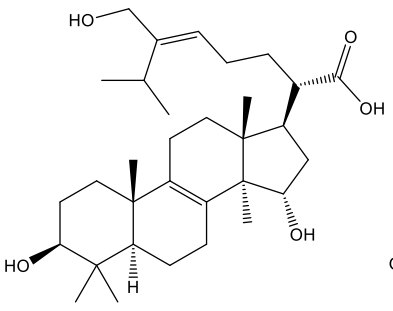
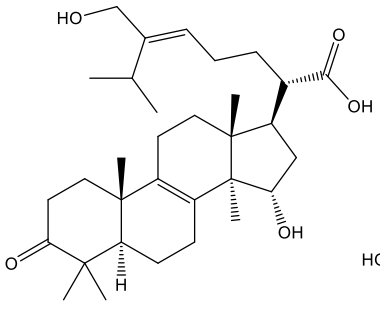


***Figure 1.3.7**. Lanostanoids from Ganoderma lucidum.*

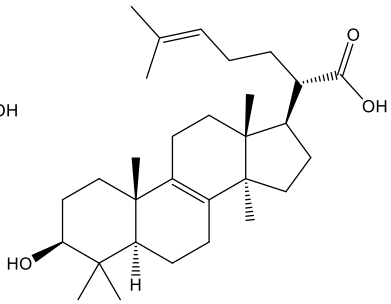
- *Lanostane triterpenoids* (***Fig.1.3.8.***), from fruiting bodies of *Laetiporus sulphureus* and from a mycelial culture of *Antrodia* sp. MUCL 56049[36]. In the first mushrooms were identified *laetiporin C* ***(43)***, *laetiporin D* ***(44)***, *trametenolic acid* ***(45)***, *eburicoic acid* ***(46)***, *15α-hydroxytrametenolic acid* ***(47)***, *sulphurenic acid* ***(48)***, *fomefficinic acid D* ***(49)***. The metabolites of the other fungus include *tumulosic acid* ***(50)***, *polyporenic acid* ***(51)***, 16α-*hydroxyeburiconic acid* ***(52)***, *dehydrotumulosic acid* ***(53)*** and *pachymic acid* ***(54)***[36]. Treatments with *sulphurenic acid* ***(48)***, 16α-*hydroxyeburiconic acid* ***(52)***, *fomefficinic acid D* ***(49)*** and *15α-hydroxytrametenolic acid* ***(47)*** significantly upregulate NGF mRNA expression levels, while *sulphurenic acid* and *15α-hydroxytrametenolic acid* significantly up-regulate *BDNF* expression. Neurite outgrowth was not observed when PC-12 cells were treated directly with the triterpenes. However, when PC-12 cells were treated with the triterpenes supplemented with 5 ng/mL NGF, neurite outgrowth was observed with ***(48)***, ***(47)***, ***(49)*** and ***(46)***[36].



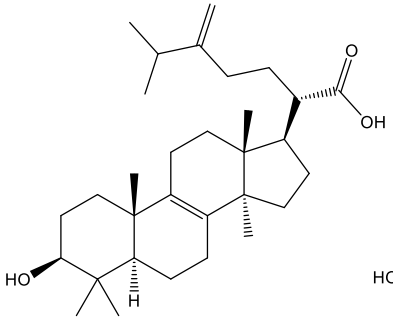
LAETIPORIN C ***(43)***



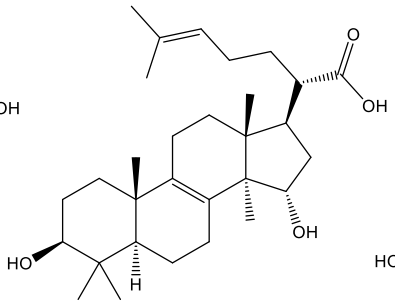
LAETIPORIN D ***(44)***



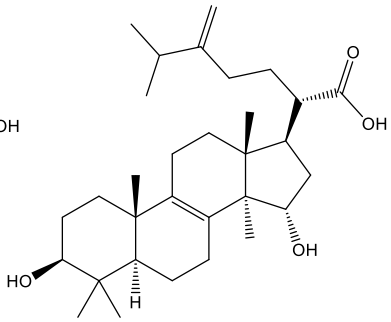
TRAMETENOLIC ACID ***(45)***



EBURICOIC ACID ***(46)***



15α-HYDROXYTRAMETENOLIC ACID ***(47)***



SULPHURENIC ACID ***(48)***

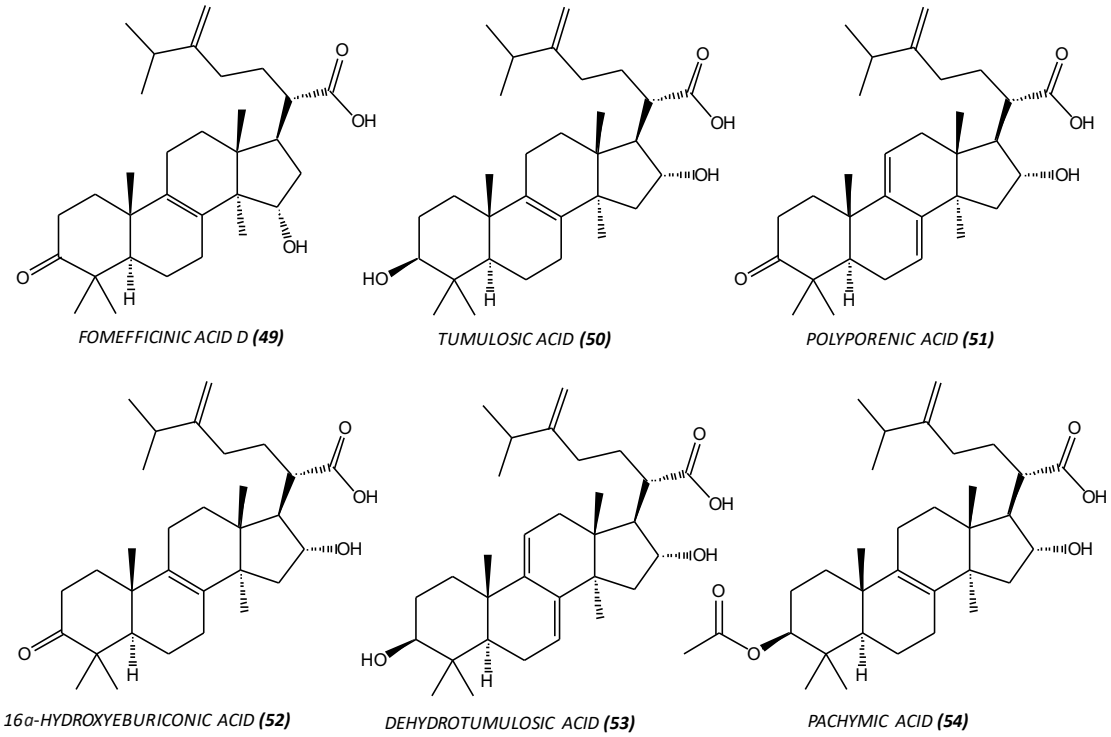


Figure 1.3.8. *Lanostane triterpenoids from Laetiporus sulphureus and Antrodia sp. MUCL*

- Drimane-Type Sesquiterpenoids isolated from cultures of the Polypore *Abundisporus violaceus* MUCL 56355[37] named *Abundisporin* *1* ***(55)***, *2****(56)***, *3****(57)***, *4****(58)***, *5****(59)*** and *6****(60)*** (***Fig.20***) were all tested demonstrating neurotrophic effects, with ***(55)*** and ***(60)*** significantly increasing outgrowth of neurites when treated with 5 ng/mL NGF; even *Abundisporin 2–5* increase the neurite outgrowth to some extent. We hereby show that drimane-type sesquiterpenoid compounds have an NGF-enhancing effect, highlighting their neurotrophic potential[37]. The structure−activity relationships of drimane derivatives and their corresponding mechanisms of action in neuroprotection remain to be established. It will be particularly interesting to study whether the molecules act as NGF substitutes and/or induce NGF synthesis, thus aiding in the development of new neuroprotective medicines[37].

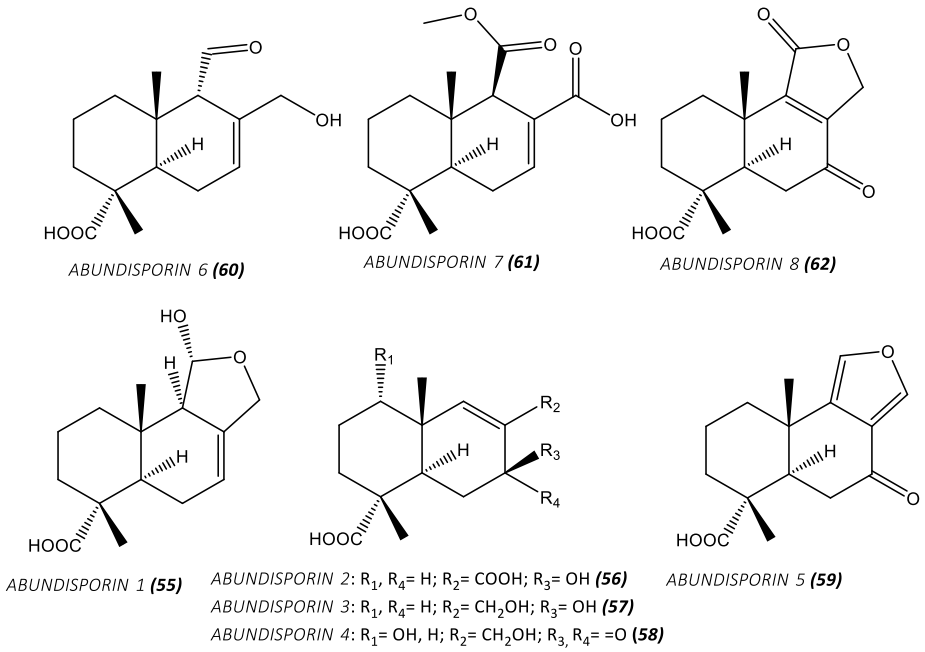
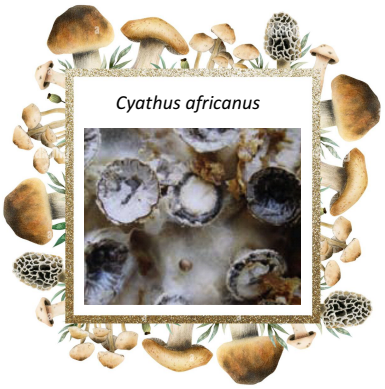


Figure 1.3.9. *Abundisporins from Abundisporus violaceus MUCL 56355.*

- Three drimane sesquiterpenoids (***Fig.1.3.10.***), one known *3β,6β-dihydroxycinnamolide* ***(63)*** and two new ones *3β,6α-dihydro-xycinnamolide* ***(64)*** and *2-keto-3β,6β -dihydroxycinnamolide* ***(65)***, were isolated from cultures of a fungal strain of *Cyathus africanus*[30] these compounds have been shown to enhance nerve growth factor (NGF)-mediated neurite outgrowth using rat pheochromocytoma (PC-12) cells at concentration 10 µM[38].



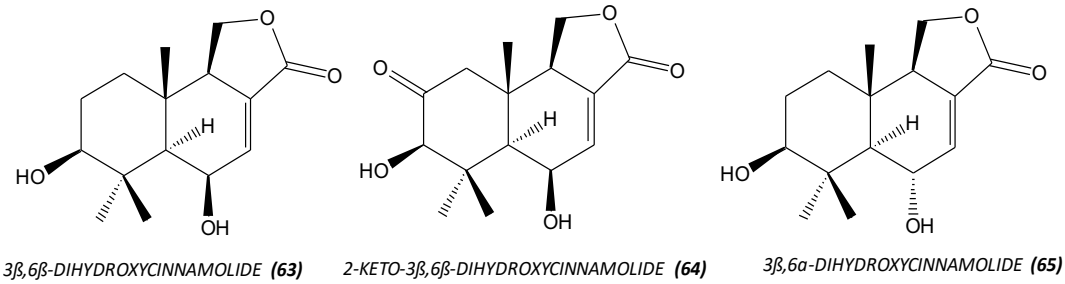


Figure 1.3.10. *Drimane sesquiterpenoids from Cyathus africanus.*

- For the first time in the *Fungal Kingdom Basidiomycota*, drimane-type sesquiterpene lactams (***Fig.1.3.11.***) were isolated alongside the known isodrimenediol and

cryptoporic acid H, from *Cerrena sp. nov*. (collected in Thailand, identified as *Cerrena* cf. *caperata*)[39].

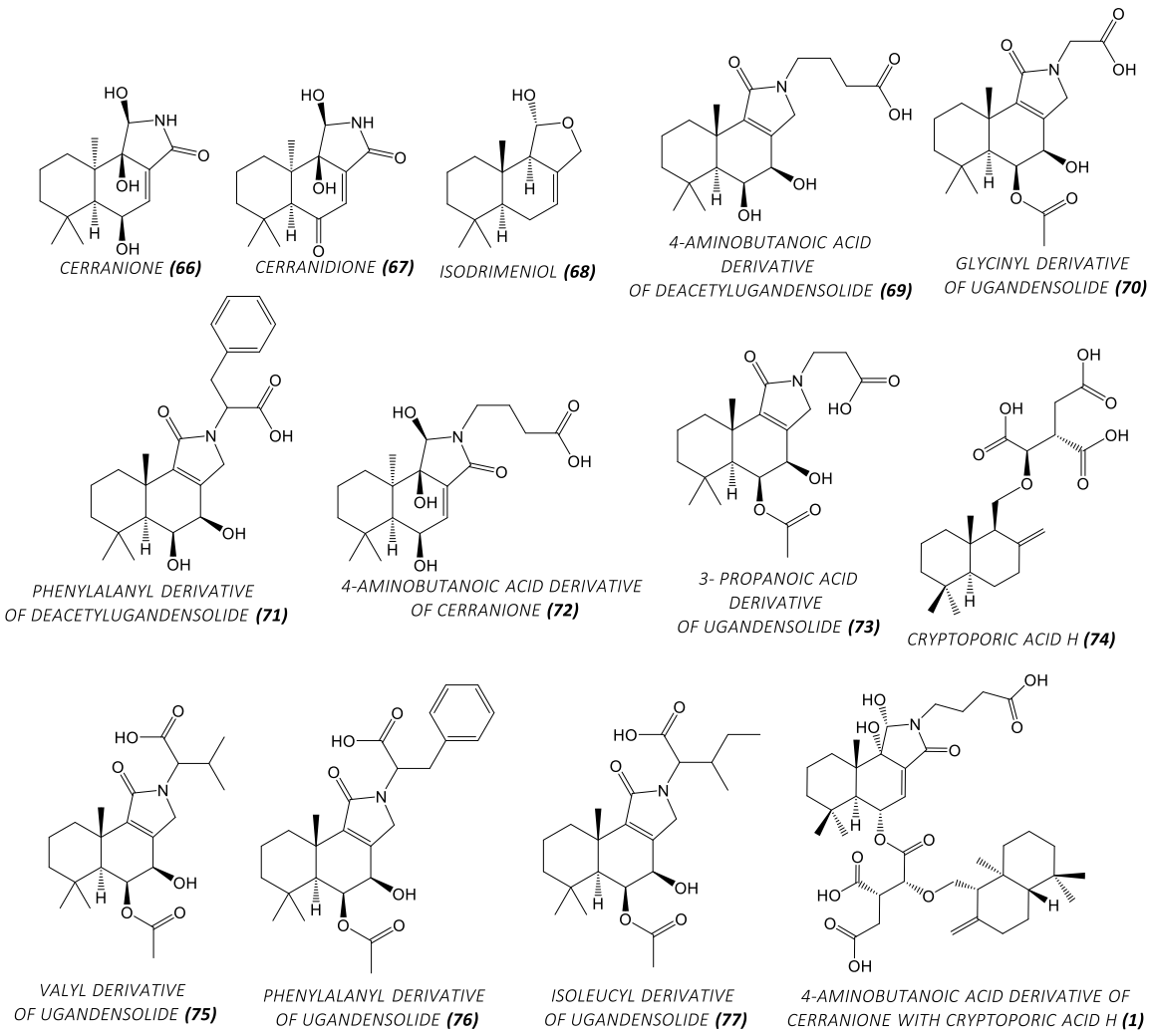


Figure 1.3.11. *Drimane-type sesquiterpenoids from Cerrena* cf. *caperata.*

Since the aim of this work was to study one of these compounds, the characteristics and activities of these metabolites will be clarified in the next chapter.

1.4. Sesquiterpenes and drimane-type sesquiterpenoids: an overview

Terpenes, a diverse class of natural compounds derived from isoprene units, serve as foundational building blocks for an array of secondary metabolites. Among these, Sesquiterpenes emerge as a prominent subclass, characterized by their intriguing structural diversity and biological significance. Their structural complexity and varied functional groups lay the groundwork for the synthesis of drimane-type sesquiterpenoids, a subgroup esteemed for its pharmacological properties and intricate molecular architectures.

The first sesquiterpene drimane, *(–)- drimenol* ***(78)***, was isolated from the bark of *Drymis winteri Forst*[40], sparking a sustained focus on isolating this class of compounds from higher plants, herbs, and various sources.

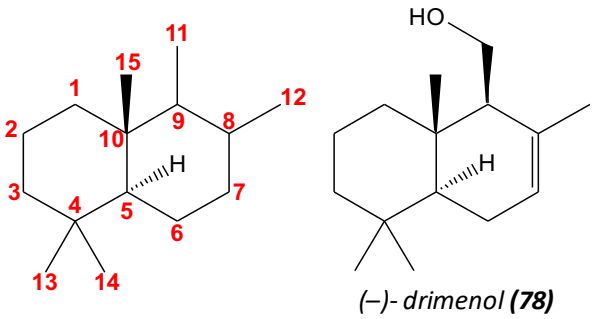
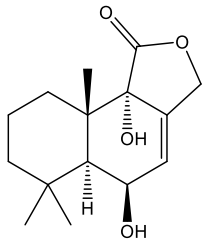
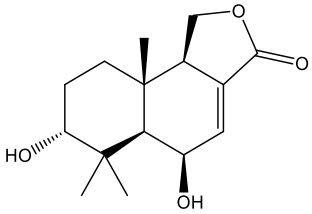
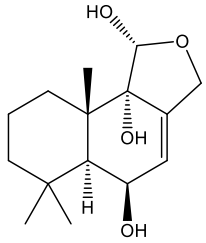
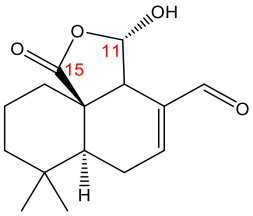
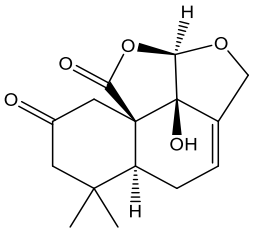
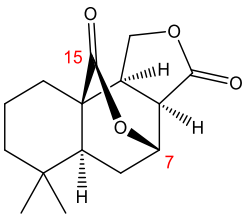


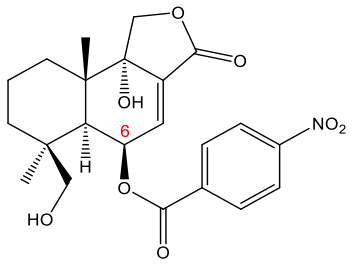
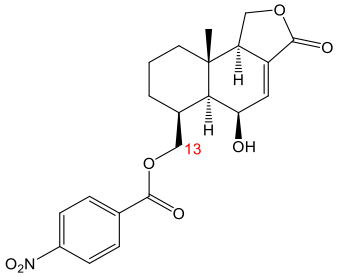
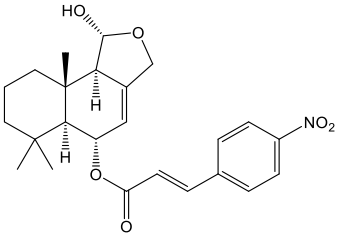
Figure 1.4.1. *Drimane carbocyclic core (left); chemical structure of (–)-drimenol (right).*

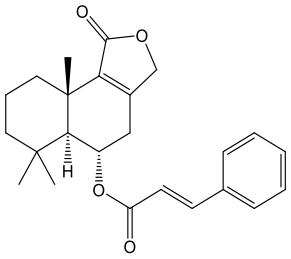
Since the isolation of the initial sesquiterpene drimane, research efforts focused on uncovering and understanding this class of compounds, particularly from botanical sources. Nonetheless, the scope of this review centers on delving into the sesquiterpenoid drimanes prevalent in the Fungal Kingdom. By elucidating the structural characteristics, and exploring their diverse biological activities, this review seeks to provide an encompassing understanding of these compounds. This exploration not only unveils the chemical intricacies but also underscores their relevance across pharmaceutical.

The majority of simple DTS (drimane-type sesquiterpenoids) isolated from fungi have a γ-lactone ring, typically formed by the proximity of an alcohol to either an aldehyde or a carboxylic acid group, resulting in the formation of α-hydroxytetrahydrofuran ***(81)*** or γ-butyrolactone ***(79)***[41].

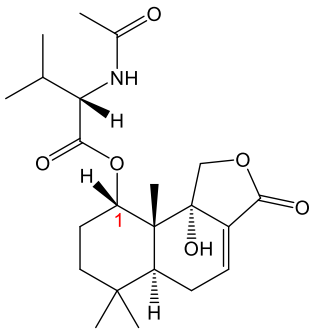
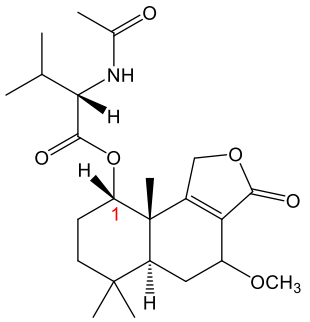
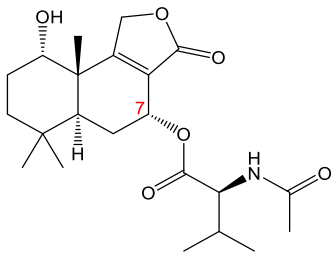
Tricyclic Lactone DTSs	Fungal source	Activity
Strobilactone A ***(79)*** 	*Strobilurus ohshimae*	Antibacterial and antifungal activity
3α,6β- dihydroxycinnamolide ***(80)*** 	*Inonotus rickii*	Moderate activity on human colon cancer cells and neurotrophic activity
P*ereniporin A* ***(81)*** 	*Perenniporia medullaepanis*	Plant growth inhibitor activity
Marasmal B ***(82)*** 	*Marasmius sp.*	Antifungal activity
Tetracyclic Lactone DTSs	**Fungal source**	**Activity**
Nigrofomin B ***(83)*** 	*Nigrofomes melanoporus*	Inhibition of the growth of leukaemia T cells
Gymnodrimane G ***(84)*** 	*Gymnopilus sp.*	-

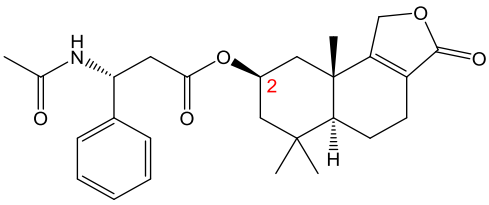
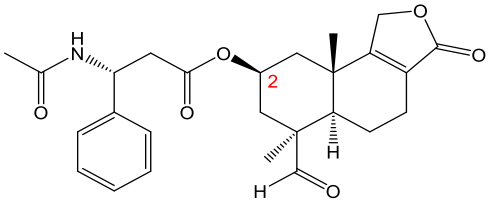
Among these tricyclic DTSs, when methyl C-15 is oxidized to a carboxylic acid and condensed with aldehyde C-11 a characteristic lactone ring is thus formed like in *Marasmal B* ***(82)***. An additional tetrahydrofuran ring may be formed in addition to the lactone ring, to get tetracyclic DTSs, like *Nigrofomin B* ***(83)*** or *Gymnodrimane G* ***(84)***, which presents a peculiar δ-lactone ring that may occur upon the condensation between C-7 hydroxyl group and C-15 carboxylic acid. Within the tricyclic structure of these drimane-type sesquiterpenoids, several instances of etherification or esterification can occur at different positions while retaining the fundamental tricyclic structure. These modifications often occur at specific sites, thus diversifying their chemical properties and potentially affecting their biological activities. Regarding the esterification, this can occur, for example, at the C-6, C-13 positions such as in *Insulicolide A* ***(85)*** and *B* ***(86)*** and with different functional groups such as nitrobenzoyl, coumaroyl and cinnamoyl moiety. These different esterification patterns testify to the structural versatility inherent in tricyclic sesquiterpenoids[41].

DTS-ester with *p*-nitrobenzoic acid moitey	**Fungal source**	**Activity**
Insulicolide A ***(85)*** 	*Aspergillus insulicola, Aspergillus ochraceus, Aspergillus versicolor*	Antiproliferative activity and good ciytotoxicity against various cell lines, antiviral activity
Insulicolide B ***(86)*** 	*Aspergillus insulicola, Aspergillus ochraceus, Aspergillus versicolor*	Antiproliferative activity and good ciytotoxicity against various cell lines, antiviral activity
DTS-ester with *p*-coumaroyl moitey	**Fungal source**	**Activity**
22-hydroxyxylodonin B ***(87)*** 	*Xylodon flaviporus*[42]	Inhibition of osteoclastogenesis

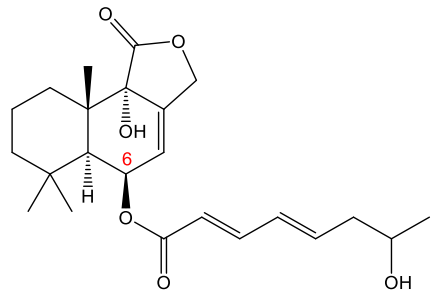
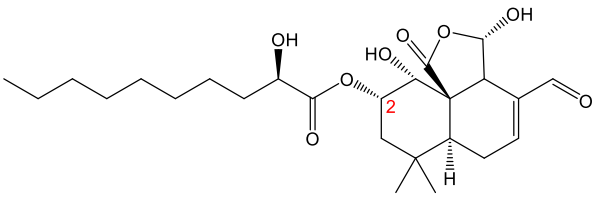
DTS-ester with *p*-cinnamoyl moitey	Fungal source	Activity
Xylodonin A ***(88)*** 	*Xylodon flaviporus*	Inhibition of osteoclastogenesis

DTSs can also form esters with aminoacids; compound like *Berkedrimane B* ***(89)*** and *Purpuride B* **(90)** are conjugated with *N*-acetyl-L-valine at C-1, *Minioluteomide E* ***(91)*** at C-7[43]. *Proversilin C* ***(92)*** and *Proversilin E* ***(93)*** form instead a conjugate with *N*-acetyl-β-phenylalanine, in both cases at C-2.

N-acetyl-L-valine-conjugated DTS-esters	Fungal source	Activity
Berkedrimane B ***(89)*** 	*Talaromyces minioluteus*	Anti-inflammatory activity
Purpuride B ***(90)*** 	*Talaromyces minioluteus*	Antimicrobial activity
Minioluteomide E ***(91)*** 	*Talaromyces minioluteus*	Antimicrobial activity

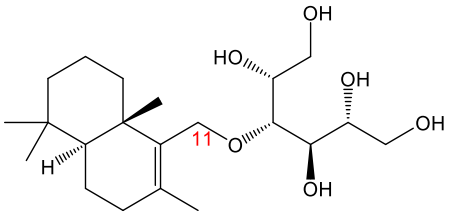
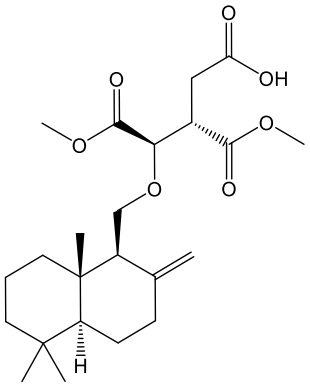
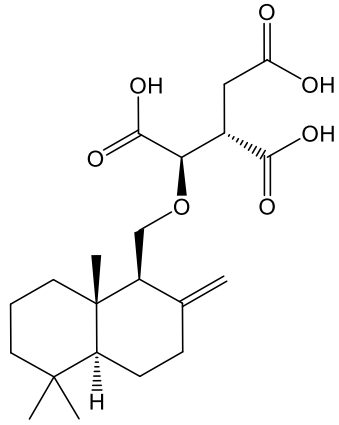
N-acetyl- β-phenylalanine -conjugated DTS-esters	Fungal source	Activity
Proversilin C ***(92)*** 	*Aspergillus versicolor*	Moderate cytotoxic activity
Proversilin E ***(93)*** 	*Aspergillus versicolor*	Moderate cytotoxic activity

Esterification can also take place at C-6 and C-2 with respectively polyunsaturated acid substituents or saturated acid substituents, like in *Ustusolate C* ***(94)*** and *Mniopetal B* ***(95)***.

DTS-ester with polyunsaturated acid substituents	Fungal source	Activity
Ustusolate C ***(94)*** 	*Aspergillus ustus*	Inhibition of the mammalian RNA-directed DNA-polymerases
DTS-ester with acyl chains	**Fungal source**	**Activity**
Mniopetal B ***(95)*** 	*Marasmius oreades*	Inhibition of the mammalian RNA-directed DNA-polymerases

Unlike the wide chemical variety of DTS-esters, ethers are usually formed at C-11[41]. Reported examples include sporulositols, such as *Sporulositol A* **(96)** containing a D-mannitol group. The relevant ethers are cryptoporic acids, with an isocitric acid moiety, initially isolated from

Cryptoporus volvatus, but, as we will report here, *Cryptoporic acid H* ***(98)*** can also be a metabolite of *Cerrena* cf. *caperata.*

DTS-ether with D-mannitol	**Fungal source**	**Activity**
Sporulositol A ***(96)*** 	*Paraconiothyrium sporulosum*	Inhibition of the mammalian RNA-directed DNA-polymerases
DTS-ethers with isocitric acid moiety	**Fungal source**	**Activity**
Cryptoporic acid A ***(97)*** 	*Cryptoporus volvatus*	Antimycobacterial activity. Cytotoxic activity, Antiplasmodial activity, Antioxidant activity
Cryptoporic acid H ***(98)*** 	Cryptoporus volvatus, *Cerrena* cf. *caperata.*	Potential neurotrophic activity

These modifications, characterized by site-specific etherification or esterification, represent pivotal points in the structural elaboration of drimane-type tricyclic sesquiterpenoids, highlighting the versatility and intricate nature of these compounds within natural product chemistry. Moreover, these structural features extend to the molecule ***(1)*** that guided this thesis project. These and other distinctive features will be explained in a dedicated section, shedding light on the specific attributes and alterations present in this focal compound.

1.4.1. Neurotrophic drimane-type sesquiterpenoids derived from a Tropical white rot fungus, *Cerrena* sp.*nov*.

According to the GenBank, the strain *Cerrena sp. nov.* collected from an unnamed rotting tree trunk, isolated and identified by T. Boonpratang, R. Choeyklin, belongs to the genus *Cerrena* in the Cerrenaceae. Based on the basidiocarps and culture morphology, T. Boonpratang, R. Choeyklin classified this fungus as *Cerrena* cf. *caperata*. At the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Professor Marc Stadler and his team worked on the isolation, structural elucidation and evaluation of the metabolites of *Cerrena* cf. *caperata* (in ***Fig. 1.4.1.1.***).

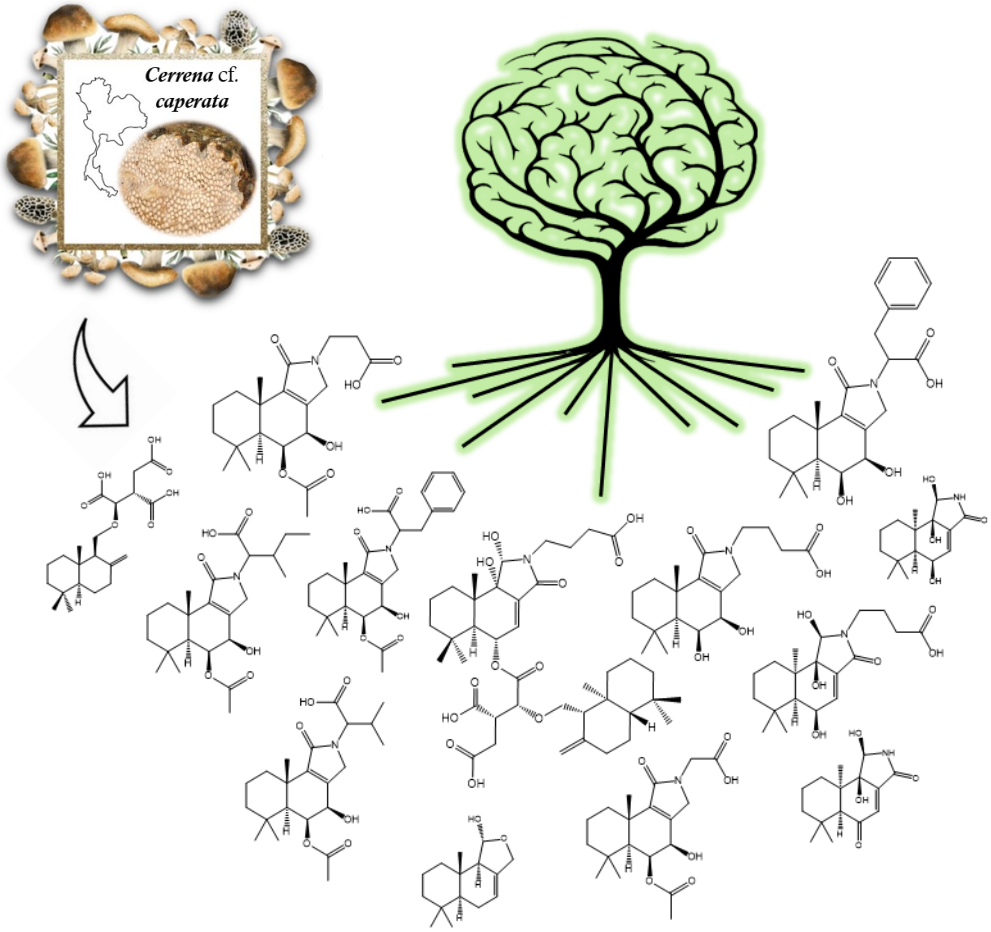


Figure 1.4.1.1. *Neurotrophic metabolites from Cerrena cf. caperata.*

Among sesquiterpene lactams that have rarely been discovered as natural products, those metabolites have attracted considerable attention since several members possess potent neurotrophic activity, while none of them showed antimicrobial activity and cytotoxicity. All compounds were screened for neurotrophic activity, using neurite outgrowth promotion of rat pheochromocytoma (PC-12) cells, a well-known model system to investigate neuritogenesis (***Fig.1.4.1.2.***). Neurons make connections through extensions of their cell bodies known as axons and dendrites, which are commonly called "neurites."

This biological phenomenon called "neuritic growth" is regulated by complex intracellular signaling events and represents a commonly used assay to study neuron development and neuronal degeneration in vitro. This analysis involves the use of PC-12 cells, rat pheochromocytoma cells characterized by their ability to respond reversibly to neuronal growth factor (NGF). Upon exposure to NGF, PC-12 cells arrest their proliferation and in culture they begin to exhibit neuronal-like behavior. In particular, NGF induces survival and differentiation through two distinct signaling cascades: the RAS/ERK cascade is necessary and sufficient only for differentiation, while the PI3-K pathway appears to be the primary cascade for NGF mediated survival[44]. When the NGF stimulus is removed, the neuron-like processes degenerate and cell growth resumes. PC-12s are also capable of secreting neurotransmitters such as dopamine and norepinephrine. Because of these characteristics, PC-12s represent a viable cell model for studies in neurobiology and neurochemistry.

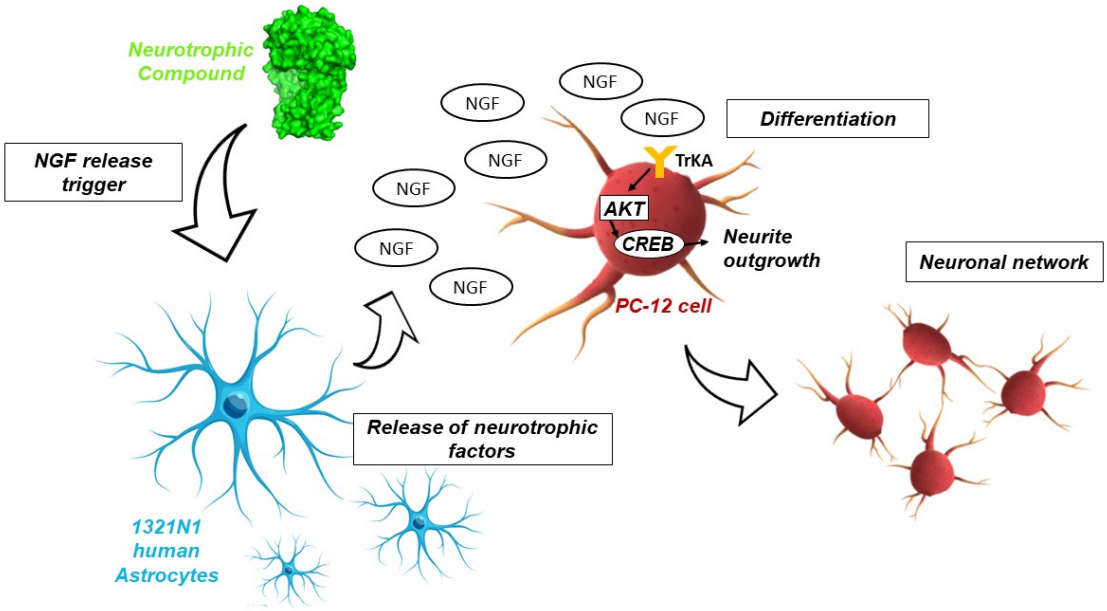


Figure 1.4.1.2. *Simplified representation of neurite outgrowth assay.*

In this model (***Fig.1.4.1.2.***) to test neurotrophic activity, PC-12 cells are cultured in the same medium of 1321N1 human astrocyte cells, known to secrete several neurotrophic factors. When PC-12 cells are treated with a potentially neurotrophic compound, if those cells differentiate into neuron-like cells, the assay indicates that the compound induced the release of neurotrophic factors from astrocyte cells by increasing protein synthesis and NGF secretion through mRNA expression. Using this assay, the potential of the metabolites of *Cerrena* cf. *caperata* in ***Fig.1.4.1.3.*** to induce rat pheocromocytoma (PC- 12 cells) neuronal cells differentiation was analyzed[45].

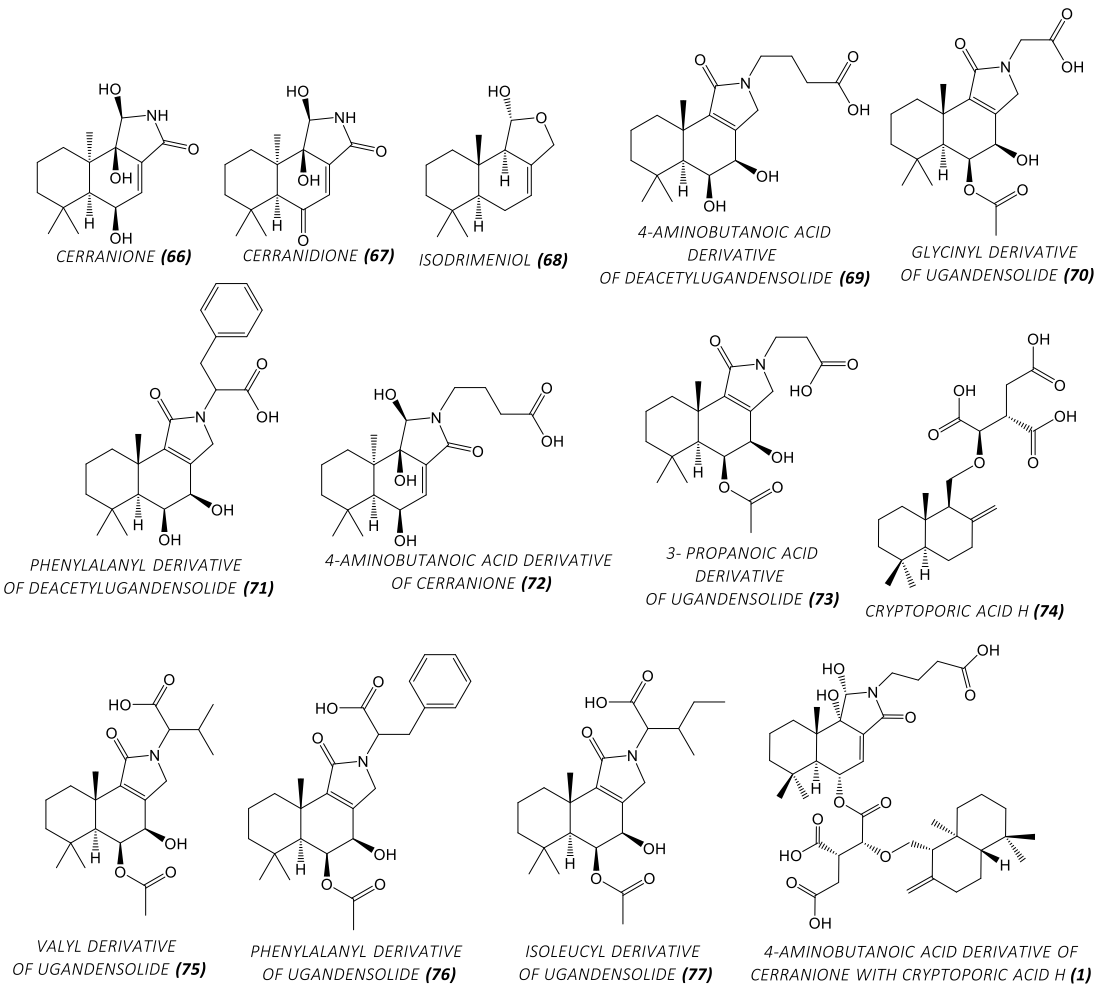


Figure 1.4.1.3. *Metabolites from Cerrena* cf. *caperata.*

For PC-12 and 1321N1 cell stimulation assays the nontoxic concentration (10 μM) was used for this experiment. PC-12 cells did not exhibit cell differentiation upon addition of compounds, but only using conditioned 1321N1 culture medium, PC-12 cells could be stimulated to differentiate compared to untreated controls. *Compounds* ***(66), (67), (70), (72), (73), (77)*** *and* ***(1)*** induced cell differentiation on PC-12 cells compared to negative control (a quantification of this assay is given in ***Fig.1.4.1.4.***). Among them, coherent with the cell differentiation analysis, NGF expression was upregulated in 1321N1 astrocytes upon stimulation by compounds (***(66), (70), (1),*** with ***(70)*** being the strongest NGF inducer followed by ***(1)*** and ***(66)*** compared to DMSO-treated controls (***Fig.1.4.1.5.***). In parallel, it has been performed quantitative RT-PCR analysis for mRNA expression of BDNF and similarly it has been observed an increase in BDNF mRNA levels for the compounds tested, and the strongest BDNF inducer was again ***(70)***, followed by ***(66)*** and lastly ***(1)*** (***Fig.1.4.1.5.***). The endogenous mRNA level of BDNF in 1321N1 astrocytes seemed to be much higher than that of NGF for ***(66)***, and the opposite was true for ***(69)*** and ***(77)***.

In conclusion, three compounds from *Cerrena* cf. *caperata*, ***(66)***, ***(70)***, and ***(1)***, induce different patterns of neurotrophin expression in human astrocytes. For the first time, a promotion effect of fungal drimanes derivatives on both NGF and BDNF expression was observed. Thus, they represent interesting tools for the investigation of neurotrophic properties.

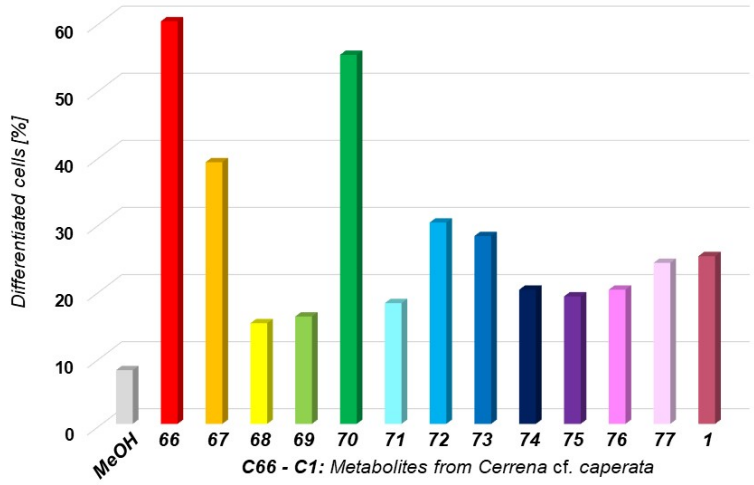


Figure 1.4.1.4. *A quantification of analyses with the number of differentiated cells [%] or neurite length [µm] of PC-12 cells incubated with conditioned medium produced by 1321N1 cells treated with drimanes* ***(66)-(1)****; negative control with methanol (MeOH).*

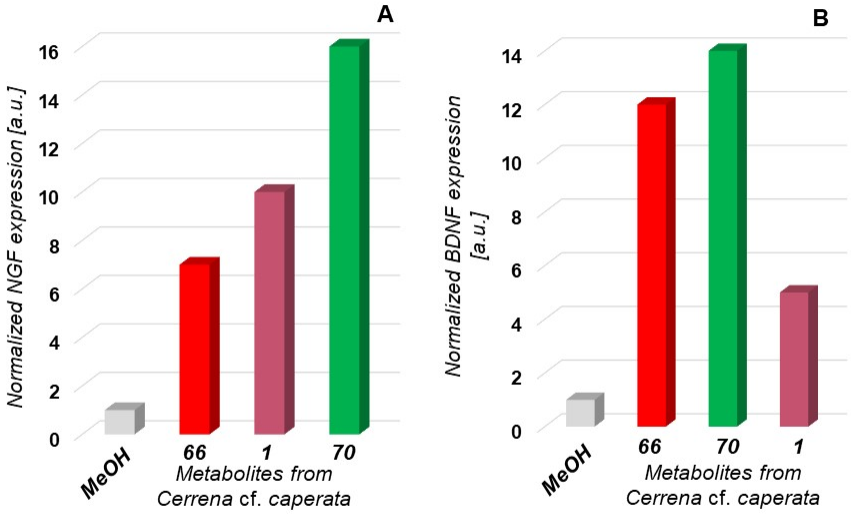


Figure 1.4.1.5. *RT-PCR analysis for mRNA of (**A**) NGF and (**B**) BDNF;* ***(A)*** *A significant increase of NGF was observed for* ***(70)*** *and* ***(1)****; (**B**) Compounds* ***(66)*** *and* ***(70)*** *showed a significantly higher BDNF mRNA amount when compared to the methanol control.*

As for the compounds mentioned in the previous chapter, although metabolites of *Cerrena* cf. *caperata* displayed neurotrophic activity, the biochemical mode of action of these compounds needs further study because, so far, it is not evident how the neurotrophic effects observed occurred.

1.5. A Novel Drimane-Type Sesquiterpenoid from Thai Basidiomycota: 4-Aminobutanoic acid derivative of cerranione with cryptoporic acid H

Among the aforementioned compounds, one in particular drew interest: the *4-Aminobutanoic acid derivative of cerranione with cryptoporic acid H* ***(1)***, whose absolute configuration was assigned successfully by X-ray crystallization by Dr. Ivana Císařová from the Department of Inorganic Chemistry at "Charles University" in Prague[46]. This compound (***Fig.1.5.1.***) is a linear dimeric drimane-related merosesquiterpenoid and it has been studied not only due to its activity and its unusual structure, but also for its captivating process of biosynthesis that links it to some of the other metabolites of *Cerrena* cf. *caperata*. However, based on its novelty and complexity compound 1 does not even have a name up to now and underlins the significance of this project.

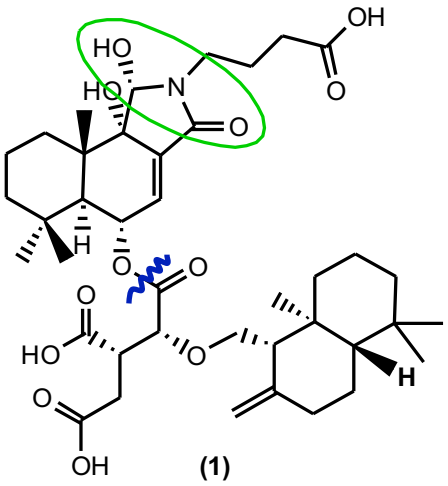


Figure 1.5.1. *4-Aminobutanoic acid derivative of cerranione with cryptoporic acid H (**1**).*

In this structure we have two of the metabolites isolated separately from *Cerrena* ***(72)*** and ***(74)*** (***Fig.1.4.1.3.***), which together give the molecule of interest. Its drimane core is equipped with an exceptionally uncommon third cycle equipped with two hydroxy-groups and a substituted cyclic amide. Thus, the molecule is provided with a lactam ring, unlike the usual occurrence of a lactone ring and in addition, the marked part in green in ***Fig.1.5.1.*** is the hemi-amidal motif. The cryptoporic acid H ***(74)*** (***Fig.1.4.1.3.***) is the second key fragment crucial to complete the structure. The final coupling resulted in the formation of the molecule's framework with the desired stereochemistry according to the natural product depicted in ***Fig.1.5.1.***

To understand the originality of those novel DTS molecules' biosynthesis pathway, it may be useful to investigate the natural process employed in nature to produce already known sesquiterpenes (***Fig.1.5.2.***). Although the biosynthesis of DTSs differs in plants, fungi, and bacteria, because each individual class uses its own enzyme kit to generate metabolites, recent advances have unveiled that the identified enzyme families responsible for the synthesis of drimane, exhibit minimal sequence similarity among different organisms[47]. These enzymes, the terpenoid synthases that catalyze cyclization reactions (also known as terpenoid cyclases of II class, TPSs- in blue in ***Fig.1.5.2.***) promote the cyclization of farnesyl pyrophosphate (FPP) by forming the drimane skeleton. This process initiates by the protonation of the terminal olefin on the terpene moiety leading to the generation of a tertiary carbocation, which can undergo further reactions. During FPP cyclization, bond formations occur at C-2/C-7 and C-6/C-11, leading to the formation of a bicyclic cationic intermediate. Subsequent deprotonation in ***(100)*** at the C-7, C-9 or C-12 positions leads to the generation of cyclized drimenylpyrophosphate intermediates. A final depyrophosphorylation step gives the natural products DTSs resulting from the three isomers: *drimenol* ***(78)*** (***Fig.30***), *drim-8-ene-11-ol* ***(101)*** and *(+)-albicanol* ***(102)*** with double bonds at Δ8-7, Δ8-9, and Δ8-12, respectively[47].

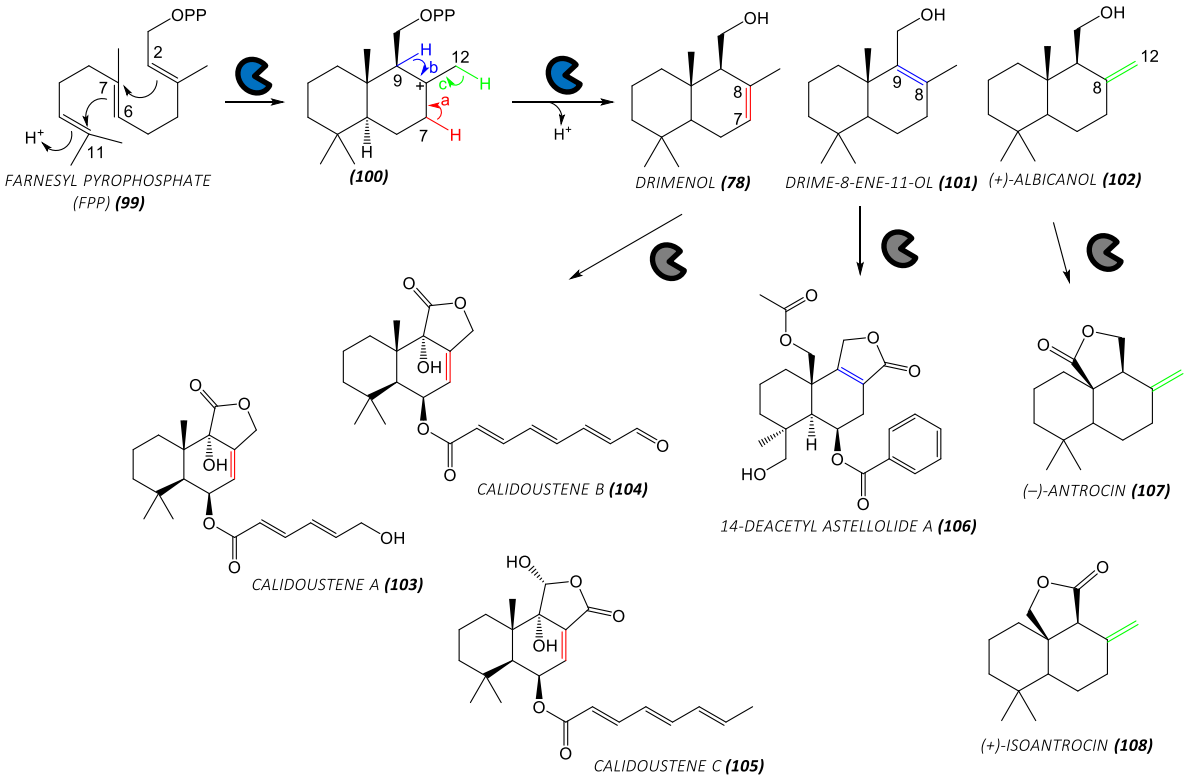


Figure 1.5.2*. Example of a biosynthetic pathway for specified DTSs.*

The fate of those compounds ***(78), (101), (102)*** depends on the enzymatic repertoire of the organisms in which they are synthesized. Overall, the tailoring enzymes (in grey in ***Fig.1.5.2.***) can be involved in:

- the formation of hydroxy groups at C-6, C-9, and C-12.
- the oxidation of hydroxy groups at C-6 and C-11 to a ketone and an aldehyde.
- the further oxidation of aldehydes at C-11 and C-12 into carboxylic acids, which are then condensed with the OH to form the butyrolactone ring.
- the synthesis of different lengths (C_6 and C_8) of PKS chains.
- the oxidation to varying degrees of PKS chains.
- the loading of the polyketide moiety on the drimane backbone.

Thus far, it is imperative to elucidate that the tremendous structural diversity of sesquiterpenoids is achieved by the types of cyclization reactions catalyzed by different STSs (sesquiterpene synthases) and by subsequent modifications of the cyclic products by additional tailoring enzymes.

As can be noticed in ***Fig.1.5.3.,*** *compounds* ***(70), (71), (75), (76)*** and ***(77)*** possess an amino acid in their structure; other metabolites lacked an amino acid at the lactam ring like ***(66)*** and ***(67),*** and others like ***(69), (72), (73)*** and ***(1)*** have 4-aminobutyl/3-aminopropyl acidic chains, resulting once again in substituted cyclic amides. Recently advanced hypotheses predicted that the *Cerrena* strain may possess two different biosynthesis gene clusters encoding for different enzymes. At this stage of the biosynthesis pathway, in addition to the presence of dehydrogenases employed in the process of closing the third ring in a lactone, there would also be aminases deputed to integrate an amino group of an amino acid to form the lactam ring. In ***(69), (72), (73)*** and ***(1)***, instead, a tailoring enzyme might catalyze the aminolysis of the lactone ring, we can speculate that a tailoring enzyme may catalyze the aminolysis of the lactone ring, a hypothesis that, if true, aligns with the strategy we have taken in our synthetic approach. Moreover, the involvement of oxidoreductases could lead to ring closure, hypothesis in accordance with the previous ones in which oxidoreductases have played a central role in facilitating third ring closure[39], in cooperation with other enzymes such as acetyltransferases, hydrolases, dehydrogenases, and cyclases, responsible for previously described functions. However, those hypotheses remain to be validated by genome sequencing and following experimental work.

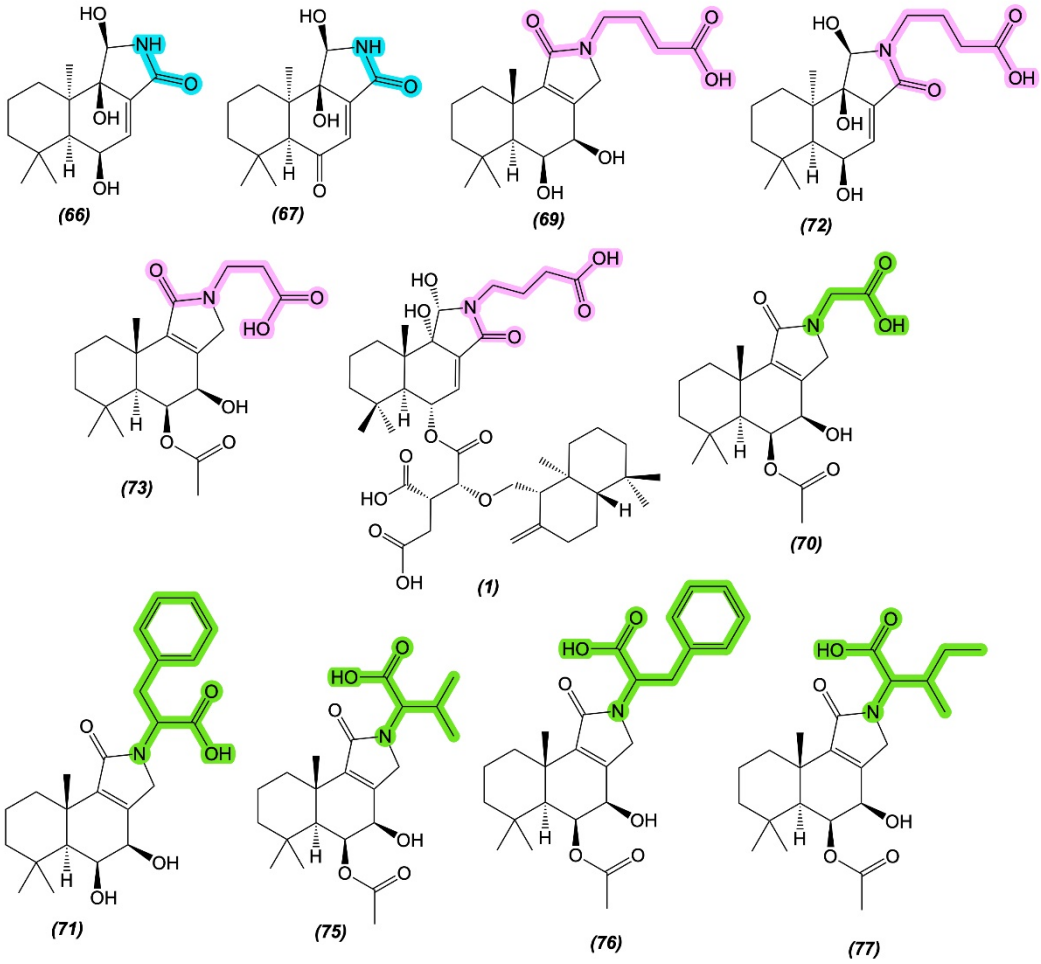


Figure 1.5.3. *Structural characteristics of drimane-type sesquiterpenoids derived from Cerrena* cf. *caperata.*

2. Objectives of the thesis

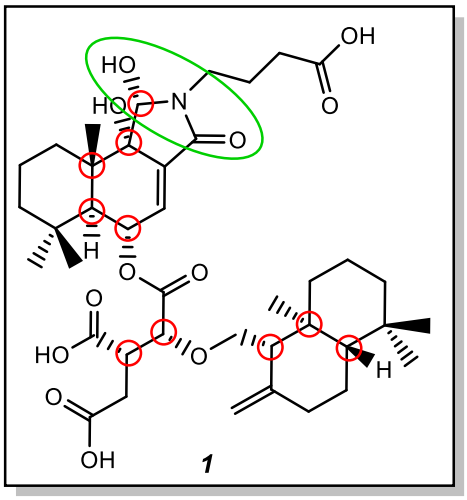


Figure 2.1. *Structure of drimane-type sesquiterpenoid* ***1*** *isolated from Thai Basidiomycota.*

Compound ***1*** is a drimane-type sesquiterpenoid endowed with neurotrophic activity, which is relatively rare compared to other biological activities found in DTSs. Furthermore, this molecule is particularly interesting because of its unusual structure. As already discussed before, compound ***1*** contains an uncommon hemi-amidal group and ten stereogenic centers. These features not only contribute to its biological activity but also represent significant challenges in the synthesis. The hemi-amidal group is particularly rare and challenging to synthesize, requiring precise control of reaction conditions to ensure its formation and stability. The presence of ten stereogenic centers adds another layer of complexity, requiring high stereoselectivity at each stage of the synthesis to achieve the desired configuration.

The main objective of this work is to develop a selective, reproducible, and sustainable synthetic strategy for the synthesis of compound ***1***, with a particular focus on the efficient control of the hemi-amidal group and stereochemistry. The aim is to optimize the yield and purity of the final products while minimizing the number of synthetic steps and the use of reagents. The synthetic process must be robust and deliver consistent results. This approach aims to balance complexity and sustainability to achieve reliable and reproducible outcomes.

3. Theoretical Section

This dissertation will describe the studies toward a novel procedure for the straightforward synthesis of bioactive fungal natural product *4-Aminobutanoic acid derivative of cerranione with cryptoporic acid H* ***(1)***. The strategy underlying this project is convergent; therefore, the main fragments were first identified ***(Figure 3.1)***, and then their synthesis and a coupling strategy were planned.

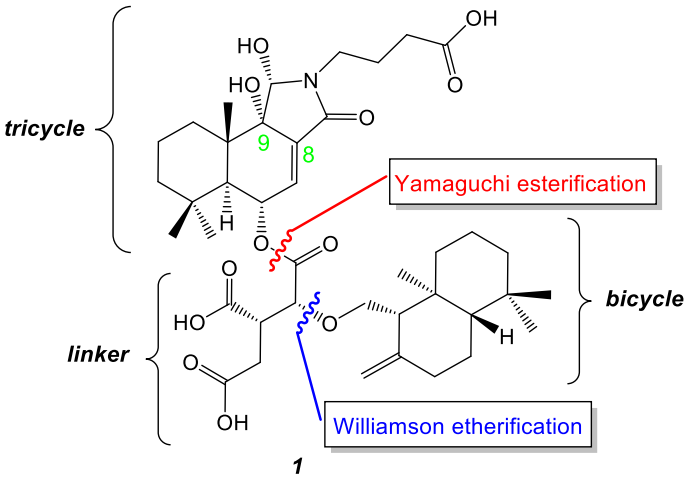
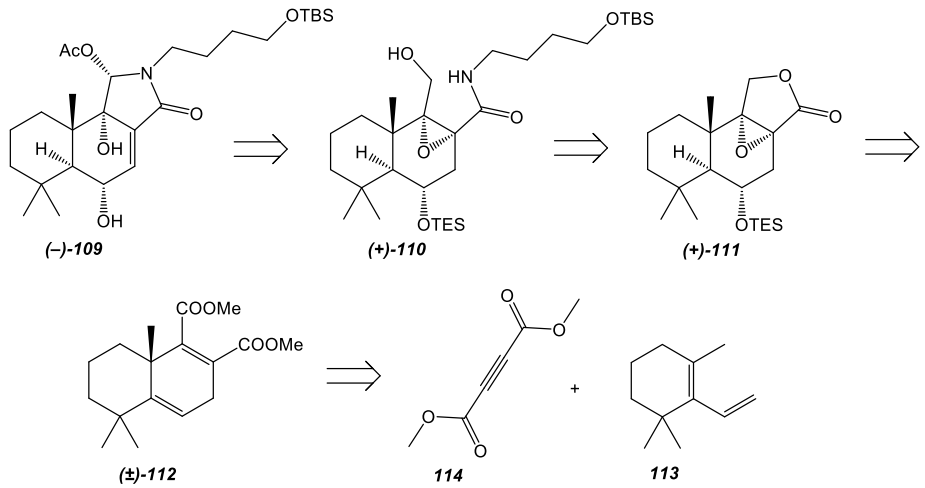


Figure 3.1. *Retrosynthetic approach to synthesize* ***1.***

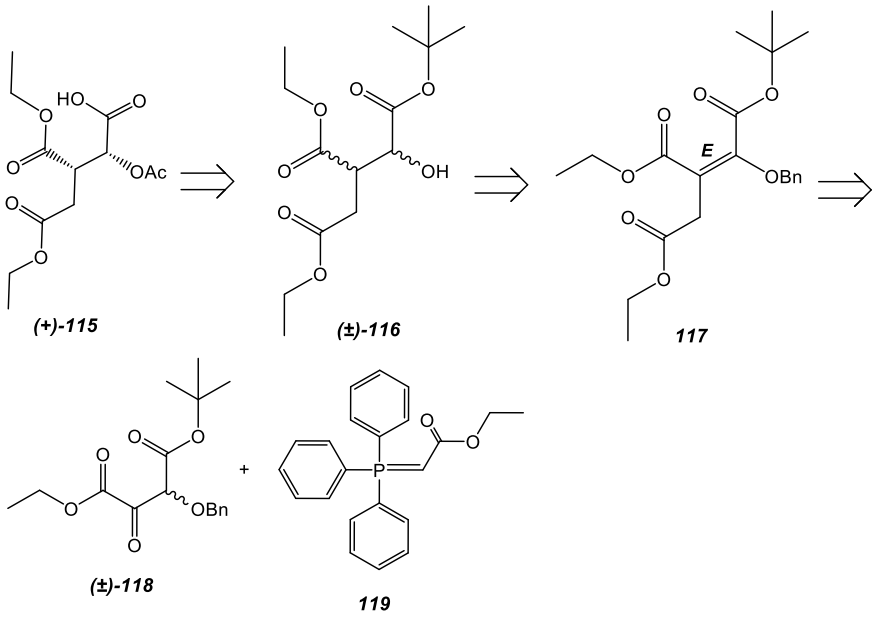
The key steps of this protocol include *Yamaguchi esterification* to couple the tricycle with the linker and *Williamson etherification* to incorporate the bicycle, the albicanyl fragment (***Figure 3.1***). Each fragment of the molecule has key steps: for the tricycle (***Scheme 3.1***), the pivotal stage is the *Diels-Alder* cycloaddition reaction between the diene ***113*** and the dienophile ***114*** to quickly construct the core of the molecule.



Scheme 3.1. *Retrosynthesis of tricycle.*

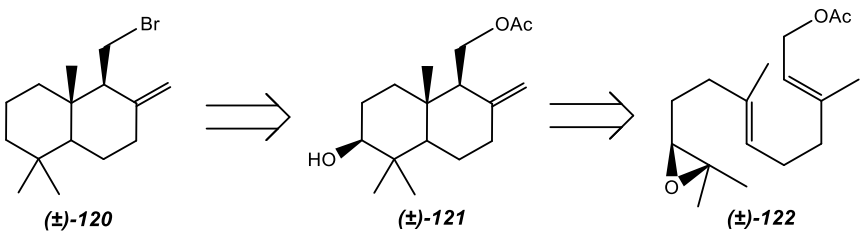
The second key step for the construction of the tricycle, essential for the subsequent coupling step, is represented by intramolecular cyclization in compound ***(+)-110*** (see ***Scheme 3.1)***, which poses a challenge for the construction of the substituted lactam ring.

Regarding the tricarboxy-linker, the synthesis involves an initial Claisen condensation. The key step is certainly the Wittig reaction (***Scheme 3.2***), to generate ***E-117.*** The subsequent asymmetric H_2 *syn*-addition reaction on ***E-117*** will yield ***(±)-116***. Several attempts were made at this stage to resolve the racemic mixture, which will be discussed later. Protection and a TFA- promoted cleavage of the *tert*-butyl ester provides ***(+)-115***, necessary for the Yamaguchi esterification with the tricycle ***(–)-109***.



Scheme 3.2. *Retrosynthesis of tricarboxy-linker.*

In the synthesis of the albicanyl fragment, the key step is the cascade cyclization, namely the *Cp_2TiCl-catalyzed radical cyclization* of the racemic ***(±)-122*** to obtain the decalin ***(±)-121***, which is further functionalized and represents the crucial intermediate for the *Williamson reaction*, after obtaining his halogenated derivative ***(±)-120*** through *Appel reaction*.



Scheme 3.3. *Retrosynthesis of bicycle.*

Initially, the asymmetric Sharpless dihydroxylation of *all-trans*-farnesyl acetate using AD-mix was evaluated, as it could have provided high enantioselectivity. In parallel, a stereoselective approach following the Corey-Zhang procedure was considered, based on an enantioselective dihydroxylation of the substrate with the aid of a chiral catalyst[48]. These strategies would have led to the formation of a chiral diol, which would in turn be converted into a mesylate (through a reaction with mesyl chloride in the presence of pyridine). The resulting mesylate would then undergo an intramolecular cyclization with the help of a base or an appropriate nucleophile, leading to the formation of the epoxide. However, both approaches encountered difficulties related to the availability of some starting materials and operational complexity, making it impractical to proceed in this way.

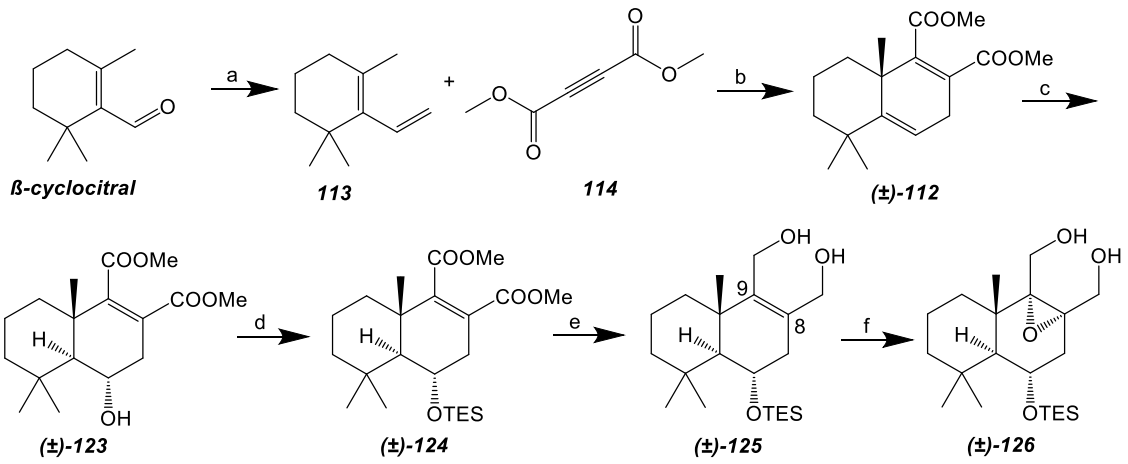
As a result, the use of the racemic compound ***(±)-122*** was chosen, as it simplified the synthetic pathway without compromising the efficiency of the radical cyclization or the subsequent functionalization, including the formation of the halogenated derivative necessary for the Williamson reaction.

3.1. Synthesis of tricycle

It is well known that the various activities exhibited by sesquiterpenoid drimanes have greatly stimulated the development of general synthetic routes; this is because in many cases only minute amounts of material are available from natural sources. Different synthetic routes have been accomplished by total synthesis, whereby the decalin skeleton has been formed by Diels-Alder (DA) cycloaddition. The use of DA to construct an appropriately functionalized decalin in a concise manner is especially attractive.

The diene, vinyl-2,6,6-trimethylcyclohex-1-ene ***113***, was first synthesized via a Wittig reaction starting from β-cyclocitral (***Scheme 3.1.1.***). Subsequently, the traditional Diels-Alder reaction, typically conducted at 110°C, has proven to be a reliable method for synthesizing cyclohexene derivatives. In this work, using this classical approach, the known procedure between the diene ***113*** and the dienophile DMAD ***114***, as first used by Brieger [49], afforded a racemic mixture with the highest yield of ***(±)-112*** at 110°C over 48 hours, resulting in good yield and limited by-product formation.

This racemic adduct was used as a substrate until a successful strategy for obtaining the tricycle was found. Therefore, the following approaches 1, 2, 3, and 4 were carried out with the racemic adduct, while the successful strategy, the fifth approach, required additional efforts.



Scheme 3.1.1. *Synthesys of diol* ***(±)-126****. Reagents and conditions: (a) $MePPh_3Br$, n-BuLi, THF, -78 °C to 0°C, 90%; (b) 110°C, 80%; (c) BH_3 ·THF, THF, 0°C, then 2N NaOH, H_2O_2, 0°C, 60%; (d) TESCl, imidazole, DMF, 0°C, 99%; (e) DIBAL-H, THF, 0°C, 68%; (f) m-CPBA, CH_2Cl_2, 0°C, 99%.*

Below, each approach will be examined in detail. Starting from compound ***(±)-123*** (***Scheme 3.1.1.***), the secondary alcohol moiety, introduced via hydroboration-oxidation of ***(±)-112***, was silylated to afford ***(±)-124*** in quantitative yield (d). From this compound, the reduction/epoxidation sequence also utilized in Watanabe's synthesis of FF8181-A[50] was envisioned. Treatment of ***(±)-124*** first with DIBAL-H (e) and subsequently with m-CPBA (f) to oxidize the Δ8-Δ9 double bond resulted in epoxide ***(±)-126*** as a single diastereoisomer. The compound ***(±)-126*** represents the common denominator of the following four synthetic strategies.

3.1.1. First approach

In the first approach, the objective was to construct the third five-membered ring (in turquoise) atop the existing bicyclic system (in green). To facilitate the formation of the cyclic amide, the bicyclic scaffold was strategically functionalized to allow for intramolecular cyclization. This was achieved by sequentially introducing a primary alcohol, later oxidized to aldehyde (in magenta), and a substituted amide (in violet), at the adjacent C-9 and C-8 positions. The following section outlines the process by which these functional groups, critical for ring closure, were incorporated.

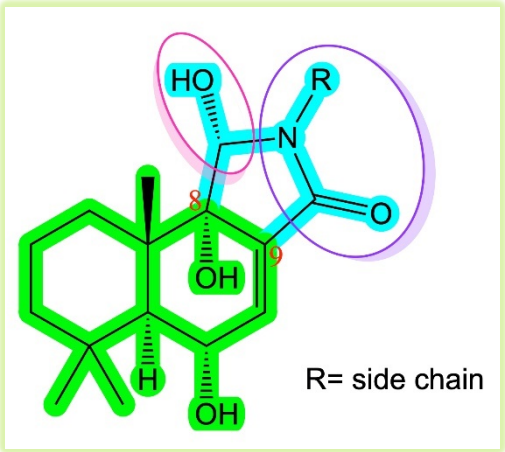
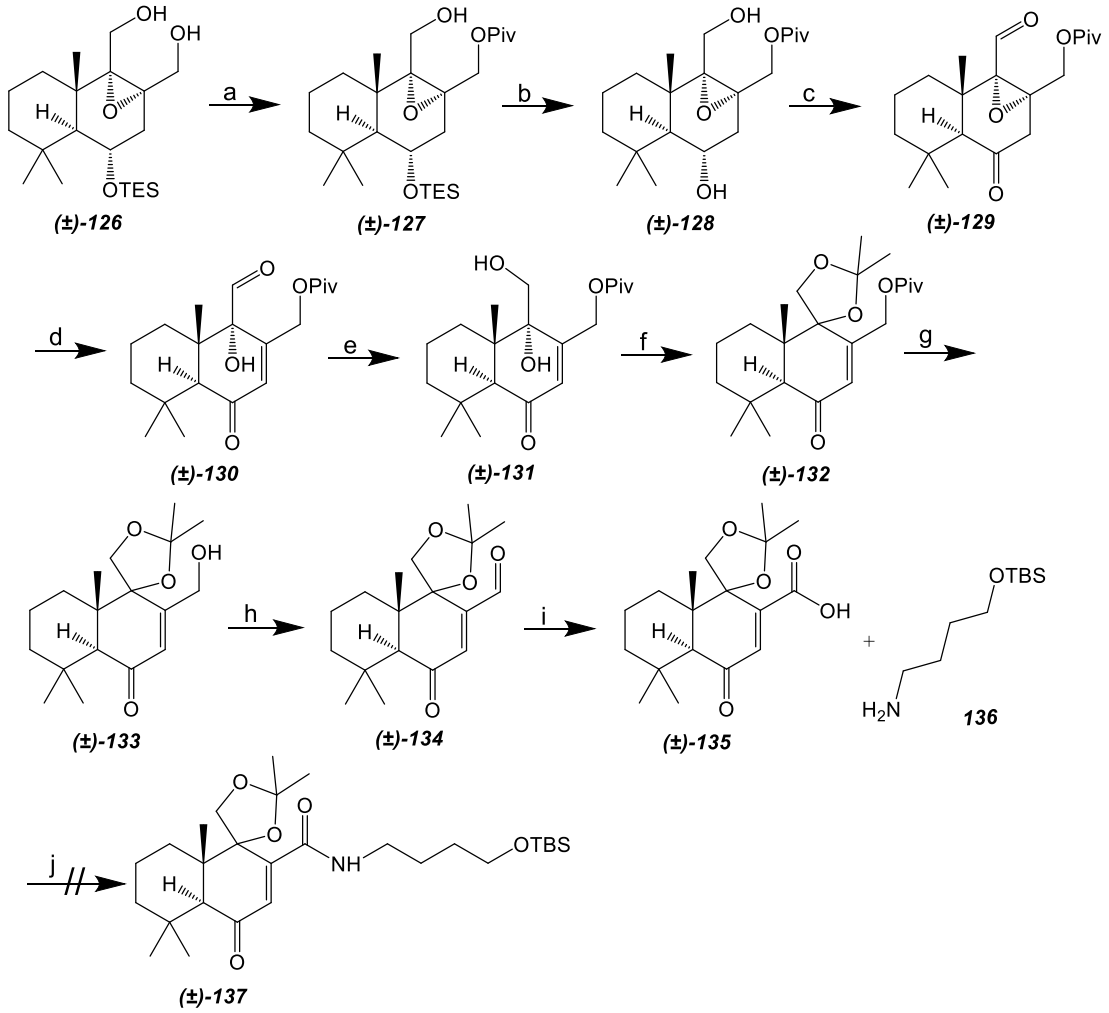


Figure 3.1.1.1*. Aim of the first approach*

After oxidation of the double bond with m-CPBA that provided ***(±)-126***, the less hindered alcohol on C-8 was protected as a pivalate ***(±)-127***. The cleavage of TES-group was followed by Dess-Martin oxidation which gave a mixture of ketoaldehyde ***(±)-129*** and a small amount of ***(±)-130***; to complete the β-elimination, ***(±)-129*** was treated with DBU, giving compound ***(±)-130***. The selective reduction of the aldehyde gave ***(±)-131***, a primary alcohol, which together with the tertiary alcohol on the same C-9 was simultaneously protected as acetonide ***(±)-132***. This way, it was possible to freely operate at the adjacent position C-8: the cleavage of the pivalate in ***(±)-132*** provided a primary alcohol which was double-oxidized to acid ***(±)-135***. The activation of carboxylic function formed a reactive intermediate that readily reacted with 4-((*tert*-butyldimethylsilyl) oxy) butan-1-amine ***136***, promoting the formation of amide bond under mild conditions. The reaction was monitored both by TLC and by LC-MS, but when transferred to chromatographic column to be purified the product degraded.



Scheme 3.1.1.1. *Synthesis of* ***(±)-135.*** *Reagents and conditions: (a) PivCl, DMAP, Py, 0°C-r.t., 60%; (b) PPTS, EtOH, r.t., 85%; (c) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t., 85 %; (d) DBU, tol., 0°C, 92% two steps; (e) $NaBH_4$, MeOH, 0°C-r.t.; (f) 2,2-DMP, CSA, CH_2Cl_2, 0°C-r.t., 80% two steps; (g) $LiOH{\cdot}H_2O$, MeOH, 0°C; (h) MnO_2, CH_3CN, 0°C, 99% two steps; (i) Jones reagent, acetone, 0°C-r.t., 99%; (j)* ***136****, HATU, DIPEA, DMF, 0°C-r.t.*

The degradation problem of the final compound during purification on a silica column can be directly correlated with the introduction of the substituted amide, since until step (i) the product did not exhibit significant stability issues. One hypothesis is the increased reactivity of the α,β-unsaturated ketone upon introducing the substituted amide. The introduction of an electron-withdrawing group like the amide could further destabilize the molecule, increasing the reactivity of the ketone.

A second hypothesis considers the proximity of the substituted amide and the acetonide cycle, which could create zones of high reactivity due to the combination of electronic and steric

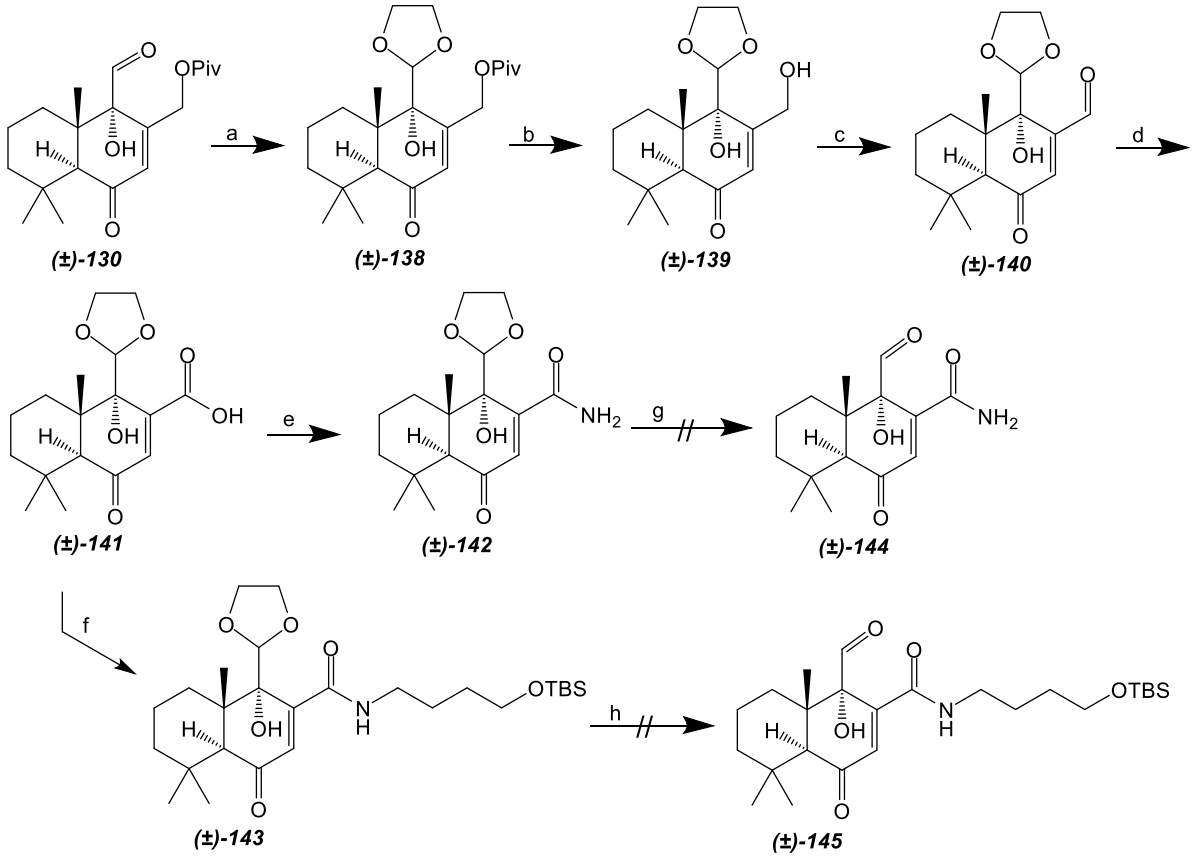
tensions caused by the proximity of bulky groups. Amides are typically characterized by their resonance stability, where the lone pair of electrons on the nitrogen is delocalized into the carbonyl group, increasing the polarity of the carbonyl carbon. When an amide is close to an acetonide, this can influence the electron density around the acetonide.

The electron-withdrawing effect of the amide carbonyl can make the acetonide more susceptible to nucleophilic attack, as it could slightly withdraw electron density from nearby oxygen atoms in the acetonide cycle, increasing their electrophilic character. Additionally, the limited conformational flexibility can destabilize the molecule, making it more prone to decomposition under chemical-physical stress.

Despite the efforts, the instability of the final product in this case led to the failure of the strategy, prompting the exploration of alternative approaches.

3.1.2. Second approach

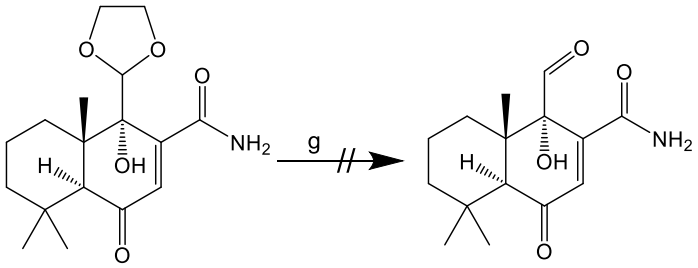
Since the previous strategy seemed promising, but it was unclear which factor contributed to the molecule's instability, leading to its degradation during column purification, a slight structural modification was deemed necessary. Therefore, to achieve the formation of the third five-membered ring, positions 8 and 9 were targeted once again, but with a different functionalization strategy on C-9 compared to the previous approach.



Scheme 3.1.2.1. *Synthesis of substituted amide* ***(±)-143.*** *Reagents and conditions: (a) PTSA, DEG, tol., 110°C, 70%; (b) $LiOH \cdot H_2O$, MeOH, 0°C; (c) MnO_2, CH_3CN, 0°C, 99% two steps; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/t-BuOH, 0°C, 99%; (e) EtOCOCl, NEt_3, NH_4OH, THF, 0°C, 99%; (f)* ***136****, HATU, DIPEA, DMF, 0°C-r.t., 80%; (g), (h) see* ***Table 3.1.2.1.***

Starting with compound ***(±)-130***, the aldehyde was protected as an ethylene glycol (EG) acetal and, after that, compound ***(±)-138*** then underwent a cleavage reaction of the pivaloyl group and subsequent double oxidation to acid ***(±)-141***. The latter lent itself well to either giving a simple amide ***(±)-142*** or a substituted amide ***(±)-143.*** It is noteworthy that, this last compound

did not degrade when purified, in contrast to its equivalent ***(±)-137***. Starting from ***(±)-142*** and ***(±)-143***, the next step involved deprotection of the aldehyde at C-9, so that the acidic environment necessary for cleavage of the protecting group could promote intramolecular cyclization. Several attempts were made to deprotect the aldehyde in the primary amide-containing compound ***(±)-141*** using different acids (see ***Table 3.1.2.1***), without achieving the expected result. In particular, none of the protocols succeeded in cleaving the EG acetal, leaving the aldehyde unavailable and unexposed for the subsequent cyclization.



(±)-142 ***(±)-144***

Reagent	*Solvent*	*T/time*	*Result*
1M HCl	THF	reflux, 8h	x
HCl *conc.*	THF	reflux, 8h	x
HCl (1M, 3M, 6M)	*acetone*	reflux, 8h	x
HCl *conc.*	*acetone*	reflux, 8h	x
1M HCl	*ethanol*	reflux, 8h	x
Pyr·TsOH	acetone/H_2O	reflux, 8h	x
Amberlyst-15	acetone/H_2O	r.t., 3h	x
CSA	acetone	r.t., 3h	x

Table 3.1.2.1. *Attempted cleavage of EG-acetal in* **(±)-*142.***

The same conditions were applied to compound ***(±)-138*** as model system and in this instance, they proved to be effective. What was obtained was the expected aldehyde ***(±)-130***, thereby indicating that the issue is not with the procedures, but it lies in the structure.

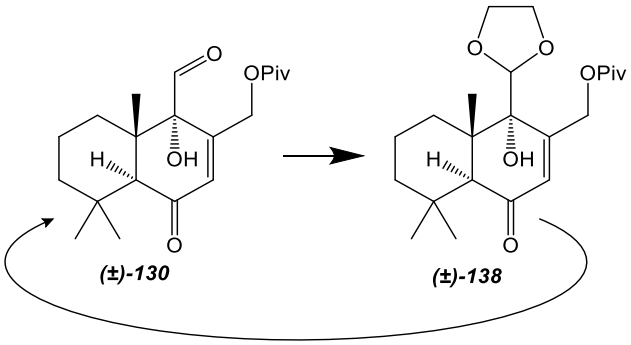


Figure 3.1.2.1. *Model compound* ***(±)-138*** *yielded the expected aldehyde* ***(±)-130*** *under the same conditions reported in* ***Table 3.1.2.1.***

All those attempts to achieve the deprotection of the aldehyde on C-9 were made with ***(±)-143*** and they did not yield the desired product ***(±)-145*** on this other substrate either.

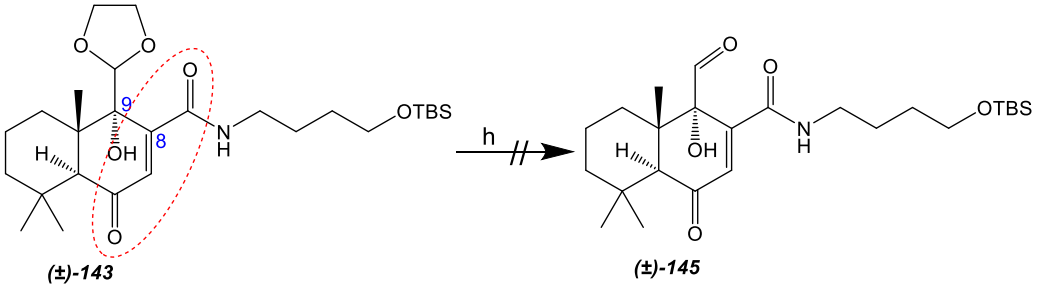


Figure 3.1.2.2. *Attempted deprotection of* ***(±)-144*** *according to the procedures in* ***Table 3.1.2.1.***

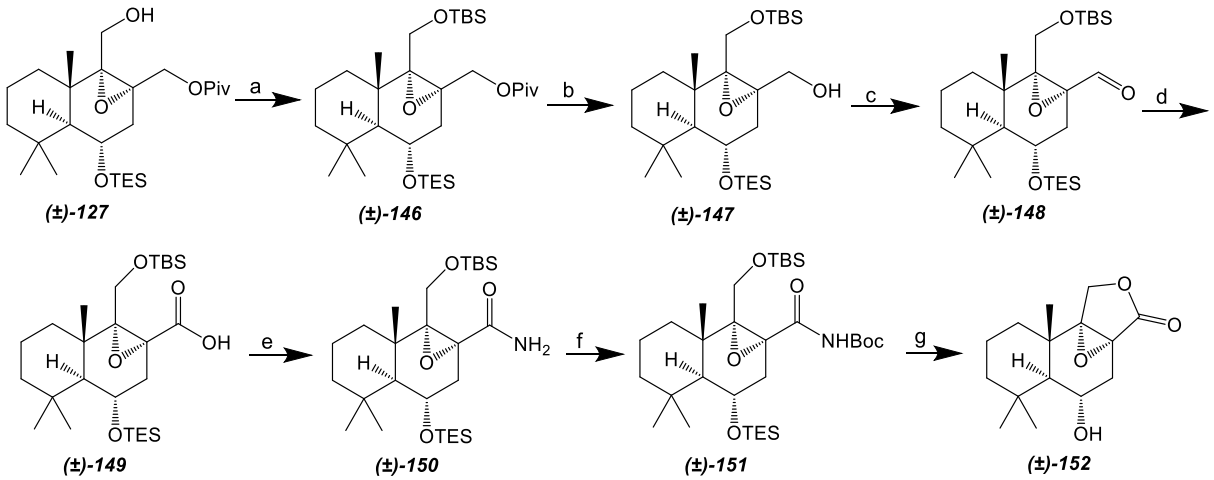
A plausible hypothesis might be that the α,β-unsaturated system could compromise operations on C-9, making it difficult to access.

The ethylene glycol acetal cannot be deprotected in the presence of the amide. The free amide may in fact reduce the effective acidity available for the protonation of the cycle and the liberation of the aldehyde, as the amide can compete for protonation, reducing the effectiveness of the acid used for the cleavage. Additionally, the substituted amide **(±)-*143*** in position 8, due to the inductive effect, might withdraw electron density from adjacent groups, making the nearby functional groups more electrophilic. This makes the acetal less reactive towards protonation, which is a necessary step for the cleavage of the acetal. Another observation considers that the effectiveness of acids in protonating the cycle could be reduced by electronic delocalization; the substituted amide conjugated with the α,β-unsaturated ketone stabilizes the structure, making deprotection in position 9 very difficult.

Unfortunately, this approach did not yield the desired outcome, prompting to explore alternative strategies.

3.1.3. Third approach

In an effort to further refine the synthetic pathway, a more strategic approach was adopted, emphasizing modifications to the protective groups and reaction sequence to optimize the deprotection and subsequent ring closure steps. The acid-sensitive group at C-9 was replaced, while the configuration at this position was preserved. The reaction sequence then proceeded prior to the epoxide opening and the installation of the α,β-unsaturated system. With this approach, the process began further upstream, starting from compound ***(±)-127.***



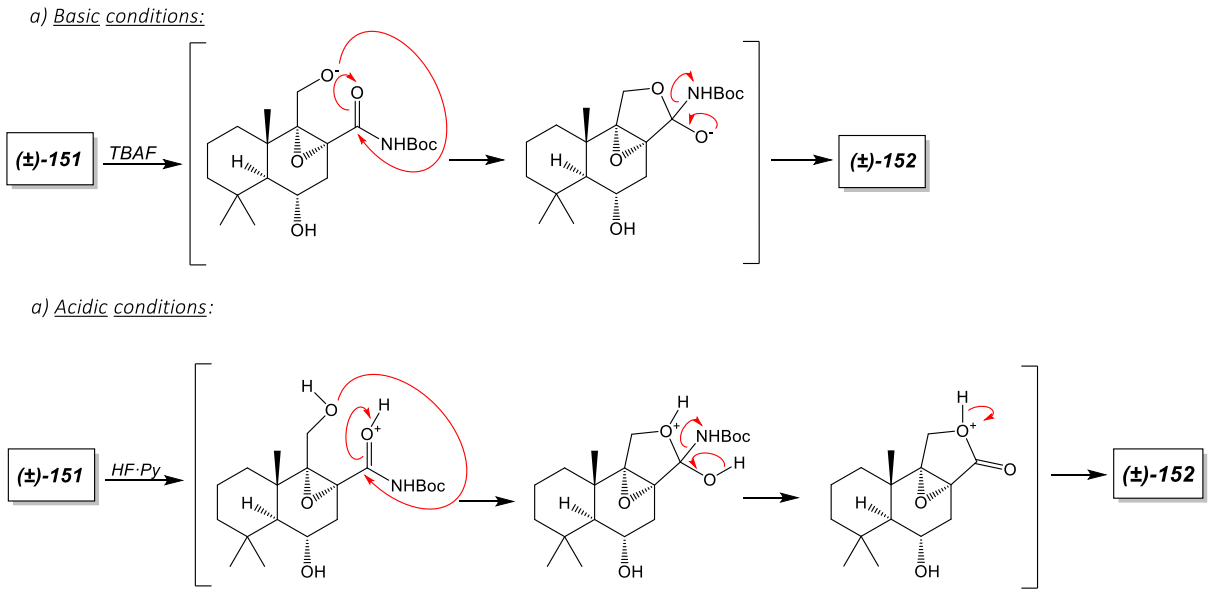
Scheme 3.1.3.1. *Synthesis of lactone* ***(±)-152****. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 90%; (b) DIBAL-H, THF, 0°C, 70%; (c) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t., 96%; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/t-BuOH, 0°C, 99%; (e) EtOCOCl, NEt_3, NH_4OH, THF, 0°C, 99%; (f) Boc_2O, DMAP, CH_2Cl_2, 0°C-r.t., 80%; (g) method A: TBAF, THF, 0°C, 40%; method B: HF·Py, THF/Py, 0°C-rt, 35%.*

The primary alcohol at C-9 was protected with a TBS-group and the subsequent deprotection of the pivaloyl group on C-8 yielded compound ***(±)-147***. The following Dess-Martin oxidation and Pinnick-Lindgren oxidation resulted in ***(±)-149***. The product of amidation ***(±)-150*** was initially protected with Fmoc, but this was replaced with a Boc protecting group resulting in a more robust and stable amide ***(±)-151***, ensuring the final compound's stability. This strategy was intended to reduce the possibility of the amide interfering with the deprotection of position 9 (or 9 and 6 in one step). After the cleavage of the two silyl groups in ***(±)-151***, the plan was to perform a double oxidation, which would have resulted in the formation of a ketone on C-6 and of an aldehyde on C-9, which, in combination with the deprotected amide, would have facilitated lactam ring closure under acidic conditions. Different deprotecting agents were tried for the efficient cleavage of TES and TBS groups, ranging from moderately basic conditions (e.g., TBAF) to progressively acidic environments.

This included both mildly acidic reagents, such as HF·Py, and PPTS, as well as strongly acidic conditions, such as those provided by CSA.

Procedures using PPTS and CSA removed only the TES group (see experimental part, compound ***(±)-152b***), while the other procedures utilizing TBAF and HF·Py led to lactonization and displacement of the Boc group, culminating in the formation of a lactone ***(±)-152*** (***Scheme 3.1.3.2***.).

The formation of the γ-butyrolactone in basic and acidic conditions can be explained by the following mechanisms; here it is clear that γ-butyrolactone ***(±)-152*** was produced via Boc protection of ***(±)-150*** followed by desilylation and resulting in direct lactonization and displacement of the Boc protection.

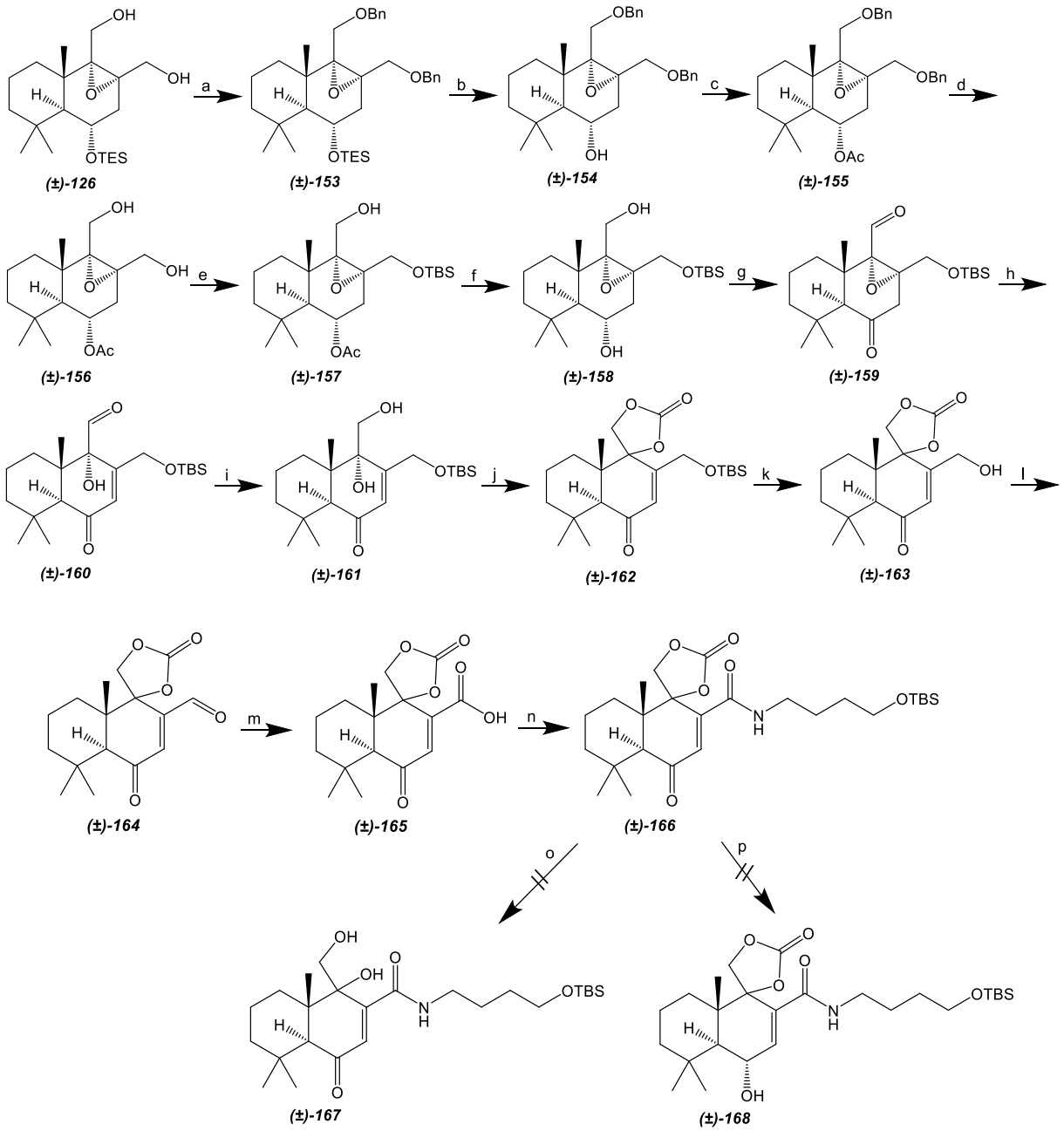


Scheme 3.1.3.2. *Mechanisms of γ-butyrolactone* ***(±)-152*** *formation.*

Those methods proved ineffective, as the cyclization obtained was not the expected one. Instead of forming the desired product, the reaction led to the formation of an alternative cyclic structure, likely due to the reactivity of the functional groups in close proximity. As a result, the intended outcome could not be achieved, necessitating a shift to a different approach that would better control the reaction pathway and promote the desired cyclization.

3.1.4. Fourth approach

Clearly, at this point, the issues were two-fold. The presence of either a primary or secondary amide compromising deprotection at position 9 and/or the presence of an acid-sensitive group at C-8. In Approach 4, the strategy was to invert the trend. A base-sensitive group was introduced at C-9 and an acid-sensitive group at C-8. Specifically, a TBS group at C-8 and a carbonate at C-9 (see compound ***(±)-162***).

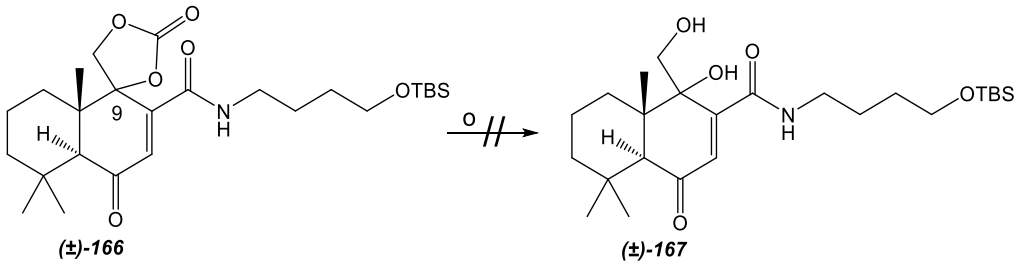


Scheme 3.1.4.1. *Synthesis of substituted amide* ***(±)-166.*** *Reagents and conditions: (a) BnBr, NaH, DMF, 0°C-r.t., 99%; (b) PPTS, EtOH, r.t., 95%; (c) Ac_2O, DMAP, Py, CH_2Cl_2, r.t., 99%; (d) 10% Pd/C, MeOH, H_2, r.t., 99%; (e) TBSCl, imidazole, DMF, 0°C, 80%; (f) DIBAL-H, THF, 0°C, 80%; (g) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t., 80%; (h) DBU,*

tol., 0°C, 90% two steps; (i) $NaBH_4$, MeOH, 0°C-r.t.; (j) CDI, toluene, reflux, 70% two steps; (k) CSA, CH_2Cl_2/MeOH, 0°C-r.t.; (l) MnO_2, CH_3CN, 0°C, 99% two steps; (m) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/t-BuOH, 0°C; (n) ***136****, HATU, DIPEA, DMF, 0°C-r.t., 60% two steps; (o) see* ***Table 3.1.4.1.****; (p) see* ***Table 3.1.4.2****.*

Therefore, primary alcohol groups in ***(±)-126*** were benzylated to afford ***(±)-153*** in quantitative yield. Secondary alcohol moiety in ***(±)-154*** was subsequently acetylated to give ***(±)-155*** and then ***(±)-156*** in quantitative yield upon hydrogenation. The less hindered alcohol of ***(±)-155*** was protected as TBS-ether and the acetyl group on C-6 was next removed by DIBAL-H to give diol ***(±)-158***. After setting the acid-sensitive protecting group on C-8, subsequent oxidation and β-elimination provided ***(±)-160***. Reduction with $NaBH_4$ without compromising the stability of the α,β-unsaturated ketone provided ***(±)-161*** with two alcohols on C-9 which were simultaneously protected as a base-sensitive carbonate ***(±)-162***. This allowed the rapid conversion of position 8 into a substituted amide ***(±)-166***.

At this point, after the cleavage of the carbonate in ***(±)-166*** in a basic environment and the oxidation of the free primary alcohol to an aldehyde, the plan was to accomplish lactam ring closure under acidic conditions. Unfortunately, at this crucial stage, the system formed in ***(±)-166*** was so stable that the various attempts did not lead to the expected product (see attempts in ***Table 3.1.4.1.***).



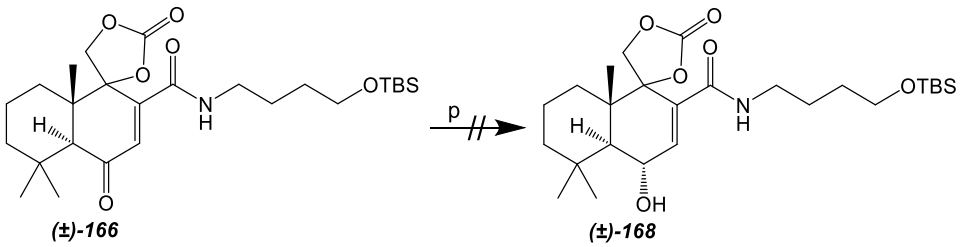
(±)-166 ***(±)-167***

Reagent	*Solvent*	*T/time*	*Result*
K_2CO_3	MeOH	0°C-r.t.	X
KOH	THF/H_2O	0°C-r.t.	X
KOH	MeOH	0°C-r.t.	X
NaOH	EtOH	0°C-r.t.	X
NaOH	MeOH/H_2O	0°C-r.t.	X

Table 3.1.4.1. *Attempted cleavage of carbonate in* ***(±)-166.***

The unsaturated alpha-beta system might have compromised operations on C-9, making access difficult. For this reason, the reduction of the α,β-unsaturated ketone in ***(±)-166*** was

considered. Multiple reduction strategies were explored, including sodium borohydride, Meerwein–Ponndorf–Verley, and Luche reductions (as detailed in ***Table 3.1.4.2***), but none successfully yielded the target compound ***(±)-168***. In each experiment, compound ***(±)-166*** exhibited signs of decomposition, which adversely affected the efficiency and outcome of the reactions.



(±)-166 ***(±)-168***

Reagent	***Solvent***	***T/time***	***Result***
$NaBH_4$	THF/MeOH	0°C-r.t.	X
STAB	CH_2Cl_2/MeOH	0°C-r.t.	X
$NaBH_4$, $CeCl_3 \cdot 7H_2O$	THF/MeOH	0°C-r.t.	X
AIP	*i*-PrOH	0°C-r.t.	X

Table 3.1.4.2*. Attempted reduction of α,β-unsaturated ketone to get* ***(±)-168.***

$NH(CH_2)_4OTBS$ group suggests several steric and electronic interactions that could influence the reactivity of the functional groups. The presence of the mobile side chain ending with a bulky group such as TBS could easily find itself near the cyclic carbonate, creating a steric barrier that prevents deprotective reagents from accessing the carbonate, slowing or preventing the deprotection reaction. This may be further hindered by the presence of the α,β-unsaturated ketone, which creates a region of high reactivity where the β-carbon is particularly electrophilic. This electrophilicity can stabilize the adjacent cyclic carbonate, making deprotection more difficult. Finally, the reduction of an α,β-unsaturated ketone can be problematic for several reasons:

- The reducing agents may be too strong and attack not only the ketone, but also other functional groups present in the molecule, leading to decomposition.
- The α,β-unsaturated ketones are highly reactive due to the conjugation between the carbonyl and the double bond, making them susceptible to various types of reactions, not just reduction.

Despite showing potential, this approach did not yield the desired outcomes, prompting us to explore an alternative strategy.

3.1.5. Fifth approach

The failure of the first four strategies is attributed to their design, which sought to introduce one functional group at a time at C-8 and C-9. In contrast, the fifth approach allowed for the simultaneous formation of the functional groups involved in the intramolecular cyclization in a single step, resulting in a more efficient and streamlined process. The strategy is presented in detail below.

As anticipated, since the classical [4+2] cycloaddition[49] was lacking enantioselectivity, two potential strategies were explored to guide synthesis with the correct stereochemistry. The first strategy, although very promising, unfortunately did not yield the expected results. What was expected is described below.

The procedure of [4+2] cycloaddition reaction using cationic cobalt catalyst suggested by *Singh* and *RajanBabu*[51] proposes a unique mechanism (arranged using diene ***113*** and dienophile ***114***, see ***Figure 3.1.5.1.***) to facilitate the formation of new bonds with high regio- and enantioselectivity. They suggested the initial formation of an intermediate complex after activation of the diene by the Co(I) catalyst (a); the dienophile attacks the coordinated diene (b), forming a six-membered cyclic transition complex. During this step, the π orbitals of the diene and dienophile interact to form new σ bonds. The cobalt may undergo oxidative cyclization (c), transitioning from Co(I) to Co(III), facilitating the formation of the transition complex, that resolves to form the cyclohexene product. The cobalt returns to its original oxidation state Co(I) through reduction (d), completing the catalytic cycle and preparing for a new reaction cycle. It is important to emphasize that the position at which the diene and dienophile interact is controlled by the nature of the catalyst and the associated ligand. The use of chiral ligand, here the [(*R,R*) BenzP*] on the Co(I) catalyst, can induce asymmetry in the final product formation, allowing for the synthesis of enantiomerically enriched compound.

In summary, the [4+2] cycloaddition mechanism proposed by Singh *et al.*[51] demonstrates how cationic cobalt catalysts can activate the diene, form a stabilized transition complex, and release products with high selectivity. This process is facilitated by the cobalt's ability to cycle through oxidation and reduction states efficiently. Even though NaBARF is not explicitly visible in the reaction mechanism, it plays a crucial role. NaBARF acts as a counterion exchange agent, replacing smaller, more coordinating counterions. This replacement helps improve the solubility and reactivity of the cationic cobalt catalyst, stabilizes highly reactive cationic

species, and maintains high catalytic efficiency and selectivity by ensuring that the anion does not interfere with the catalysis. When attempting the reaction with ***113***, the activation of the cationic Co(I) was observed, indicated by a color change from dark green-brown to light brown.

However, the reaction ultimately did not succeed, suggesting that the activation step of the diene by the catalyst may have been the issue.

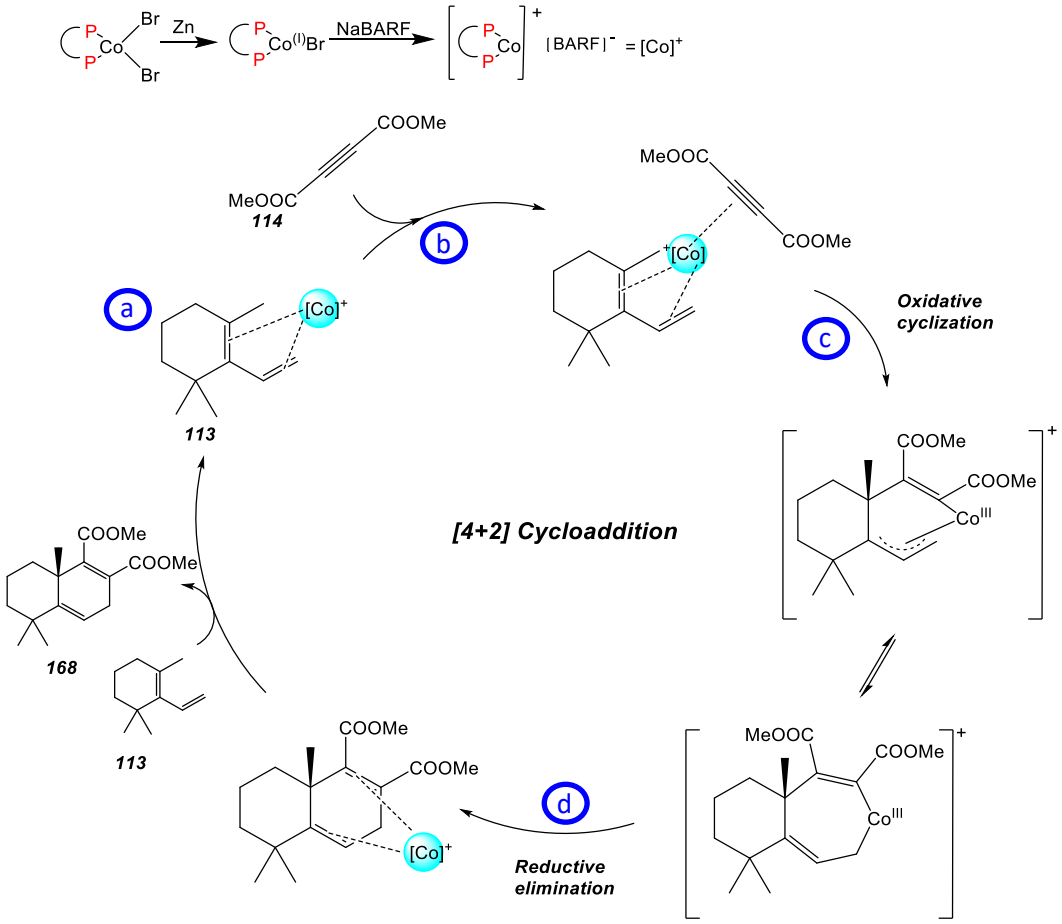
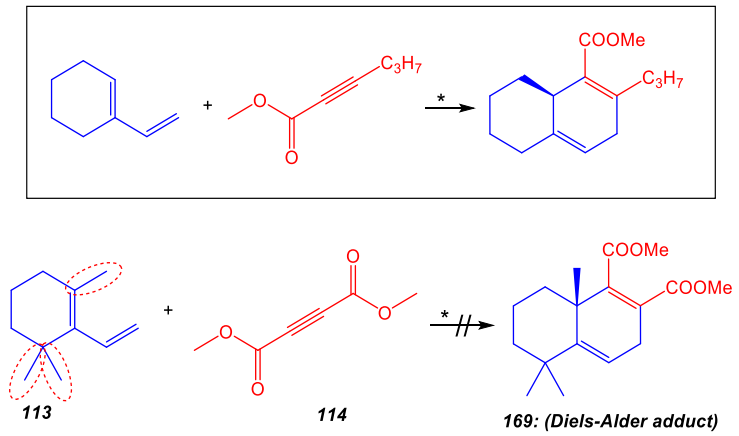


Figure 3.1.5.1. *Plausible mechanism of [4+2] cycloaddition.*

Therefore, analyzing the various examples reported in the article, it can be deduced that, in this case, the diene ***113*** was likely too bulky compared to the diene used by Singh *et al*.[51]

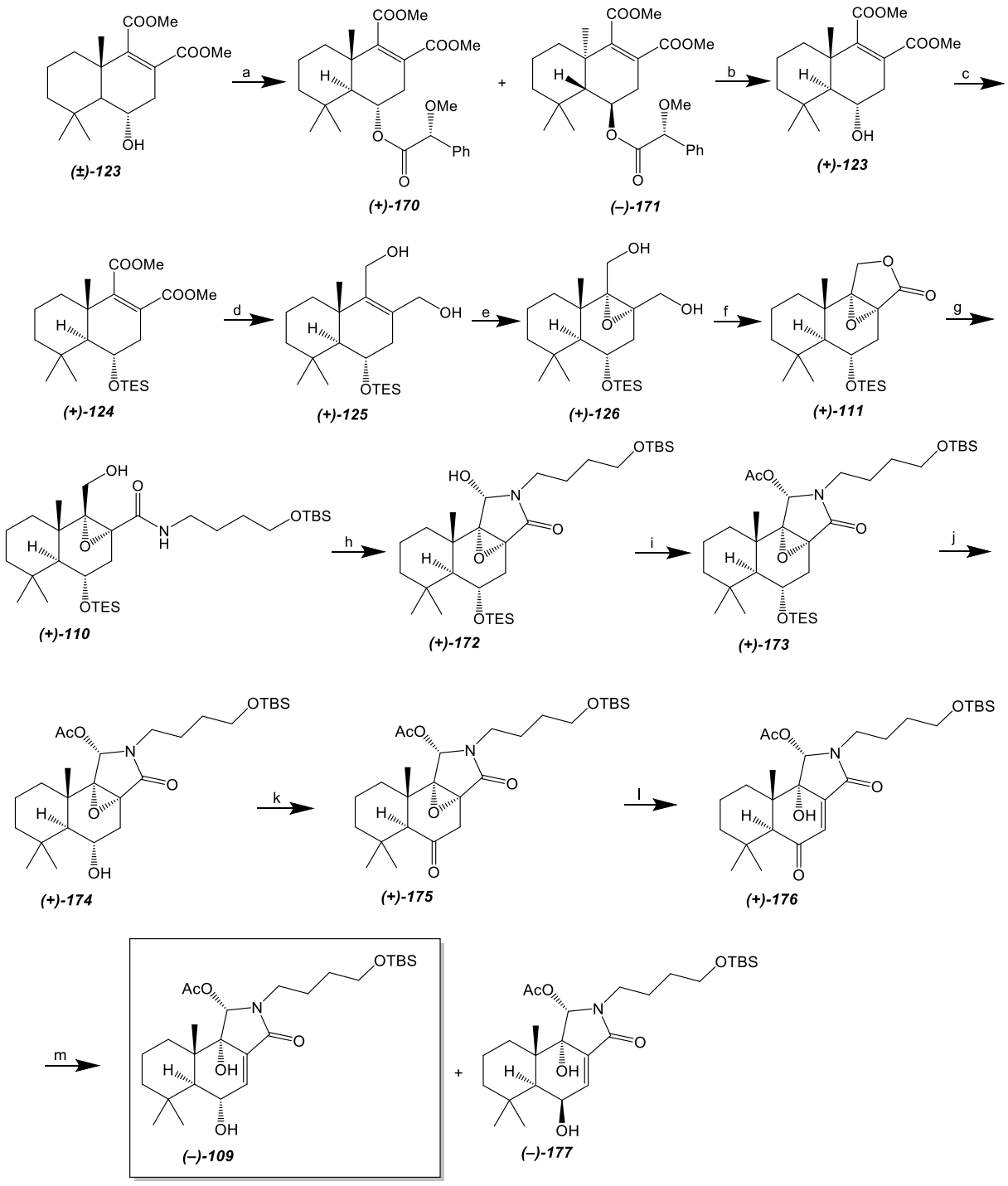


Scheme 3.1.5.1. *Comparison of dienes with bulky and non-bulky grades.*

Due to the failure of that strategy, a different one was adopted. This involved introducing an additional chiral center to separate the mixture of diastereomers and continue the synthesis with the desired isomer. Specifically, in alignment with the findings of Jang *et al*.[52], the alcohol (***Scheme 3.1.5.2.***) in position 6 of ***(±)-123*** was first obtained through a hydroboration-oxidation reaction. Subsequently, the racemic mixture was reacted with (R)-2-methoxy-2-phenylacetic acid in the presence of EDC·HCl and DMAP. This reaction yielded two diastereomers ***(+)-170*** and ***(–)-171***, which were separable by silica gel flash chromatography. Subsequent hydrolysis of the ester in ***(+)-170*** regenerated the alcohol and the synthesis was continued using only the right isomer ***(+)-123***. The compound ***(+)-123*** was subjected to silylation, ester reduction, and double bond oxidation to yield ***(+)-126***.

This successful strategy led to the synthesis of lactone ***(+)-111*** under mild reaction conditions using TEMPO and BAIB[53].

The result was a couple of isomers: ***(+)-111*** and its regioisomer ***(–)-111b*** (***Scheme 3.1.5.2.***).



Scheme 3.1.5.2. *Synthesis of tricycle* ***(–)-109****. Reagents and conditions: (a) (R)-2-methoxy-2-phenylacetic acid, EDCl, DMAP, CH_2Cl_2, r.t., 39%* ***(+)-170*** *and 29%* ***(–)-171****; (b) K_2CO_3, MeOH, r.t., 85%; (c) TESCl, imidazole, DMF, 0°C, 99%; (d) DIBAL-H, THF, 0°C, 68% ; (e) m-CPBA, CH_2Cl_2, 0°C, 99%; (f) BAIB, TEMPO, CH_2Cl_2, 0°C, 75%; (g) TBD, 4-((tert-butyldimethylsilyl)oxy)butan-1-amine, toluene, 110°C, 80%; (h) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t., 70%; (i) Ac_2O, NEt_3, CH_2Cl_2, 0°C-r.t, 99%; (j) TBAF, THF, 0°C, 99%.(k) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t., 85%; (l) DBU, toluene, 0°C, 90%, two steps; (m) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 0°C, 48%* ***(–)-109*** *and 45%* ***(–)-177****.*

The analysis of HMBC correlations (results in ***Figure 3.1.5.2.***) successfully revealed which structure corresponded to the compound of interest. The HMBC correlations from H-7 to C-12

(δ_H 2.57 ppm and δ_C 172.5ppm; δ_H 2.00 ppm and δ_C 172.5 ppm) indicated that on C-12 a carbonyl group was placed and revealed the spectrum with these interactions belongs to ***(+)-111***. Those correlations, absent in ***(–)-111b***, are replaced by the HMBC correlation from H-7 to C-12 (δ_H 2.30 ppm and δ_C 67.2 ppm; δ_H 2.10 ppm and δ_C 67.2 ppm), revealing that was the spectrum of compound ***(–)-111b.***

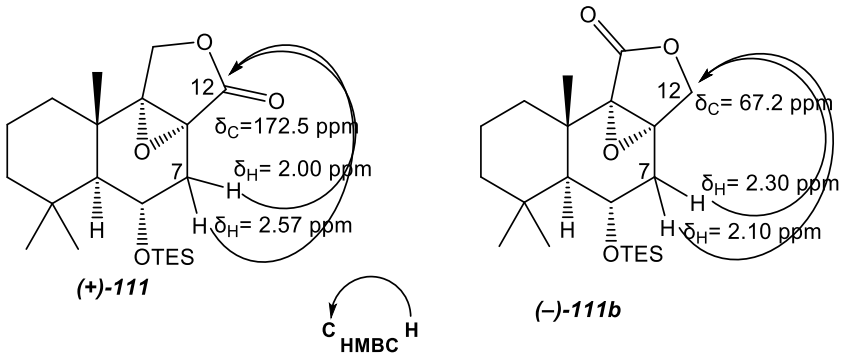


Figure 3.1.5.2. *HMBC correlations of* ***(+)-111*** *and of* ***(–)-111b****. Arrowheads denote C and arrow tails H.*

The aminolysis of ***(+)-111*** was performed using TBD[54] and the primary amine 4-((*tert*-butyldimethylsilyl) oxy) butan-1-amine ***(136)*** in order to obtain, in a single step, ***(+)-110,*** featuring a free primary alcohol and a secondary amide.

The **Figure 3.1.5.3.** below illustrates the mechanism by which the lactone opens and releases a primary alcohol and the amide. The first attempt was made using a primary amine equipped with a primary TES-group, but the cyclization with this chain generated a compound visible on TLC but unstable on the column. The second attempt was made with a primary amine equipped with a primary TBS-group instead and it successfully gave ***(+)-110***.

The mechanism of the aminolysis of the lactone could be summarized in five steps:

- Activation step: The active monomer of TBD, which is in equilibrium with its dimer, initiates the reaction by nucleophilically attacking the lactone, forming a reactive acyl-TBD intermediate.
- Nucleophilic attack: The primary amine then attacks the activated carbonyl group of the acyl-TBD intermediate, leading to the formation of a tetrahedral intermediate.
- Intermediate stabilization: This tetrahedral intermediate is stabilized through hydrogen bonding with one or two additional amine molecules, similar to the stabilization observed in the oxyanion hole of enzymes.

- Proton transfer: A proton is transferred to the nitrogen of TBD, which participates in hydrogen bonding, further stabilizing the intermediate.
- Collapse and product formation: The intermediate collapses to produce the desired amide product, regenerating the TBD catalyst. The product may form a product-catalyst adduct with TBD, causing some degree of product inhibition due to hydrogen bonding.

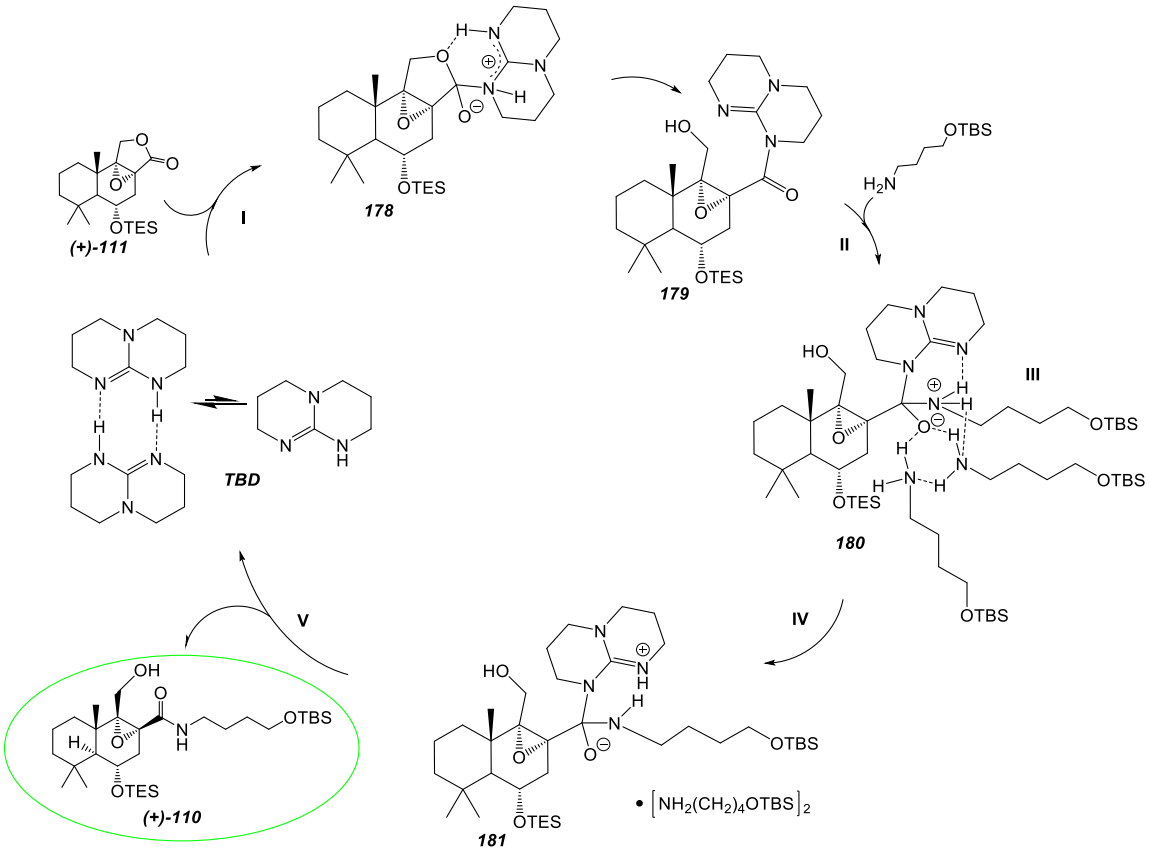


Figure 3.1.5.3. *Proposed mechanism for the TBD-catalyzed aminolysis of lactone* ***(+)-110.***

Oxidation of ***(+)-110*** prompted intramolecular cyclization, resulting in a cyclic amide with a hydroxy group and forming a 5-membered ring with the hemi-amidal group, identified as compound ***(+)-172***. Furthermore, for this molecule ***(+)-172***, NOESY 2D NMR spectrum confirmed the stereochemistry of two centers, C-6 and C-11 (see ***Figure 3.1.5.4***.).

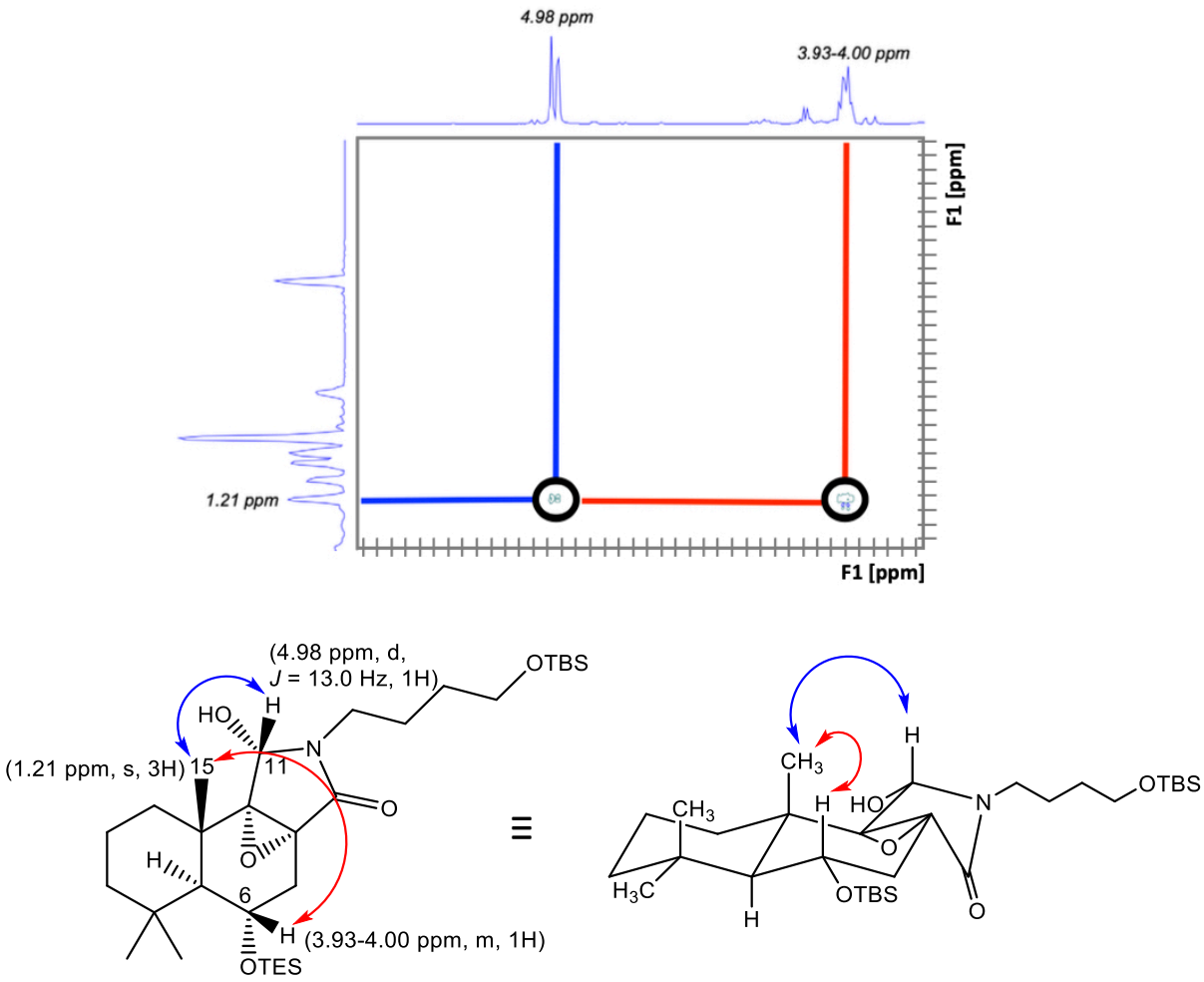


Figure 3.1.5.4. *Phase sensitive NOE correlations of* ***(+)-172.***

The phase-sensitive nuclear Overhauser exchange (NOE) correlation between H-11 and H_3-15 placed the hydroxy group in position 11 in equatorial orientation; the NOE between H_3-15 and H-6, together with the big coupling constant between H-5 and H-6 (J = 10.8 Hz) indicated that the silyl ether in C-6 is also in equatorial orientation.

What happens with the successful procedure? The first key step is the aminolysis of the lactone; then using DMP, the primary alcohol is oxidized to an aldehyde, whose proximity to the substituted amide creates an opportunity for intramolecular cyclization *(**Figure 3.1.5.5.**)*.

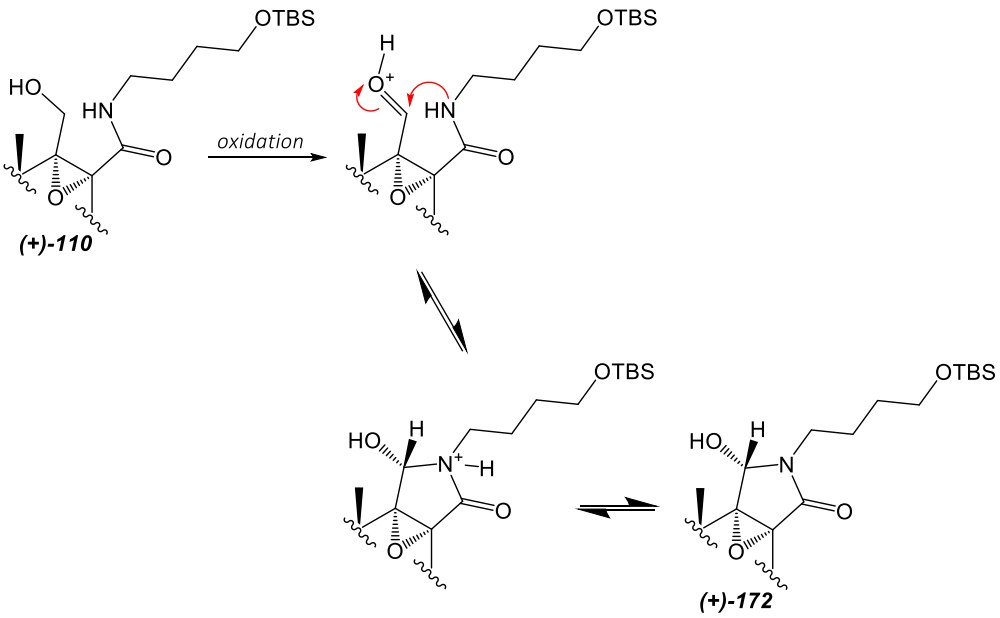


***Figure 3.1.5.5**. Proposed mechanism for intramolecular cyclization.*

As a byproduct of the oxidation reaction using DMP, acetic acid is formed, which could play two roles in the subsequent spontaneous cyclization:

- The acidic environment created by acetic acid stabilizes the reactive intermediates, facilitating cyclization.
- Even though protonation is mild, it can facilitate the cyclization reactions without the risk of excessive decomposition or undesirable side products.
- Cyclization involves a nucleophilic attack by the amide on the carbonyl of the aldehyde.

The secondary alcohol generated from cyclization was quickly protected with an acetyl group ***(+)-177*** (***Scheme 3.1.5.2***.). In compound ***(+)-173***, the hydrogen on C-11 resonates as a singlet as expected; in ***(+)-172*** instead the H-11 resonates as a doublet, due to spin-spin coupling with the hydrogen of the hydroxyl (OH) group attached to the same carbon (see ***Figure 3.1.5.6.)***. To confirm that, when the NMR analysis of ***(+)-172*** is performed in deuterated water, the hydrogen of the OH group can rapidly exchange with the protons of the aqueous solvent. This rapid exchange leads to the averaging out of the spin-spin coupling, causing the hydrogen that would otherwise resonate as a doublet to appear as a singlet.

Consequently, the hydrogen that typically resonates as a doublet in non-protic solvents like deuterated chloroform ($CDCl_3$) will resonate as a singlet in water and in addition when the

analysis is performed in deuterated water, the peak of the OH group on C-11 is no longer visible.

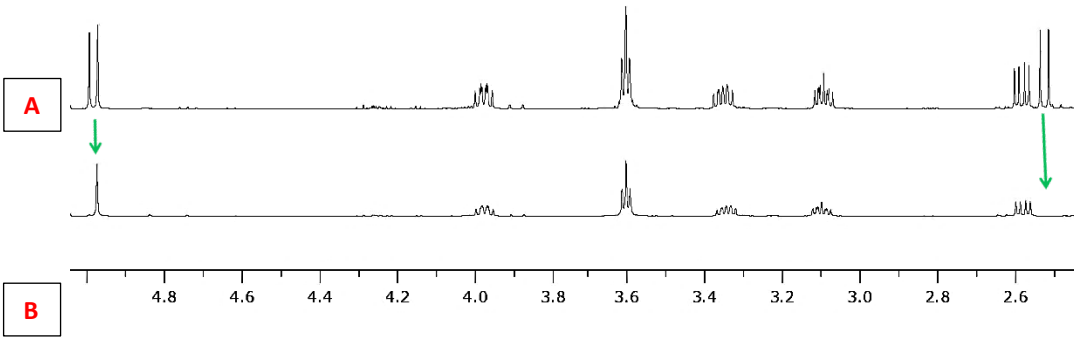
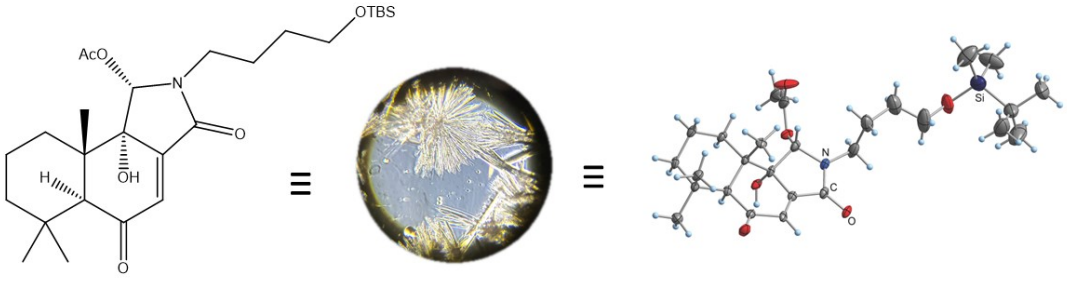


Figure 3.1.5.6. *NMR spectra of* ***(+)-172***: ***A***, ***^{1}H-NMR*** *in $CDCl_3$;* ***B***, ***^{1}H-NMR*** *in D_2O. In $CDCl_3$, H-11 appears as a doublet at 4.98 ppm (d, J = 13.0 Hz, 1H), while in D_2O, it appears as a singlet at 4.98 ppm (s, 1H). In D_2O, the peak of the OH group on C-11, which appears as a doublet at 2.55 ppm (d, J = 12.9 Hz, 1H) in $CDCl_3$, is no longer visible.*

The compound ***(+)-173*** was subjected to various reaction conditions:

- Double cleavage of the silyl groups (on C-6 and on the side chain) using the Olah's reagent, but the subsequent double oxidation to get ketone on C-6 and aldehyde on the side chain resulted in a less stable compound that underwent decomposition.
- Deprotection of only the TES group using TBAF at 0°C provided the desired compound in one hour. Subsequent oxidation of the secondary alcohol and β-elimination gave ***(+)-176.***

The stereochemistry of this stable tricycle was confirmed by crystallographic analysis (***Figure 3.1.5.7***) conducted by Dr. Phil Liebing[55] at the Institut für Anorganische und Analytische Chemie (Friedrich-Schiller-Universität of Jena).



a. ***b.*** ***c.***

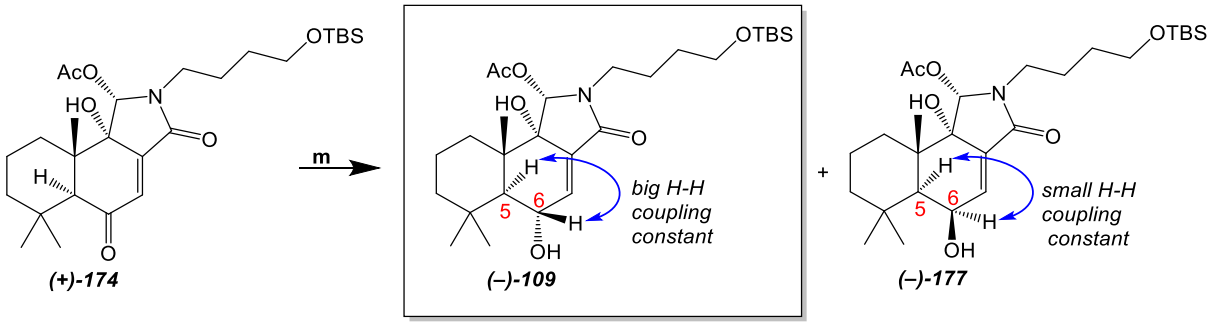
Figure 3.1.5.7. a. *Stereochemistry of* ***(+)-176****;* ***b.*** *Crystal structure as observed under the inverted bright-field microscope (Axio Vert.A1, Carl Zeiss, Oberkochen);* ***c.*** *Structure of the molecule as determined by crystallographic*

Attempts were made to perform selective reduction of the ketone in ***(+)-176*** using the CBS reagent and L-Selectride, but both methods were unsuccessful.

When employing the CBS reagent, no reaction occurred, leaving the substrate unchanged even after the expected reaction period. This outcome suggested that the CBS reagent was ineffective, when used in combination with N,N-diethyl aniline and catecholborane on substrates like ***(+)-176*** .

On the other hand, L-Selectride failed to accomplish the desired selective reduction as it also reduced the lactam group in the substrate. This indicated a lack of selectivity, resulting in unintended over-reduction.

Overall, both approaches were unsuccessful in achieving the desired selectivity, demanding the consideration of alternative reducing agents to reach the desired outcome. Through the Luche reduction, cerium trichloride heptahydrate mediated $NaBH_4$ reduction, affording a ~ 1:1 epimeric mixture of alcohols and generating two easily separable compounds: ***(–)-109*** and ***(–)-177***.



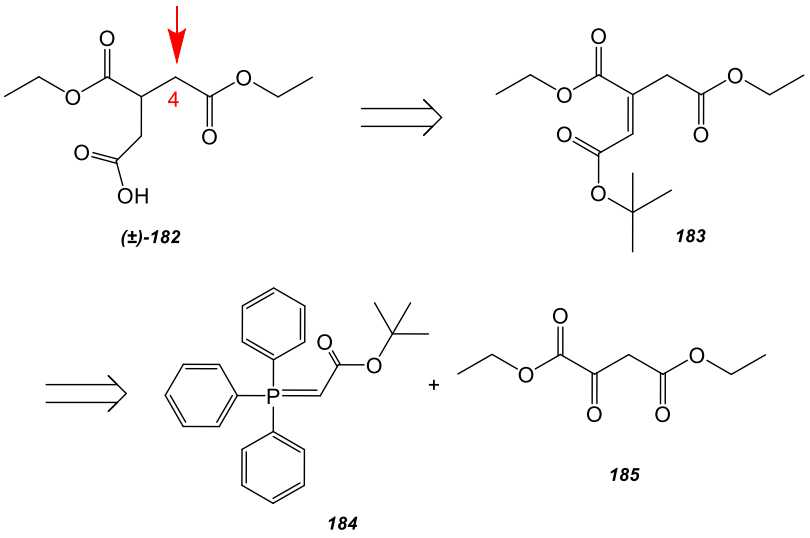
Scheme 3.1.5.3. Synthesis and identification of diastereoisomer ***(–)-109*** *and* ***(–)-177.*** *Reagents and conditions: (m)* $NaBH_4$, $CeCl_3 \cdot 7H_2O$, *0°C, 48%* ***(–)-109*** *and 45%* ***(–)-177***.

Judging from the negligible H-H coupling constant (*J* ~4 Hz) between H-5 and H-6 in ***(–)-177*** and the big one (*J* ~10 Hz) in ***(–)-109***, it can be deduced that the OH group at position 6 was in an axial orientation in ***(–)-177*** and in an equatorial in ***(–)-109***. After the identification of the isomer of interest (***Scheme 3.1.5.3.****)*, it was ready to undergo the Yamaguchi coupling.

3.2. Synthesis of the linker

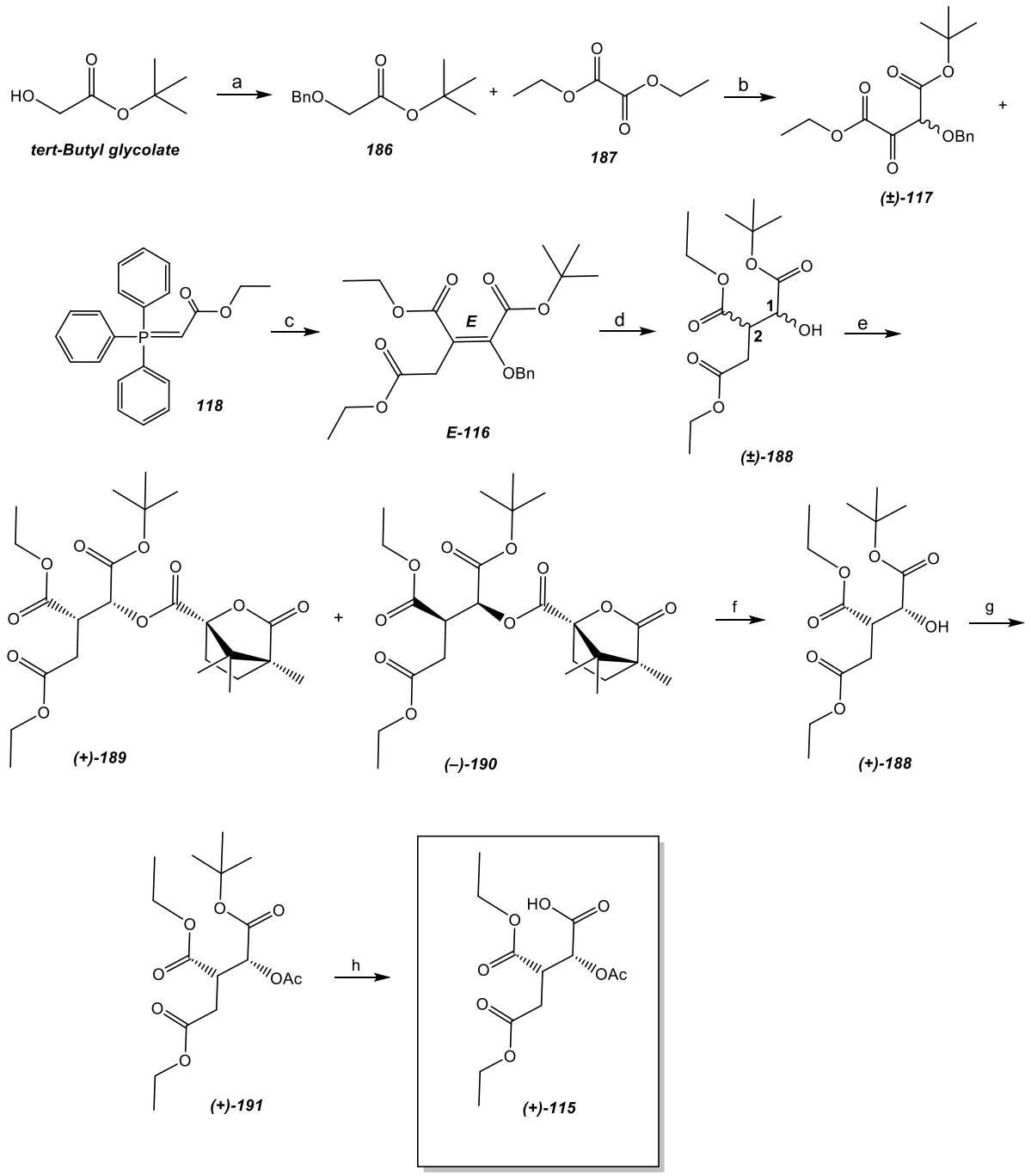
As anticipated, the molecule ***1*** is composed of the tricycle and cryptoporic acid H. In this case, the strategy considered involved the construction of cryptoporic acid onto the molecule. Cryptoporic acid H is in fact composed of a linker and the albicanyl fragment. The synthesis of the linker will be addressed first.

Compound ***(±)-182*** found in the literature[56] could serve as a reference model (***Scheme 3.2.1.***) to obtain the linker. However, direct use of ***(±)-182*** is not feasible in this case due to the absence of an essential hydroxyl group required for the Williamson reaction. Furthermore, the compound is available only as a racemic mixture, complicating its direct application. Consequently, an alternative method was explored to obtain the tricarboxy-linker ***(+)-115*** with the correct stereochemistry.



Scheme 3.2.1. *Retrosynthetic strategy for 5-ethoxy-3-(ethoxycarbonyl)-5-oxopentanoic acid* ***(±)-182***[56].

This obviously changes the synthesis approach. The sequence of reactions to get ***(±)-182*** was Wittig-hydrogenation-hydrolysis of the *tert*-butyl ester; however, for the tricarboxyl linker ***(+)-115***, the first step involved a Claisen condensation reaction between an enolizable ester ***186*** and a diester, the diethyl oxalate ***187*** (***Scheme 3.2.2.***).



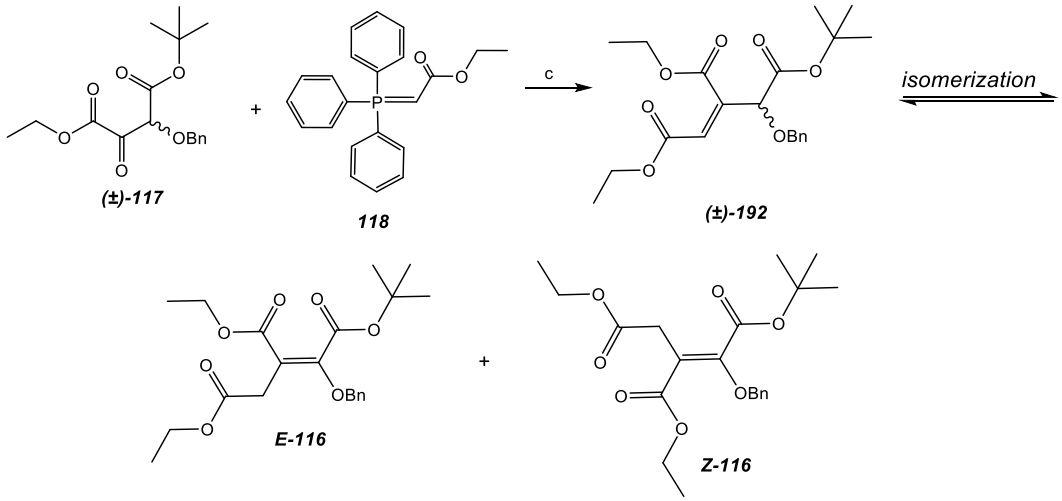
***Scheme 3.2.2**. Synthesis of tricarboxy linker **(+)-115.** Reagents and conditions: (a) BnBr, NaH, DMF, 0°C-r.t., 99%; (b), (c) LDA, Et_2O, -78°C-r.t., then **118**, CH_3CN, 55°C, 60% two steps; (d) 10% Pd/C, MeOH, H_2, r.t., 99%; (e) (–)-Camphanic chloride, DMAP, Py, CH_2Cl_2, 0°C-r.t., 45% **(+)-189** and 40% **(–)-190**; (f) K_2CO_3, MeOH, r.t., 60%; (g) Ac_2O, NEt_3, CH_2Cl_2, 0°C-r.t, 80%; (h) TFA, CH_2Cl_2, r.t., 99%.*

Various reaction conditions (different bases, solvents and temperatures) were tested to improve the efficiency of the Claisen reaction (***Table 3.2.1.***); LDA in Et_2O at -78°C was identified as the most effective condition, although it leads to the formation of the racemate ***(±)-117.***

Reagent	*Solvent*	*T/time*	*Result*
EtONa	Me-THF	r.t.	x
EtONa	Et_2O	reflux	x
EtONa	MTBE	reflux	x
t-BuOK	THF	reflux	x
LDA	Et_2O	-78°C, r.t.	✓

Table 3.2.1. *Summary of evaluated reaction conditions for Claisen condensation reaction*

This did not affect the overall strategy since, during the subsequent Wittig reaction, the newly formed double bond isomerized producing a mixture of *E/Z* isomers. As a result of the Wittig reaction, the *E/Z* selectivity was 6:1, and the two geometric isomers were readily separated using silica gel column chromatography (***Scheme 3.2.3.***).



Scheme 3.2.3 *Spontaneous isomerization during Wittig reaction between* ***118*** *and* ***(±)-117.***

To identify the predominant isomer, potential interactions were analyzed using the NOESY NMR spectrum (***Figure 3.2.1***.). The crucial interactions highlighted that the spectrum aligns with ***E-116***, the most abundant isomer. The interactions in green (NOE_C) and purple (NOE_D) highlight the proximity between the tert-butyl group and the aromatic ring and between the tert-butyl group and the benzylic-CH_2 (NOE_D), respectively.

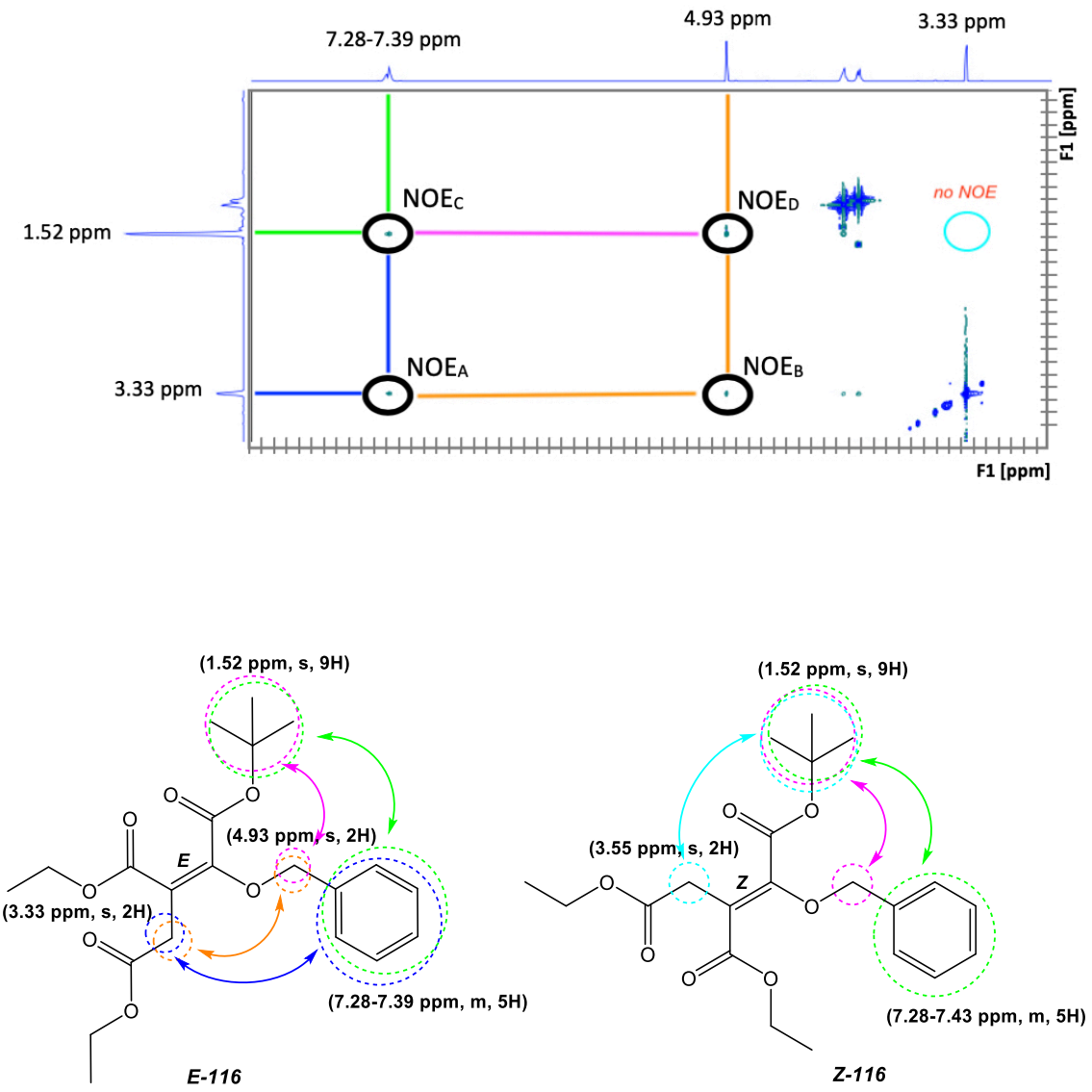


Figure 3.2.1. *Phase sensitive NOE correlations of* ***E-116*** *and* ***Z-116****.*

The interactions in orange and in blue position the benzyl group on the same side relative to -CH_2COOEt (NOE_A and NOE_B) in *E* structure. In the *Z* isomer, those interactions are not present; also, an additional interaction (light blue) is absent in the *E* isomer (no NOE) and it can be observed in ***Z-116***.

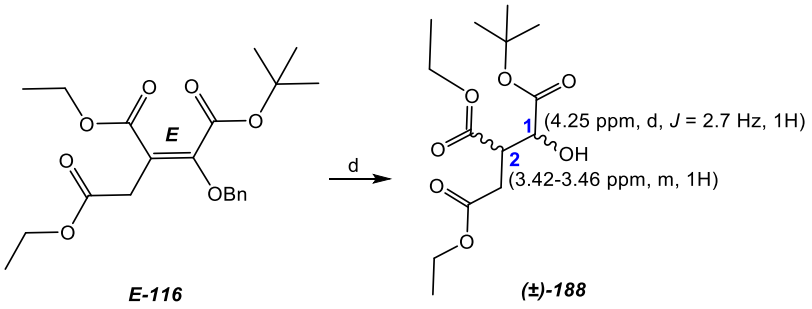
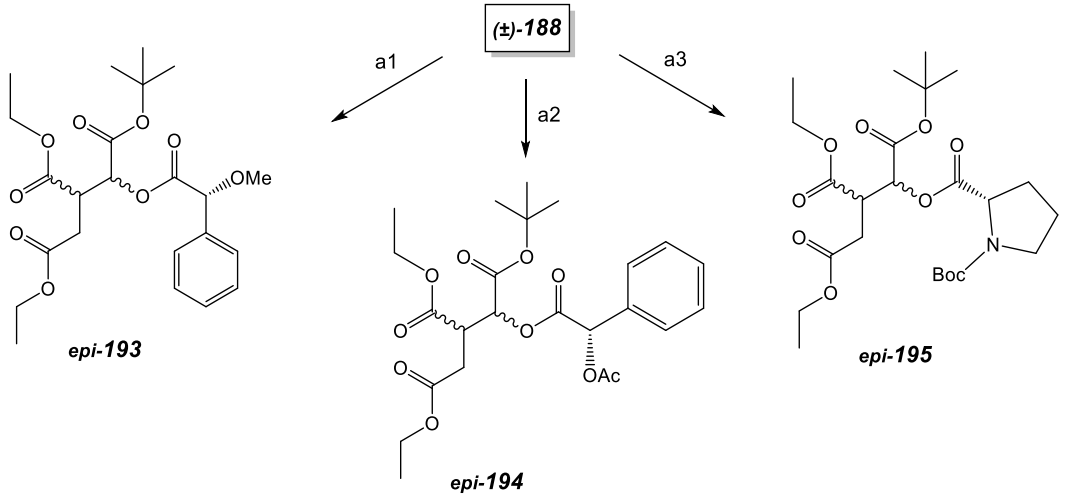


Figure 3.2.2. *H_2-syn addition reaction on* ***E-116****.*

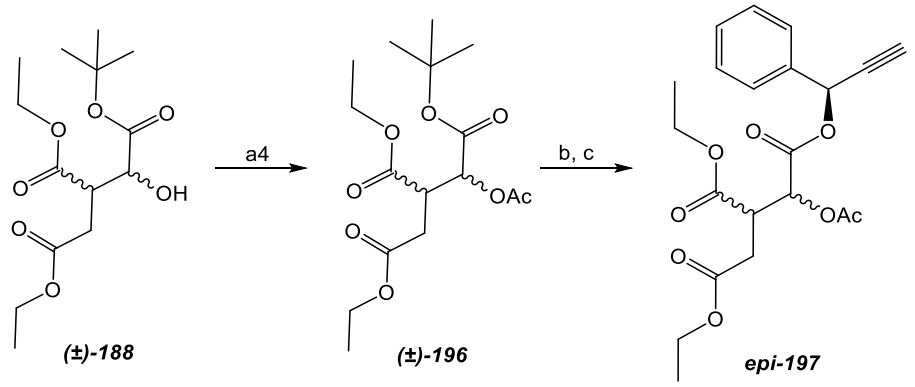
Based on these observations, once the desired isomer was isolated ***E-116***, catalytic hydrogenation with Pd/C was employed to generate a racemic mixture of ***(±)-188***. NMR data confirmed the *cis* stereochemistry of protons at C-1 and C-2 with a peak assignable to H-1 at δ 4.25 (d, J = 2.7 Hz).

To separate the two enantiomers, the strategy involved the introduction of a chiral group to perform the resolution of the alcohol. Therefore, different endeavors were made in order to get two separable diastereoisomers: mandelic ester derivatives (*(R)-2-methoxy-2-phenylacetic acid*[52] and *(R)-2-Acetoxy-2-phenylacetic acid*[57]*),* and a chiral amino acid, such as N-Boc-L-Pro*,* as shown in ***Scheme 3.2.4***.



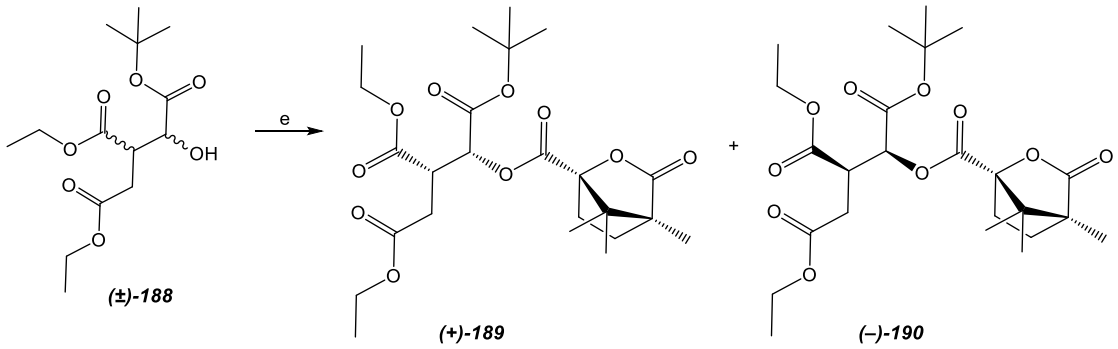
Scheme 3.2.4. *Attempts for resolution of alcohol* ***(±)-188****. Reagents and conditions: (a1) (R)-2-methoxy-2-phenylacetic acid, EDCl, DMAP,* CH_2Cl_2*, 0°C-r.t., 80%; (a2) (S)-O-Acetylmandelic acid, EDCl, DMAP,* CH_2Cl_2*, 0°C-r.t., 70%; (a3) Boc-Pro-OH, EDCl, DMAP,* CH_2Cl_2*, 0°C-r.t., 60%.*

All the procedures used were successful, although on TLC the isomers were not visibly separable. The next attempt involved a known procedure[58] for the optical resolution of carboxylic acids using Copper(I)-promoted removal of propargylic esters under neutral conditions[58]. To generate a free carboxylic acid, the free alcohol in ***(±)-188*** was protected with an acetyl group and then the *tert*-butyl ester was hydrolyzed (***Scheme 3.2.5.***). The resulting carboxylic acid was subjected to reaction with (*R*)-1-phenylpropargyl alcohol, but unfortunately this procedure didn't generate two distinguishable products on TLC (***Scheme 3.2.5.).***



Scheme 3.2.5. *Attempts for resolution of carboxylic acid. Reagents and conditions: (a4) Ac_2O, NEt_3, CH_2Cl_2, 0°C-r.t, 60%; (b) TFA, CH_2Cl_2, r.t., 99%; (c) (R)-1-Phenylpropargyl alcohol, EDCl, DMAP, CH_2Cl_2, 0°C-r.t., 80%.*

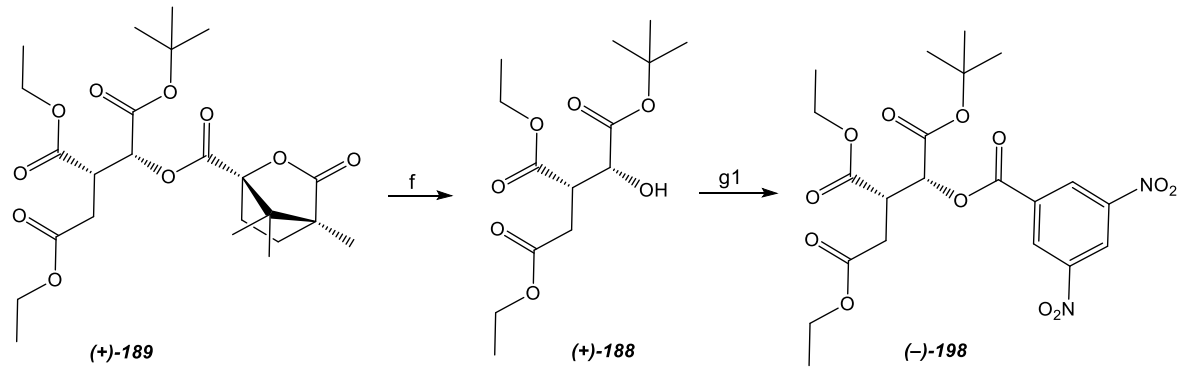
Resolution of the enantiomers succeeded after the reaction with (–)-camphanic chloride; racemic alcohol ***(±)-188*** was converted to the corresponding camphanates. The diastereoisomers were readily separated by silica gel column chromatography to afford ***(–)-189*** and ***(+)-190***-camphanates in 45% and 40% yield respectively.



Scheme 3.2.6. *Resolution of racemate* ***(±)-188.*** *Reagents and conditions:* (e) (–)-Camphanic chloride, DMAP, Py, CH_2Cl_2, 0°C-r.t., 45% ***(+)-189*** and 40% ***(–)-190.***

Since this procedure did not produce crystalline compounds, whose crystallographic analysis could have easily revealed the stereochemistry of each diastereoisomer, a methodology involving the use of another reagent was attempted.

One of those diastereoisomers was firstly deprotected giving ***(+)-189*** and then protected using 3,5-dinitrobenzoyl chloride, a reagent known for its tendency to form crystals.



Scheme 3.2.7. *Crystallization attempt with 3,5-DNB-Cl: compound* ***(–)-198*** *did not achieve crystalline form required for crystallographic analysis. Reagents and conditions: (f)* K_2CO_3*, EtOH, r.t., 60%; (g1) 3,5-DNB-Cl,* Et_3N*,* CH_2Cl_2*, 0°C-r.t., 60%*

However, this method did not yield crystalline ***(–)-198*** either, despite the use of various solvents for crystallization such as diethyl ether, pentane and hexane. The likely reason could lie in the substrates' structure. Compounds with a carbon skeleton endowed with many ester groups may fail to crystallize due to steric hindrance and increased molecular flexibility, which prevent proper molecular alignment. In addition, ester groups tend to form weak dipole-dipole interactions rather than strong hydrogen bonds, which are more favorable for crystallization. Esters also enhance solubility in organic solvents and stabilize various conformations, compromising the formation of consistent crystals.

Examining the diastereoisomers obtained in earlier experiments, ***(+)-189*** and ***(–)-190***, the analysis of their spectra revealed a notable difference in the NMR signals of the methyl groups (marked in red and green in **Figure 3.2.3.**).

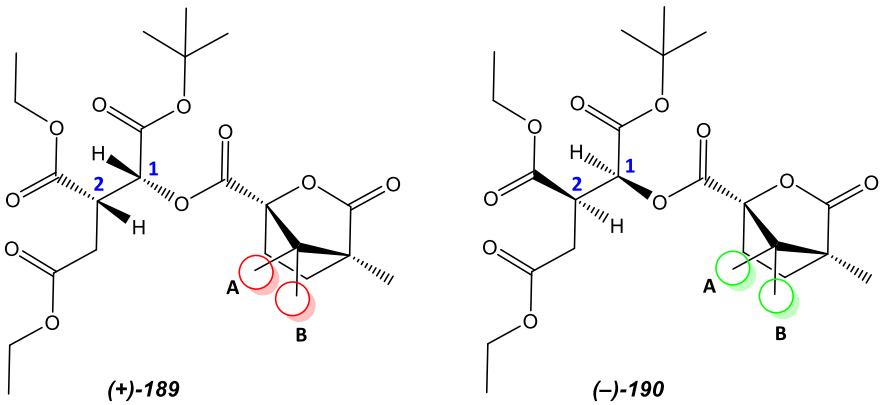


Figure 3.2.3. *Camphanates* ***(+)-189*** *and* ***(–)-190***

In one of the two structures, methyl signals in the ^{1}H-NMR appeared more shifted due to the likely orientation of the molecule, positioning them near an electron-withdrawing group, such

as an ester group. The hypothesis was corroborated using the Molecular Operating Environment software (MOE, 2022.02 Chemical Computing Group ULC), which, by taking into account conformation optimization, conformational exploration, and molecular property analysis, confirmed that:

- The hydrogens attached to C-1 and C-2 are in *cis* to each other.
- In one of the two molecules the distance between methyl groups and the -CH_2COOEt is less than 5 Å (see ***Fig. 3.2.4***).

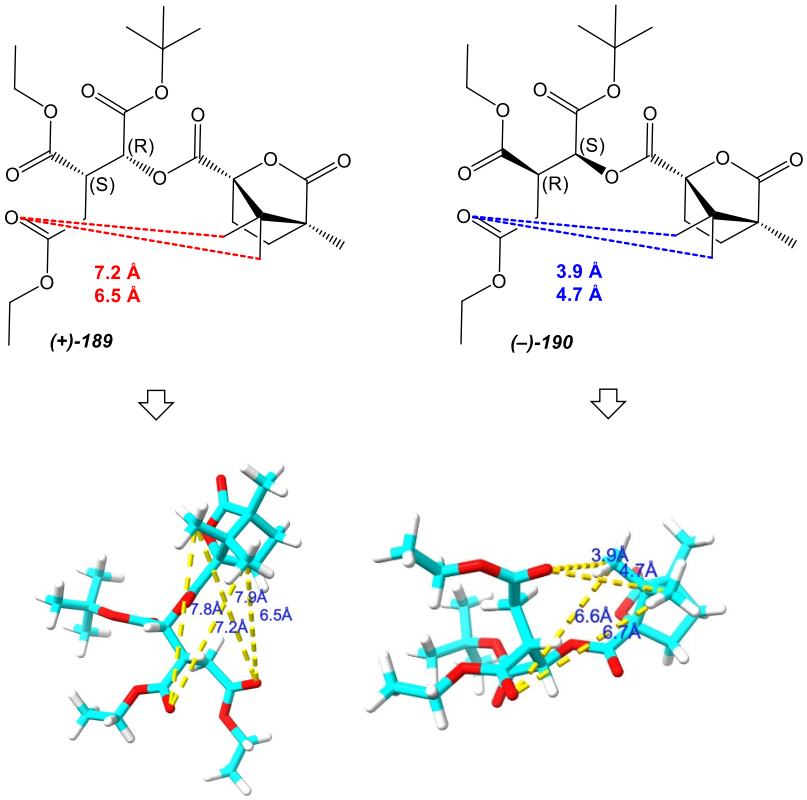
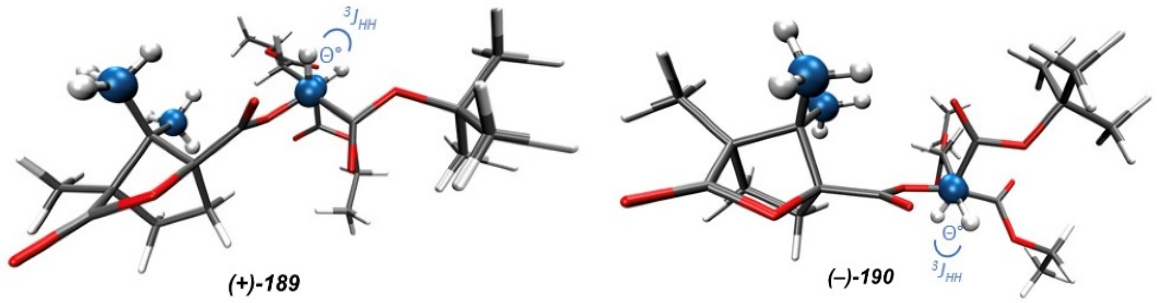


Figure 3.2.4. *Structural differences highlighted in NMR analysis.*

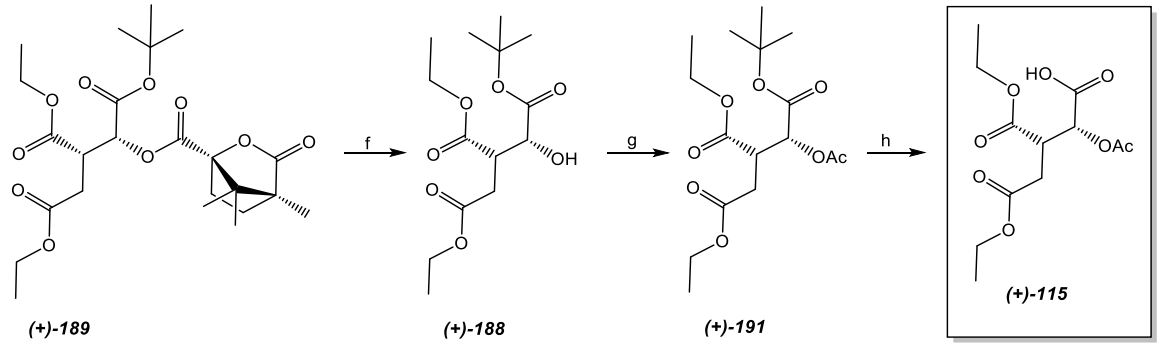
According to the previous prediction, the hypothesis was confirmed by the dihedral angle analysis conducted by Matthias Stein *et al*[59] at the Max-Planck-Institut in Magdeburg. Based on the optimized structures, the J coupling was also calculated, which turned out to be very close to the experimental data (see ***Table 3.2.2.***). The measurements of the dihedral angles further revealed the cis nature of the H-1 and H-2 (see ***Figure 3.2.3.***). The speculative data support the experimental data and the hypothesis that the shorter distance between the methyl groups and the nearest ester corresponds to diastereoisomer ***(–)-190***. In agreement with the stereochemistry of the molecule, the synthetic pathway was pursued using diastereoisomer ***(+)-189***.



Comp.	Θ°	$^{exp}J_{HH}$/Hz	$^{theo}J_{HH}$/Hz	Methyl	δexp./ppm	Δδ exp./ppm	δtheo./ppm	Δδ theo./ppm
(+)-189	57	3.60	3.72	A	1.06		1.06	
				B	1.04	0.02	0.98	0.08
(–)-190	69	3.60	3.60	A	1.10		1.07	
				B	1.03	0.07	0.93	0.14

Table 3.2.2. *Molecular conformations resulting from the application of the CREST-CENSO constrained method. The table presents the chemical shifts and J coupling constants obtained experimentally and theoretically for methyl groups, highlighting a good correlation between the experimental data and the predictions from the computational model.*

Treatment of ***(+)-189*** with potassium carbonate in ethanol afforded ***(+)-188***, which was promptly protected to form ***(+)-191***. Subsequent hydrolysis of the *tert*-butyl ester in the presence of TFA, yielded ***(+)-115***, ready to be coupled with ***(–)-109***.



Scheme 3.2.8. *Synthesis of tricarboxy linker* ***(+)-115.*** *Reagents and conditions: (f) K_2CO_3, MeOH, r.t., 60%; (g) Ac_2O, NEt_3, CH_2Cl_2, 0°C-r.t, 80%; (h) TFA, CH_2Cl_2, r.t., 99%.*

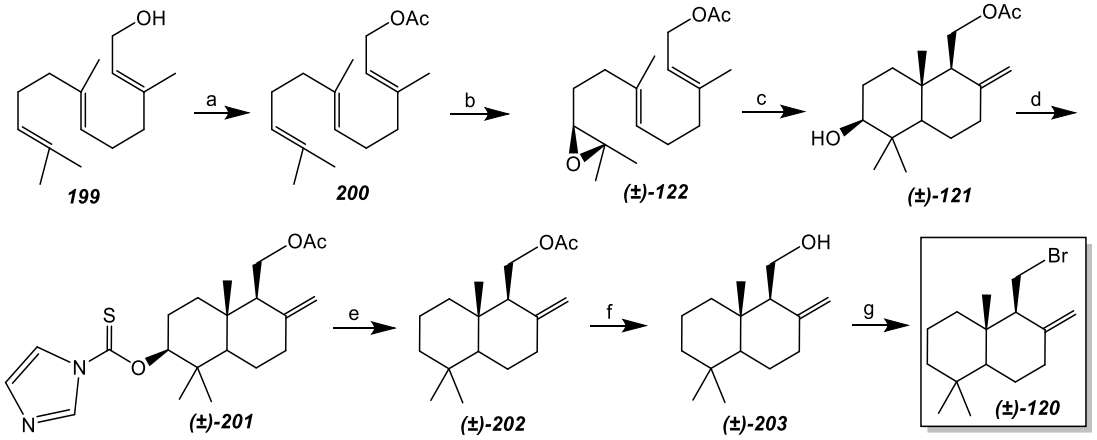
3.3. Synthesis of *(±)-albicanol*

Albicanol (and its precursor, the *albicanyl acetate*), isolated from the liverworts *Diplofyllum albicans*[60] and later from the dorid nudibranch *Cadlina luteomarginata*[61], is a chiral compound containing the bicyclo [4.4.0] ring system with three pendant methyl groups, and represents a useful starting material for the synthesis of more complex biologically active terpenes. Therefore, it has attracted considerable interest over the decades and several asymmetrical syntheses of this drimane sesquiterpenoid have been consequently performed. Some of those are mentioned below:

- *1985, Synthesis via the electrophilic cyclization of olefinic allylsilanes*[62]: Only the performing cyclization of a specific allylsilane with stannic chloride yielded an epimeric mixture of the non-separable albicanyl acetate precursor.
- *1990*, *Synthesis via cycloaddition reaction*[63]: This involves a nitrile oxide as a key step of a highly diastereoselective intramolecular [3+2] dipolar cycloaddition that results in the desired albicanol.
- *1995 & 2004, Synthesis via transformation of natural products*: By conversion of higher terpenes such as sclareol[64] and manool[65].
- *2000*, *Synthesis via enzymatic resolution*[66]: To obtain an optically pure drimane by cyclization and subsequent exposure to the enzyme PL-266 from *Alcaligenes* sp.
- *2001, Synthesis via kinetic resolution with N-Boc-L-proline*[67]: To obtain an optically pure albicanyl acetate via esterification of a suitable synthetic precursor -a bicyclic diol- with the chiral aminoacid- N-Boc-Pro.
- *2003, Synthesis via acid-mediated polyene cyclization and subsequent selenocatalytic allylic clorination*[68]: The Vlad's fluorosulfonic acid-mediated cyclization of (*E*, *E*)-farnesol, followed by the key step of this synthesis gave an inseparable mixture of two chlorinated epimers, which, subjected to the reduction with Zinc dust and then to the treatment with methanolic K_2CO_3, provided the desired drimane.
- *2003, Synthesis via cation polyolefin cyclization*[65]: This is exactly what occurs in nature. A cation is generated (by protonation or electrophilic activation of an olefinic group), which then attacks a double bond within the same molecule, leading to the formation of a cyclic structure. This intermediate is stabilized either by the loss of a proton or by

nucleophilic attack, such as the addition of a water molecule, ultimately yielding the final cyclic product.

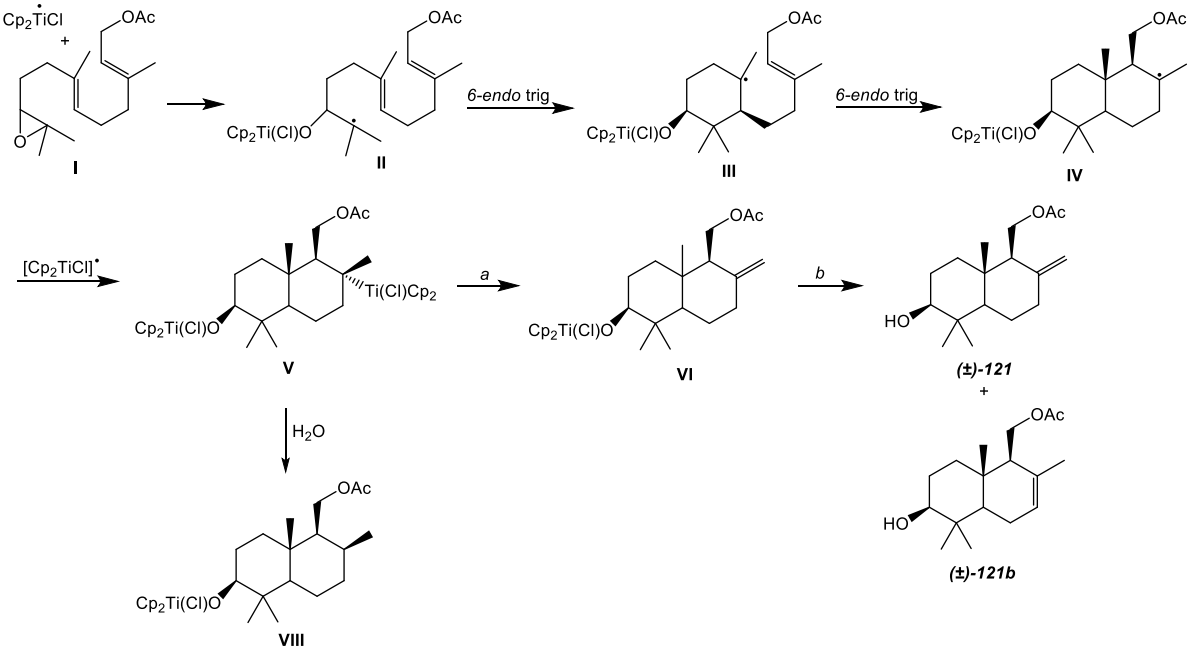
- *2009*, *Synthesis via a concise Diels-Alder*[69]: A well-known natural intermediate- dihydrodrimenin- was obtained using the traditional diene (1,3,3-trimethyl-2-vinylcyclohex-1-ene), together with different trans-substituted olefins, in the presence of a mild Lewis acid. This intermediate serves, in turn, as a substrate for further modifications, culminating in the final step of deacetylation of albicanyl acetate to give (+)- albicanol.
- *2014, Synthesis via radical polyolefin cyclization*[48]: It was deemed that, taking inspiration from what occurs in nature, epoxyfarnesol would be well-suited for the synthesis of albicanol. Indeed, as previously reported[48], this synthesis could be efficiently achieved through a key Titanocene (III)-catalyzed cascade cyclization of the acyclic epoxypolyene (***Scheme 3.3.2***). This procedure describes a radical process in which the presence of radical mediators, the Titanocene (III), transforms highly functionalized polyenic precursors into trans-decalins with remarkable relative stereocontrol[70].



Scheme 3.3.1. *Synthesis of bicycle* ***(±)-120****. Reagents and conditions: (a) Ac_2O, Py, DMAP, CH_2Cl_2, r.t., 99%; (b) NBS, THF/H_20, O°C, then DBU, THF, 0°C, 60%; (c) Cp_2TiCl_2, Mn-dust, THF, 2,4,6-collidine, TMSCl, r.t., 35%; (d) TCDI, DMAP, tol., 80 °C, 90%; (e) Bu_3SnH, AIBN, tol., 125 °C, 90%; (f) K_2CO_3, MeOH, r.t., 99%; (g) PBr_3, THF, 0°C.*

Unlike the procedure reported in 2014 by Göhl and Seifert[48], this project used a racemic mixture of epoxyfarnesyl acetate as the starting material for the synthesis of albicanol. This initial prerequisite, in addition to the stereochemical control exerted by the titanocene-mediated radical cyclization, will enable us to obtain a racemic mixture of only two enantiomers of the final desired product. In particular, the opening of racemic epoxyfarnesyl

acetate under strictly anhydrous conditions with a substoichiometric quantity of [Cp_2TiCl_2], Mn dust, and a combination of TMSCl/2,4,6-collidine in THF at room temperature ultimately gave ***(±)-121*** (and isomer ***(±)-121b***) after fluoride workup. The result of this radical cascade cyclization was a trans-bicyclic decalin with a drimane skeleton bearing an exocyclic alkene derived from two consecutive 6 endo-trig cyclizations[71] (See ***Scheme 3.3.2*** for the proposed mechanism).



Scheme 3.3.2. *Proposed mechanism for the titanocene(iii)-mediated cyclization of epoxyfarnesyl acetate; a. [Cp_2Ti (Cl)H] elimination under anhydrous conditions; b. acidic quenching after the [Cp_2Ti (Cl)H] elimination.*

The product formed can be explained by the Beckwith-Houk rules, which aim to predict the preferential formation of a specific stereoisomer based on the spatial arrangement of the reacting group considering the thermodynamic, kinetic and stereospecific control. The result is the prediction of the most stable product, the most reactive one and the prediction of the stereoelectronic effect on orbital interactions[72]. The product of the cyclization was then subjected to a deoxygenation reaction, using the Barton-McCombie method (***Scheme 3.3.2***.), after transformation into its trifluoromethoxythionocarbonyl derivative. Following this, ***(±)-201*** was converted into albicanyl acetate ***(±)-202*** by radical reduction with tributyltin hydride. Subsequently, a simple saponification of the acetate gave albicanol ***(±)-203*** in 85% yield, followed by Appel reaction to get a racemic mixture of ***(±)-120***, ready to be coupled through Williamson etherification.

3.4. Coupling reactions: Yamaguchi & Williamson

This section details the synthetic strategy employed to couple three key fragments, using both *Yamaguchi esterification* and *Williamson etherification* to achieve the final target molecule.

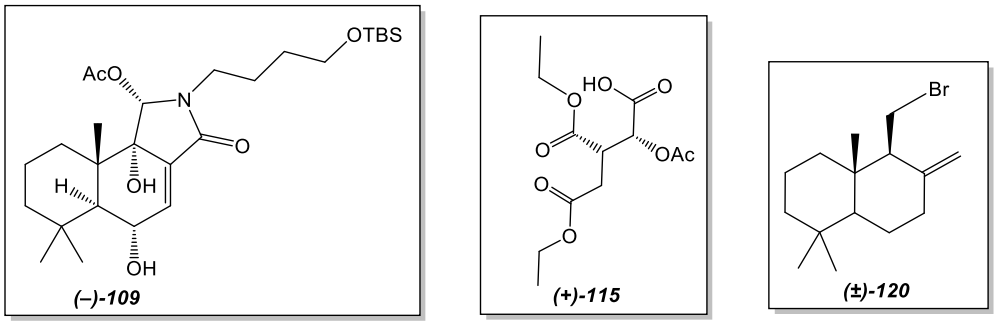
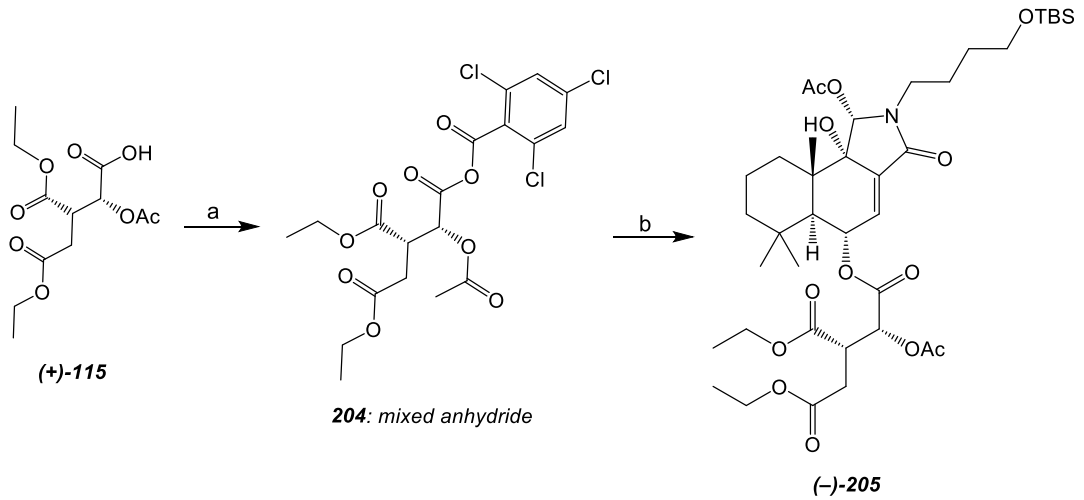


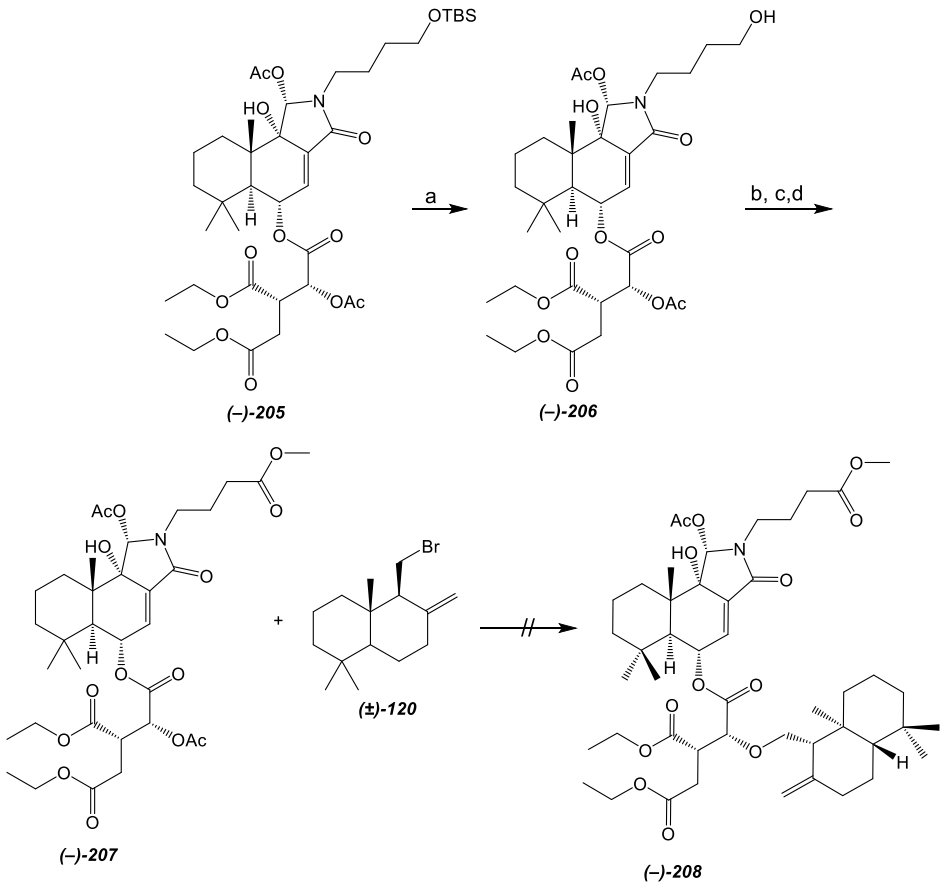
Figure 3.4.1. *Key fragments:* ***(–)-109*** *tricycle;* ***(115)*** *tricarboxy-linker;* ***(±)-120*** *albicanyl bromide.*

The first coupling reaction is particularly advantageous due to its mild reaction conditions, essential for the preservation of sensitive functional groups. Tricarboxy-linker ***(+)-115*** reacted in 2 hours with TCBC in the presence of the base, giving the mixed anhydride (***Scheme 3.4.1.***). After the addition of the activated acid to alcohol ***(–)-109*** and DMAP, the reaction was complete in 3 hours at room temperature, affording ***(–)-205*** in 60% yield.



Scheme 3.4.1. *Activation of the carboxylic acid* ***(+)-115*** *to form the mixed anhydride* ***204*** *and subsequent reaction with alcohol* ***(–)-109****. Ragents and conditions: (a)TCBC,* Et_3N*, THF, r.t.; (b)* ***(–)-109****, DMAP, tol, r.t., 60%.*

The next goal before the second coupling is to make modifications to the side chain by converting the TBS group into a methyl ester (see ***Scheme 3.4.2.***).



Scheme 3.4.2. *Synthesis of synthon* ***(–)-207****. Reagents and conditions: (a) TBAF, THF, 0°C, 99%; (b) Dess-Martin periodinane, CH_2Cl_2, 0°C-r.t.,99%; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/t-BuOH, r.t., 99%; (d) CH_2N_2, Et_2O, 0°C-r.t., 70%.*

The silyl ether was cleaved and rapidly oxidized to an aldehyde. The carboxylic function obtained through further oxidation was quickly methylated to yield compound ***(–)-207***. At this point, the completion of the skeleton for compound ***1*** via Williamson etherification was planned. This involved the reaction of an alkoxide ion (obtained after cleaving the acetyl groups from ***(–)-207*** and treatment with sodium hydride) with a primary alkyl halide ***(±)-120***. This step was crucial to achieve the desired ether linkage, which is typically a key step in the synthesis of complex molecular architectures. Unfortunately, the Williamson etherification could not be carried out. Although the Appel reaction succeeded in converting albicanol ***(±)-203*** into a useful halogenated derivative for the final coupling, it seemed that ***(±)-120*** degraded shortly after working up the reaction. The most credible hypothesis is that a spontaneous isomerization occurred, generating allyl bromide, making the molecule susceptible to rapid degradation. This degradation was due to the formation of a carbocation following the elimination of the bromine atom. Although this carbocation was stabilized

through resonance with the allyl group's double bond, it remained highly reactive. It could easily react with nucleophiles or solvents, leading to various decomposition products. These reactions compromised the stability of the molecule, ultimately impeding the successful coupling and formation of the desired product.

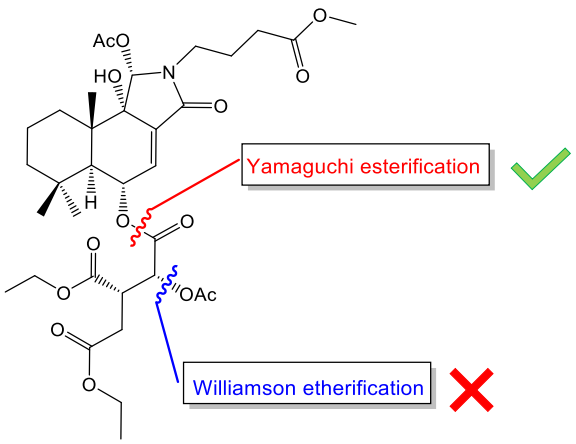


Figure 3.4.2. Outcomes of Coupling Reactions: Success and Failure.

Future work will focus on further optimizing this final reaction; the free alcohol could be functionalized differently, for instance, as an attachment point for more stable decalins or isosteres. Another potential modification could involve the chlorinated intermediate instead of the brominated one, where treatment with catalytic NaI for in situ exchange might offer an alternative functionalization option for the final coupling. The direction the synthesis will take may also depend on SAR (Structure-Activity Relationship) studies, which will reveal which parts of the molecule are critical for biological activity, ultimately contributing to the synthesis of a more potent molecule. This is especially significant given that the biological activity we aim for is rare among sesquiterpenoids.

4. Summary and outlook

The outcome of this synthetic effort was a robust and scalable process that produced the driman-type structure with the desired stereochemistry, in accordance with ***1***. Although similar structures have been reported in the literature[73], which are relatively recent, these are often obtained as racemic mixtures. This work is distinguished for employing a synthetic approach with precise stereochemical control, enabling the synthesis of complex sesquiterpenoids in enantiomerically pure form. Moreover, the process demonstrates the potential to produce other complex sesquiterpenoids with the same attention to stereochemical control.

This strategy highlights the importance of integrating traditional organic synthesis with modern catalytic methods to address the challenges posed by complex natural products. It also underscores the value of interdisciplinary approaches, combining knowledge from biology, pharmacology, advanced chemistry to develop new therapeutic agents. However, there remains room for improvement, such as through an asymmetric synthesis of the halogenated albicanyl compound or by employing a catalytic Diels–Alder reaction to construct the tricyclic amide core.

In conclusion, the synthesis of compound ***1*** exemplifies the intricate balance between creativity and precision required in modern organic synthesis. Although the complete synthesis has not yet been accomplished, finding a way to develop the drimane core is undoubtedly valuable and could serve as a starting point for the synthesis of other sesquiterpenoids. By focusing on efficiency, selectivity, reproducibility, and sustainability, significant synthetic challenges were overcome. The successful implementation of these strategies may also pave the way for the synthesis of other complex natural products discovered in the future, highlighting the broader applicability and impact of this research.

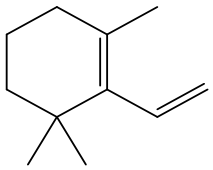
5. Experimental procedures and Analytical Data

5.1. General Methods

Solvents were dried by standard procedures and redistilled under N_2 atmosphere prior to use. All reactions were run under nitrogen unless otherwise stated. For reactions that require heating, an oil bath was used. For reaction that require cooling, ice (for reaction condition at 0°C) or dry ice and acetone (for reaction condition at -78°C) were used. The products were purified by flash chromatography on Merck silica gel 60 (40-63 µm); in some cases, automated flash chromatography was performed using a Biotage Selekt system. POLYGRAM SIL G/UV254 prefabricated TLC plates with fluorescent indicator from Macherey-Nagel have been used for analytical thin layer chromatography (TLC). The separated substances were detected by irradiation with UV light with a wavelength of 254 nm or staining with vanillin or Cerium-Molybdate and subsequent warming with a heat gun. Electrospray ionization (ESI) and electron ionisation (EI) mass spectra were recorded on Finnigan MAT 95 and Waters Xevo G2-TOF spectrometers. ^{1}H, ^{13}C and 2D (NOESY) NMR spectra were recorded on Bruker AVIII 400 and Bruker AVI 600 spectrometers. Chemical shifts (δ) are reported in ppm from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration (^{1}H NMR = $CDCl_3$: δ 7.26, D_2O: δ 4.79; ^{13}C NMR= $CDCl_3$: δ 77.16). Data are reported as follows: chemical shift, multiplicity (s= singlet, d= doublet, t= triplet, br= broad, m= multiplet), coupling constants (Hz) and integration. Optical rotations were recorded on Perkin-Elmer 341 and Anton Paar MCP150 polarimeters. Melting points were recorded on Büchi Melting Point B-540 apparatus. (IR) spectra were recorded on Bruker Vertex 70v. Bands are characterized as strong (s), medium (m), weak (w) or broad (br).

5.1.1. Synthesis of the linker: fom compound *113* to *(–)-181*

1,3,3-Trimethyl-2-vinyl-1-cyclohexene:



113

A suspension of 1.5 eq of methyltriphenylphosphonium bromide (195.33 mmol, 69.78 g) in dry THF (200 mL) was treated with 1,75 eq (227.89 mmol, 91 mL) of a 2.5 M solution of *n*-butyllithium in hexane at 0°C. The mixture was then stirred at room temperature for 1 h until all the solid had disappeared. A solution of β-cyclocitral (1 eq, 130.22 mmol, 19.82 g, 21 mL) in dry THF (15 mL) was added dropwise at –78°C and stirring was continued for a further 3 h at room temperature. The reaction was quenched with NH_4Cl (sat. aq. solution) and extracted with Et_2O, filtered through a Na_2SO_4 plug, rinsed with Et_2O, and carefully concentrated to give the crude alkene product. Flash chromatography with Biotage Selekt (hexane 100%) afforded the diene ***113*** (90%, 117.20 mmol,17.61 g, colorless oil).

General Data: $C_{11}H_{18}$; FW: 150.14; TLC: R_f = 0.9 (hexane); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

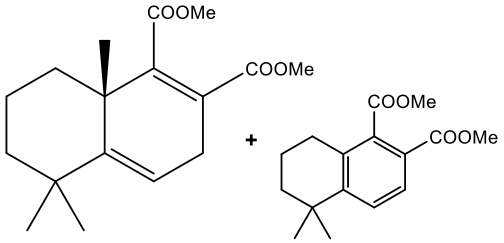
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.21 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.23 (d, *J* = 11.3, 2.6 Hz, 1H), 4.96 (d, *J* = 17.7, 2.8 Hz, 1H), 1.98 (t, *J* = 6.2 Hz, 2H), 1.69 (s, 3H), 1.57-1.64 (m, 2H), 1.43-1.47 (m, 2H), 1.00 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 138.4, 135.6, 128.6, 118.0, 39.6, 33.9, 32.9, 28.9, 21.5, 19.4.

IR (neat): 2958 (s), 2925 (s), 2864 (s), 1456 (m), 1374 (m), 1359 (m), 1189 (w), 971 (s), 707 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{11}H_{19}$ $[M+H]^+$: 151.1487; found: 151.1481.

Dimethyl 5,5,8a-trimethyl-3,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate:



(±)-112 ***112b***

A mixture of 1.50 g (2 eq, 10 mmol) of ***113*** and 1 eq of the known alkyne dienophile dimethylacetylenedicarboxylate (5 mmol, 0.61 mL) was mechanically stirred and heated at 110 °C for 72 h. After cooling, purification with flash column chromatography (Biotage Selekt, EtOAc in hexane, 0 to 20 %) yielded the Diels-Alder adduct ***(±)-112*** in 70% yield (3.5 mmol, 1.02 g, clear, light-yellow oil) and 15% of dimethyl 5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate ***112b*** (0.75 mmol, 207 mg, light oil). Starting material ***113*** was recovered in 14%.

General Data *(±)-112*: $C_{17}H_{24}O_4$; FW: 292.17; TLC: R_f = 0.5 (hexane/EtOAc 7:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.69 (dd, *J* = 5.7, 2.2 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.14 (dd, *J* = 22.3, 5.6 Hz, 1H), 2.77 (dd, *J* = 22.5, 2.2 Hz, 1H), 1.24-1.84 (m, 6H), 1.41 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.8, 166.5, 150.8, 147.7, 125.6, 117.0, 52.2, 52.0, 40.2, 39.0, 36.0, 35.9, 32.6, 31.3, 26.7, 26.2, 18.3.

IR (neat): 2938 (m), 1720 (s), 1433 (m), 1249 (s), 1125 (m), 1022 (s), 767 (m), 738 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{25}O_4$ $[M+H]^+$: 293.1753; found: 293.1755.

General Data *112b*: $C_{16}H_{20}O_4$; FW: 276.14; TLC: R_f = 0.35 (hexane/EtOAc 7:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

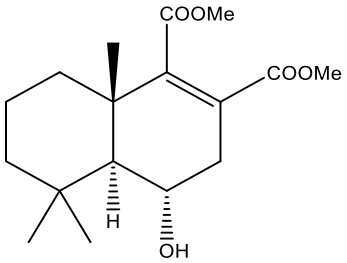
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.78 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 2.72 (t, J = 6.4 Hz, 2H), 1.68-1.80 (m, 2H), 1.63-1.66 (m, 2H), 1.29 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.5, 166.3, 152.0, 135.8, 133.5, 127.9, 127.4, 124.5, 52.6, 52.5, 38.4, 34.7, 31.8, 27.4, 19.1.

IR (neat): 2938 (m), 1720 (s), 1601 (w), 1433 (m), 1249 (s), 1125 (m), 1022 (s), 846 (w), 767 (m), 738 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1440; found: 277.1451.

Dimethyl 4-hydroxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate:



(±)-123

A 1.0 M solution of BH_3·THF in THF (1.5 eq, 28.73 mmol, 28.7 mL) was added at 0°C to a solution of ***(±)-112*** (1 eq, 19.15 mmol, 5.60 g) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 8 h. Water (3 mL), a 2N aqueous NaOH solution (6 mL) and 35% aqueous H_2O_2 (4 mL) were added to the reaction mixture, and stirring was continued for 16 h at 0°C. The reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (2:1) gave alcohol ***(±)-132*** (60%, 11.50 mmol, 3.57 g, colorless needles).

General Data: $C_{17}H_{26}O_5$; FW: 310.18; TLC: R_f = 0.4 (hexane/EtOAc 2:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; Mp 80-85 °C.

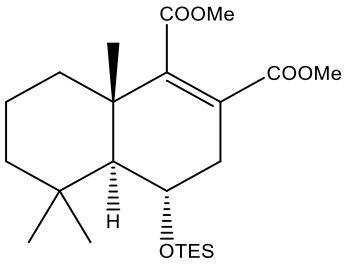
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.16-4.23 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.85 (dd, *J* = 18.2, 6.7 Hz, 1H), 2.37 (dd, *J* = 18.3, 8.1 Hz, 1H), 1.35-1.59 (m, 6H), 1.33 (d, *J* = 11.04 Hz, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.3, 166.6, 152.9, 124.5, 67.7, 55.1, 52.3, 52.1, 43.3, 40.5, 37.4, 36.6, 36.2, 34.0, 22.2, 21.2, 18.5.

IR (neat): 3523 (br), 2931 (m), 1712 (s), 1644 (w), 1424 (m), 1246 (s), 1203 (m), 1069 (m), 837 (w), 758 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{27}O_5$ $[M+H]^+$: 311.1858; found: 311.1858.

Dimethyl 5,5,8a-trimethyl-4-((triethylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate:



(±)-124

To a solution of ***(±)-123*** (1 eq, 13.34 mmol, 4.14 g) in dry DMF (65 mL) with imidazole (6 eq, 80.04 mmol, 5.45 g) was added TESCl (3 eq, 40.02 mmol, 6.7 mL) at 0°C and the reaction was stirred for 2 h at the same temperature. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 10:1) to afford the protected alcohol ***(±)-124*** (99%, 13.21 mmol, 5.60 g, sticky liquid).

General Data: $C_{23}H_{40}O_5Si$; FW: 424,26; TLC: R_f = 0.8 (hexane/EtOAc 4:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

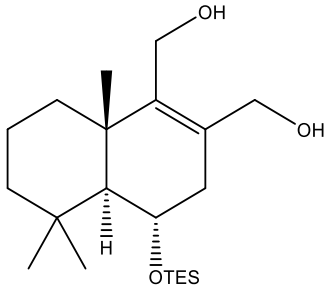
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm):): 4.24 (ddd, *J* = 10.7, 8.7, 6.2 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.73 (dd, *J* = 18.0, 6.2 Hz, 1H), 2.37 (dd, *J* = 18.1, 8.9 Hz, 1H), 1.14-1.58 (s, 6H), 1.37 (d, *J* = 10.7 Hz, 1H), 1.27 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.66 (q, *J* = 8 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 169.4, 166.7, 152.5, 124.8, 68.2, 54.7, 52.3, 52.0, 43.7, 40.4, 38.0, 37.0, 36.1, 33.8, 22.2, 21.5, 18.4, 7.2, 5.6.

IR (neat): 1724 (s), 1649 (w), 1246 (s), 1086 (m), 1006 (m), 818 (w), 726 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{44}NO_5Si$ $[M+NH_4]^+$: 442.2989; found: 442.2992.

(5,5,8a-trimethyl-4-((triethylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-diyl) dimethanol:



(±)-125

To a solution of ***(±)-124*** (1 eq, 16.0 mmol, 6.79 g) in dry THF (300 mL) was added 1M DIBAL-H in hexane (6 eq, 96 mmol, 96 mL) dropwise at 0°C for 3 h. The reaction mixture was quenched with MeOH, poured into a saturated aqueous Rochelle's salt solution, and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (2:1), yielding ***(±)-125*** (68%, 10.88 mmol, 4.01 g, white powder).

General Data: $C_{21}H_{40}O_3Si$; FW: 368.27; TLC: R_f = 0.2 (hexane/EtOAc 2:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; Mp 47-52 °C.

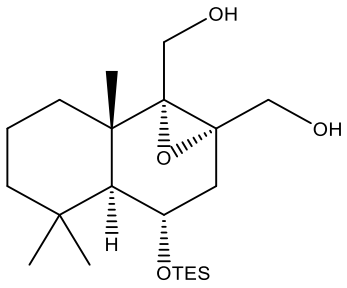
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.00-4.20 (m, 5H), 2.52 (dd, *J* = 17.4, 5.9 Hz, 1H), 2.29 (dd, *J* = 17.4, 9.2 Hz, 1H), 2.04 (s, 1H), 1.80 (d, *J* = 12.7 Hz, 1H), 1.12-1.64 (m, 4H), 1.31 (d, *J* =10.7 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.98 (t, *J* = 8 Hz, 9H), 0.65 (q, *J* = 7.6 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 146.0, 134.1, 69.0, 63.6, 57.9, 56.2, 43.8, 43.0, 41.0, 36.9, 36.2, 33.6, 22.3, 21.8, 18.8, 7.3, 5.7.

IR (neat): 3321 (br), 2929 (m), 1121 (m), 1085 (s), 1001 (s), 981 (s), 834 (m), 724 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{41}O_3Si$ $[M+H]^+$: 369.2825; found: 369.2817.

(4,4,7a-trimethyl-3-((triethylsilyl) oxy) octahydronaphtho [1,2-b] oxirane-1a,7b-diyl) dimethanol:



(±)-126

To a stirred solution of ***(±)-125*** (1 eq, 20.62 mmol, 7.60 g) in CH_2Cl_2 (300 mL) was added 1 eq of m-CPBA (ca. 77%, 20.62 mmol, 4.62 g), and stirring was continued at 0°C for 3 h. The reaction mixture was poured into a 5% aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to afford ***(±)-126*** (99%, 20.41 mmol, 7.85 g, white powder).

General Data: $C_{21}H_{40}O_4Si$; FW: 384.27; TLC: R_f = 0.3 (hexane/EtOAc 2:1); UV (-); Vanillin: brown; Mp 80-82 °C.

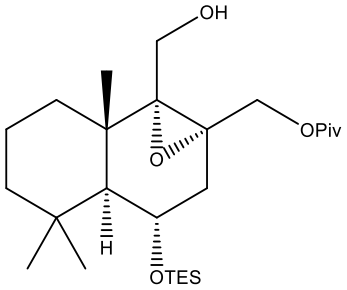
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.09 (d, *J* = 11.6 Hz, 1H), 3.99 (ddd, *J* = 10.7, 8.9, 6.9 Hz, 1H), 3.67 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 11.8 Hz, 1H), 3.55 (d, *J* = 11.3 Hz, 1H), 2.46 (dd, *J* = 14.7, 6.8 Hz, 1H), 1.87 (dd, *J* = 14.9, 8.9 Hz, 1H), 1.70 (d br, *J* = 12.7 Hz, 1H), 1.18-1.59 (m, 5H), 1.48 (d, *J* = 10.6 Hz, 1H), 1.17 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.64 (q, *J* = 8 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 71.4, 67.6, 65.8, 64.8, 61.8, 49.0, 43.5, 38.8, 37.9, 36.3, 35.6, 33.2, 22.6, 18.5, 18.3, 7.2, 5.6.

IR (neat): 3340 (br), 2927 (s), 1458 (m), 1239 (m), 1117 (m), 1086 (s), 1016 (s), 838 (m), 723 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{41}O_4Si$ $[M+H]^+$: 385.2774; found: 385.2769.

(7b-(hydroxymethyl)-4,4,7a-trimethyl-3-((triethylsilyl) oxy) octahydronaphtho[1,2-b] oxiran-1a(2H)-yl) methyl pivalate:



(±)-127

To a solution of the epoxide ***(±)-126*** (1 eq, 4.55 mmol, 1.75 g) in dry pyridine (50 mL) was added first DMAP (0.1 eq, 0.46 mmol, 56.20 mg) and then dropwise at 0°C during 5 min PivCl (1 eq, 4.55 mmol, 0.56 mL) and stirring was continued at room temperature for 8 h. The reaction mixture was poured into water and extracted with Et_2O. The organic layer was washed with 1M HCl and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification with flash chromatography (pentane/Et_2O 12:1) gave ***(±)-127*** (60%, 2.73 mmol, 1.28 g, colorless needles) together with dipivalate product (10%, 0.46 mmol, 253 mg).

General Data: $C_{26}H_{48}O_5Si$; FW: 468.33; TLC: R_f = 0.4 (hexane/EtOAc 3.5:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; Mp 85-90 °C.

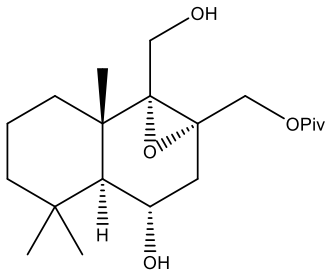
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.14 (d, *J* = 11.8 Hz, 1H), 4.11 (d, *J* = 11.8 Hz, 1H), 3.96 (ddd, *J* = 10.8, 8.8, 7.2 Hz, 1H), 3.78 (d, *J* = 12.0 Hz, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 2.27 (dd, *J* = 15.2, 6.9 Hz, 1H), 1.94 (dd, *J* = 15.1, 8.6 Hz, 1H), 1.60-1.80 (m, 1H), 1.51 (d, *J* = 10.6 Hz, 1H), 1.44-1.57 (m, 2H), 1.29-1.37 (m, 3H), 1.23 (s, 9H), 1.10 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 178.3, 71.0, 67.3, 66.2, 63.1, 58.4, 49.0, 43.5, 39.0, 38.7, 37.3, 36.2, 35.4, 33.3, 27.3, 22.6, 18.5, 18.2, 7.2, 5.7.

IR (neat): 3465 (br), 2955 (s), 1731 (s), 1282 (m), 1151 (s), 1085 (m), 1004 (m), 743 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{49}O_5Si$ $[M+H]^+$: 469.3349; found: 469.3358.

(3-hydroxy-7b-(hydroxymethyl)-4,4,7a-trimethyloctahydronaphtho[1,2-b] oxiran-1a(2H)-yl) methyl pivalate:



(±)-128

Compound ***(±)-127*** (1 eq, 2.80 mmol, 1.30 g) was dissolved in EtOH (90 mL), PPTS (0.1 eq, 0.60 mmol, 151 mg) was added at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (3:1), yielding ***(±)-128*** (85%, 2.40 mmol, 851 mg) as colorless needles.

General Data: $C_{20}H_{34}O_5$; FW: 354.24; TLC: R_f = 0.4 (hexane/EtOAc 2:1); UV (-); Vanillin: brown; Mp 100-103 °C.

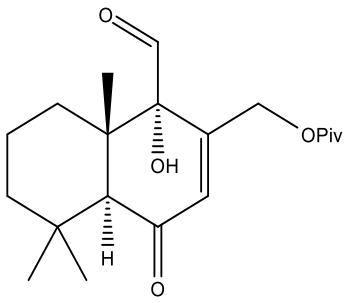
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.33 (d, *J* = 11.8 Hz, 1H), 4.13 (d, *J* = 11.8 Hz, 1H), 3.92 (d, *J* = 12.5 Hz, 1H), 3.78 (d, *J* = 12.7 Hz, 1H), 3.60-3.74 (m, 1H), 2.40 (dd, *J* = 15.9, 6.4 Hz, 1H), 2.11 (dd, *J* = 15.8, 3.2 Hz, 1H), 1.88 (d br, *J* = 9.2 Hz, 1H), 1.40-1.80 (m, 6H), 1.22 (s, 9H), 1.10 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 178.7, 71.0, 66.2, 65.1, 62.9, 59.6, 55.3, 42.2, 39.0, 37.8, 36.0, 34.1, 27.4, 27.3, 27.2, 22.5, 18.9, 18.6.

IR (neat): 3460 (br), 2924 (s), 1726 (m), 1282 (m), 1155 (s), 1041 (m), 1021 (m), 975 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{20}H_{35}O_5$ $[M+H]^+$: 355.2484; found: 355.2488.

(1-formyl-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl) methyl pivalate:



(±)-130

Dess-Martin periodinane (4.6 eq, 9.2 mmol, 3.9 g) was added to a stirred solution of ***(±)-128*** (1 eq, 2 mmol, 709 mg) in CH_2Cl_2 (40 mL) at 0°C, and stirring was continued at room temperature for 8 h. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (5:1) gave the corresponding ketoaldehyde ***(±)-129*** (85%, 1.7 mmol, 596.0 mg) and ***(±)-130*** (12%, 0.24 mmol, 84 mg). Compound ***(±)-129*** was dissolved in toluene (30 mL) and DBU (0.1 eq, 0.2 mmol, 25 µL) was added at 0°C. After stirring the solution for 1.5 h, the solvent was evaporated under vacuum, the reaction mixture was poured into a saturated aqueous NaCl solution and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (5:1), affording ***(±)-130*** as colorless needles (80% based on ***(±)-129***, 1.36 mmol, 477 mg, for a total yield of 92% of ***(±)-130***).

General Data: $C_{20}H_{30}O_5$; FW: 350,21; TLC: R_f = 0.64 (hexane/EtOAc 4:1); UV (+); Vanillin: blue; Mp 110-113 °C.

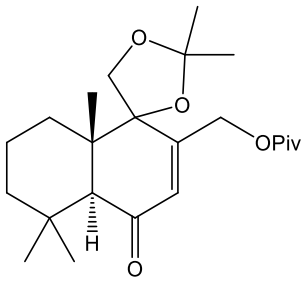
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 9.95 (s, 1H), 6.05 (s, 1H), 4.48 (q, *J* = 14.6 Hz, 2H), 2.80 (s, 1H), 1.90 (td, *J* = 17.2, 13.0, 4.5 Hz, 1H), 1.43-1.65 (m, 4H), 1.4 (d br, *J* = 13.3 Hz, 1H), 1.3 (s, 3H), 1.17-1.30 (m, 2H), 1.21 (s, 9H), 1.15 (s, 3H), 1.00-1.06 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 202.9, 198.8, 178.0, 147.1, 130.5, 81.5, 62.8, 55.5, 45.4, 42.4, 39.0, 33.7, 32.5, 32.4, 27.2, 21.8, 19.5, 17.4.

IR (neat): 3373 (br), 1723 (s),1667 (s), 1337 (m), 1271 (m), 1143 (s), 1024 (m), 790 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{20}H_{31}O_5$ $[M+H]^+$: 351.2171; found: 351.2160.

(2',2',5,5,8a-pentamethyl-4-oxo-4a,5,6,7,8,8a-hexahydro-4H-spiro [naphthalene-1,4'- [1,3] dioxolan] -2-yl) methyl pivalate:



(±)-132

To a stirred solution of ***(±)-130*** (1 eq, 0.60 mmol, 210 mg) in MeOH (20 mL) was added $NaBH_4$ (4 eq, 2.40 mmol, 91 mg) at 0°C, and stirring was continued at room temperature for 1 h. The reaction mixture was poured in water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The mixture ***(±)-131*** was used for the next reaction without further purification. To a stirred solution of the crude mixture in CH_2Cl_2 (5 mL), CSA (1.2 eq, 0.71 mmol, 166 mg) and 2,2-DMP (13 eq, 7.67 mmol, 892 µL) were added at 0°C and the stirring was continued at room temperature. After 2 h, the mixture was cooled to 0°C, saturated aqueous $NaHCO_3$ solution was added, and the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification with flash chromatography (pentane/Et_2O 10:1) yielded ***(±)-132*** (80% over two steps, 0.48 mmol, 188 mg) as a sticky oil.

General Data: $C_{23}H_{36}O_5$; FW: 392.26; TLC: R_f = 0.54 (hexane/EtOAc 5:1); UV (+); Vanillin: brown.

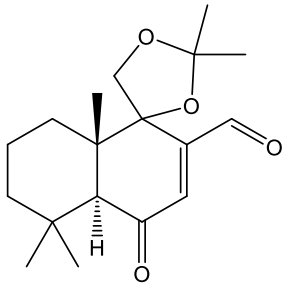
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.90 (s, 1H), 4.97 (dd, *J* = 15.8, 1.8 Hz, 1H), 4.85 (dd, *J* = 15.5, 1.34 Hz, 1H), 4.14 (d, *J* = 10.0 Hz, 1H), 4.02 (d, *J* = 10.0 Hz, 1H), 2.7 (s, 1H), 1.90 (td, *J* = 18.1, 13.7, 4.8 Hz, 1H), 1.55- 1.74 (m, 5H), 1.50 (s, 3H), 1.43 (s, 3H), 1.23 (s, 9H), 1.17 (s, 3H), 1.14 (s, 3H), 0.95 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 199.6, 178.0, 151.6, 127.2, 110.8, 85.6, 66.3, 61.8, 57.3, 43.7, 42.9, 39.0, 33.5, 32.7, 32.8, 27.9, 27.4, 26.7, 21.9, 19.6, 18.1.

IR (neat): 3726 (m), 3566 (m), 2349 (s), 2323 (s), 1745 (w), 1512 (w), 1094 (m), 608 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{37}O_5$ $[M+H]^+$: 393.2641; found: 393.2630.

2',2',5,5,8a-pentamethyl-4-oxo-4a,5,6,7,8,8a-hexahydro-4H-spiro[naphthalene-1,4'-[1,3] dioxolane]-2-carbaldehyde:



(±)-134

Compound ***(±)-132*** (1 eq, 1.53 mmol, 600 mg) was dissolved in 40 mL of MeOH and cooled to 0°C. After adding Lithium hydroxide monohydrate (1.5 eq, 2.30 mmol, 96 mg), the stirring was continued overnight at 0°C. The reaction mixture was poured in water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude ***(±)-133*** mixture was dissolved in 17 mL of CH_3CN, manganese dioxide (25 eq, 37.75 mmol, 3.28 g) was added at 0°C and the mixture was stirred for 1 h at this temperature. Filtration of the reaction mixture through a short pad of silica with EtOAc gave in 99% yield over two steps compound ***(±)-134*** (1.51 mmol, 464 mg, oil).

General Data: $C_{18}H_{26}O_4$; FW: 306.18; TLC: R_f = 0.65 (hexane/EtOAc 3:1); UV (+); Vanillin: brown.

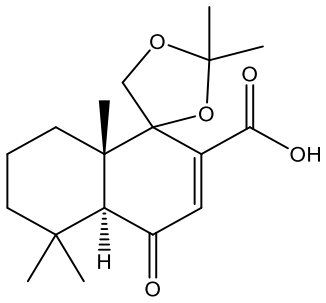
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 10.10 (s, 1H), 6.40 (s, 1H), 4.41 (d, *J* = 10.2 Hz, 1H), 4.15 (d, *J* = 10.5 Hz, 1H), 2.7 (s, 1H), 1.50-1.70 (m, 4H), 1.47 (s, 3H), 1.43 (s, 3H), 1.29-1.38 (m, 2H), 1.17 (s, 3H), 1.14 (s, 3H), 0.95 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 202.0, 199.5, 151.5, 127.1, 110.6, 85.4, 66.2, 65.8, 57.1, 43.5, 42.7, 34.1, 33.4, 27.7, 26.5, 21.6, 19.5, 17.9.

IR (neat): 3726 (m), 3566 (m), 2349 (s), 2323 (s), 1745 (w), 1512 (w), 1094 (m), 608 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{18}H_{27}O_4$ $[M+H]^+$: 307.1909; found: 307.1907.

2',2',5,5,8a-pentamethyl-4-oxo-4a,5,6,7,8,8a-hexahydro-4H-spiro [naphthalene-1,4'-[1,3] dioxolane] -2-carboxylic acid:



(±)-135

A solution of ***(±)-134*** (1 eq, 0.33 mmol, 100 mg) and acetone (5 mL) was cooled to 0°C and then the mixture of Jones reagent -(prepared with 1.3 eq, 0.43 mmol, 43 mg of CrO_3, 37 eq, 12.2 mmol, 0.66 mL of H_2SO_4 in 0.2 mL of water)- was added dropwise over a period of 20 min until an orange tint persisted in the solution. The stirring was continued for 1 h at room temperature. Then isopropyl alcohol was added to destroy excess Jones reagent, as indicated by the reappearance of a greenish solution. The reaction mixture was then extracted with Et_2O, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo yielded 105 mg (99%, 0.33 mmol) of yellow oil ***(±)-135***.

General Data: $C_{18}H_{26}O_5$; FW: 322.18; TLC: R_f = 0.10 (hexane/EtOAc 1:1); UV (+); Vanillin: brown.

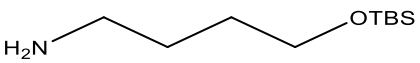
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.12 (s, 1H), 4.41 (d, *J* = 9.64 Hz, 1H), 3.97 (d, *J* = 9.68 Hz, 1H), 2.7 (s, 1H), 1.50-1.70 (m, 4H), 1.47 (s, 3H), 1.43 (s, 3H), 1.29-1.38 (m, 2H), 1.17 (s, 3H), 1.14 (s, 3H), 0.95 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 199.9, 171.5, 146.1, 130.7, 110.6, 85.0, 65.3, 57.7, 44.5, 42.6, 33.3, 32.7, 32.2, 27.6, 26.1, 21.7, 19.7, 18.0.

IR (neat): 3066 (s), 1645 (w), 1510 (w), 1094 (m), 610 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{18}H_{27}O_5$ $[M+H]^+$: 323.1878; found: 323.1890.

4-((Tert-butyldimethylsilyl) oxy) butan-1-amine:



136

To a solution of 4-Amino-1-butanol (1 eq, 2.24 mmol, 200 mg) and imidazole (3 eq, 6.72 mmol, 457 mg) in 2.5 mL of CH_2Cl_2, TBSCl (1.2 eq, 2.69 mmol, 405 mg) was added at 0°C and the reaction mixture was stirred overnight at room temperature. The mixture was poured in water and extracted with CH_2Cl_2. The organic layer was washed with a saturated solution of $NaHCO_3$ and then with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was diluted in EtOAc and the filtration through a short pad of silica with EtOAc gave after evaporation in 99% yield (2.22 mmol, 451 mg, oil) the desired compound ***136***.

General Data: $C_{10}H_{25}NOSi$; FW: 203.17.

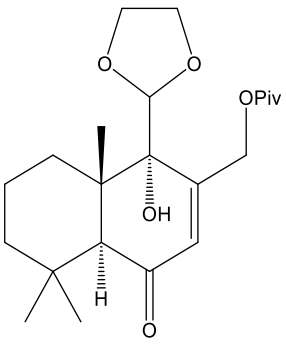
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 3.59 (t, *J* = 632 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 1.59-1.65 (m, 2H), 1.51-1.57 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 62.8, 41.0, 30.1, 27.7, 26.0, 18.4, -5.2.

IR (neat): 2929 (m), 1253 (m), 1097 (s), 833 (s), 773 (s), 662 (M) cm^{-1}.

HRMS (ESI): calculated for $C_{10}H_{26}NOSi$ $[M+H]^+$: 204.1783; found: 204.1783.

(1-(1,3-dioxolan-2-yl)-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl) methyl pivalate:



(±)-138

To a solution of ***(±)-130*** (1 eq, 1.43 mmol, 500 mg) in toluene (4 mL), PTSA (0.01 eq, 0.01 mmol, 2.4 mg) and DEG (16.5 eq, 23.60 mmol, 1.3 mL) were added and the reaction mixture was refluxed at 110 °C for 24 h. After evaporating toluene, the crude product was diluted with hexane and extracted successively with saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash

chromatography (pentane/Et_2O 4:1) to afford the protected product as ethylene glycol acetal ***(±)-138*** (70%, 1 mmol, 395 mg, light-yellow powder).

General Data: $C_{22}H_{34}O_6$; FW: 394.24; TLC: R_f = 0.3 (hexane/EtOAc 4:1); UV (+); Vanillin: blue; Mp 153-155 °C.

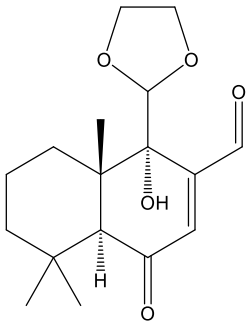
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.00 (s, 1H), 5.01 (d, *J* = 15.1 Hz, 2H), 4.58 (dd, *J* = 15.5, 1.8 Hz, 1H), 4.17 (q, *J* = 7.6 Hz, 1H), 3.83-4.00 (m, 2H), 3.70 (q, *J* = 7.6 Hz, 1H), 3.53 (s, 1H), 2.90 (s, 1H), 2.07 (td, *J* = 16.9, 12.1, 4.5 Hz, 1H), 1.46-1.70 (m, 3H), 1.29-1.44 (m, 1H), 1.22 (s, 9H), 1.20 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 200.1, 178.6, 151.1, 128.2, 103.0, 77.4, 66.4, 63.0, 62.4, 55.7, 45.2, 42.5, 39.0, 33.7, 32.3, 31.8, 27.3, 22.0, 18.1, 17.9.

IR (neat): 3314 (br), 2822 (m), 1733 (m), 1657 (s), 1151 (s), 1070 (s), 979 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{35}O_6$ $[M+H]^+$: 395.2434; found: 395.2429.

(1S)-1-(1,3-dioxolan-2-yl)-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydro-naphthalene-2-carbaldehyde:



(±)-140

Compound ***(±)-138*** (1 eq, 2.53 mmol, 1 g) was dissolved in 64 mL of MeOH and cooled to 0°C. After adding lithium hydroxide monohydrate (1.5 eq, 3.80 mmol, 160 mg), the stirring was continued overnight at 0°C. The reaction mixture was poured in water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash chromatography (pentane/Et_2O 1:2) to give free alcohol ***(±)-139*** in quantitative yield (2.50 mmol, 777 mg). The allylic alcohol was dissolved in 30 mL of CH_3CN and oxidized adding manganese dioxide (25 eq, 62.50 mmol, 5.43 g) at 0°C. The stirring was continued for 2 h at this temperature. Filtration of the reaction mixture

through a short pad of silica with EtOAc gave in 99% yield over two steps compound ***(±)-140*** (2.50 mmol, 772 mg, oil).

General Data: $C_{17}H_{24}O_5$; FW: 308.16; TLC: R_f = 0.7 (hexane/EtOAc 1:1); UV (+); Vanillin: green.

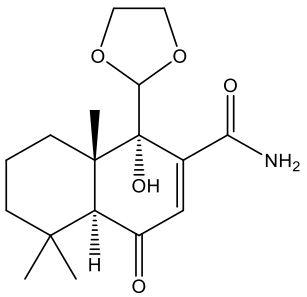
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.83 (s, 1H), 6.24 (s, 1H), 5.10 (s, 1H), 4.10 (td, *J* = 15.7, 12.0, 4.2 Hz, 2H), 3.95 (td, *J* = 15.76, 12.3, 4.4 Hz, 2H), 3.73 (s, 1H), 2.84 (s, 1H), 2.07 (td, *J* = 17.8, 13.1, 4.9 Hz, 1H), 1.50-1.67 (m, 1H), 1.46 (d br, *J* = 13.8 Hz, 1H), 1.36 (d br, *J* = 12.6 Hz, 1H), 1.18-1.25 (m, 1H), 1.21 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 200.5, 193.4, 149.5, 133.1, 102.0, 77.1, 66.7, 64.1, 56.8, 44.4, 42.4, 33.4, 32.4, 31.2, 21.9, 18.2, 17.7.

IR (neat): 3489 (br), 2922 (s), 2853 (m), 2322 (w), 1673 (s), 1462 (m), 1152 (m), 1079 (m), 971 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{25}O_5$ $[M+H]^+$: 309.1702; found: 309.1690.

1-(1,3-dioxolan-2-yl)-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide:



(±)-142

$NaClO_2$ (2 eq, 3.24 mmol, 296 mg) and NaH_2PO_4 (4 eq, 6.50 mmol, 1.01 g) were dissolved in water (2 mL) at 0 °C and stirred for 1 h. Compound ***(±)-140*** (1 eq, 1.62 mmol, 500 mg) was dissolved in *t*-BuOH (7 mL) and 2-methyl-2-butene (8.1 eq, 13.12 mmol, 1.4 mL). The system was stirred for half an hour, then the aqueous $NaClO_2$/ NaH_2PO_4 aqueous was added slowly over 15 min at 0 °C. After the reaction was kept for 2 h at this temperature, saturated NH_4Cl was poured into the system. The aqueous layer was extracted with Et_2O, then the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under

reduced pressure to afford in quantitative yield the oxidized product ***(±)-141*** (1.60 mmol, 520 mg).

Carboxylic acid ***(±)-141*** was dissolved in THF (20 mL), cooled to 0 °C and ethyl chloroformate (1.3 eq, 2.08 mmol, 198 µL) was added dropwise, followed by NEt_3 (1.4 eq, 2.24 mmol, 312 µL). The mixture was stirred for 30 min at 0 °C and then 25% aqueous NH_4OH solution (0.7 mL) was added. The mixture was stirred for 30 min at 0 °C and for 1 h at room temperature. The solution was washed with H_2O and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford in 99% yield the amide as colorless oil ***(±)-142*** (1.58 mmol, 519 mg), which was used for the next step without further purification.

General Data: $C_{17}H_{25}NO_5$; FW: 323.17; TLC: R_f = 0.1 (hexane/EtOAc 1:1); UV (+); Vanillin: brown.

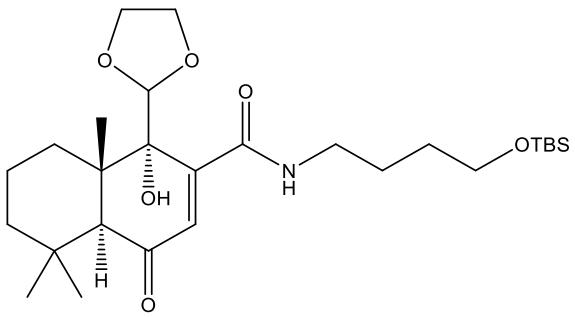
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.20 (s, 1H), 5.10 (s, 1H), 4.07-4.10 (m, 2H), 3.80-3.95 (m, 2H), 3.73 (s, 1H), 2.82 (s, 1H), 2.08 (td, *J* = 17.7, 12.9, 4.8 Hz, 1H), 1.49-1.66 (m, 1H), 1.47 (d br, *J* = 13.6Hz, 1H), 1.37 (d br, *J* = 12.6 Hz, 1H), 1.17-1.25 (m, 1H), 1.21 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 198.7, 168.0, 155.4, 143.9, 135.1, 102.3, 85.9, 66.2, 64.6, 56.7, 48.9, 42.2, 34.2, 33.0, 21.6, 18.8, 17.9.

IR (neat): 3396 (br), 2821 (m), 1746 (m), 1663 (s), 1464 (w), 1251 (s), 1014 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{26}NO_5$ $[M+H]^+$: 324.1811; found: 324.1804.

N-(4-((tert-butyldimethylsilyl) oxy) butyl)-1-(1,3-dioxolan-2-yl)-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene-2-carboxamide:



(±)-143

Compound ***(±)-141*** (1 eq, 0.52 mmol, 170 mg) was dissolved in DMF (13 mL) and cooled to 0°C. DIPEA (5 eq, 2.60 mmol, 453 µL), HATU (1.5 eq, 0.80 mmol, 296 mg), and ***136*** (1 eq, 0.52 mmol, 106 mg) were added and the reaction mixture was stirred at room temperature for 3 h. The solution was poured in the H_2O and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification with flash chromatography (pentane/Et_2O 2:1) afforded ***(±)-143*** (80%, 0.42 mmol, 214 mg, yellow powder).

General Data: $C_{27}H_{47}NO_6Si$; FW: 509.32; TLC: R_f = 0.7 (hexane/EtOAc 1:1); UV (+); Vanillin: brown; Mp 153-155 °C.

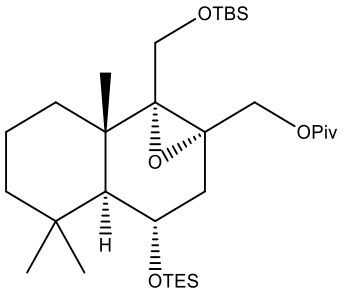
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.87 (s, 1H), 4.99 (s, 1H), 4.60 (s, 1H), 3.92 (q, *J* = 6.2 Hz, 1H), 3.76-3.89 (m, 3H), 3.60 (t, *J* = 5.8 Hz, 1H), 3.31-3.38 (m, 1H), 3.16- 3.24 (m, 1H), 2.85 (s, 1H), 1.18-1.33 (m, 11H), 1.21 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H), 0.84 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 200.8, 170.0, 148.2, 128.8, 103.4, 77.7, 66.3, 66.0, 64.1, 62.7, 56.5, 44.2, 42.4, 39.3, 33.5, 32.2, 30.9, 30.2, 26.1, 22.1, 18.5, 18.0, 17.7, -5.1, -5.2.

IR (neat): 3397 (br), 2821 (m), 2843 (m), 1739 (m), 1664 (s), 1462 (m), 1251 (s), 1014 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{48}NO_7Si$ $[M+H]^+$: 510.3251; found: 510.3250.

(7b-(((tert-butyldimethylsilyl) oxy) methyl) -4,4,7a-trimethyl-3-((triethylsilyl) oxy) octahydronaphtho[1,2-b] oxiran-1a(2H)-yl) methyl pivalate:



(±)-146

To a stirred solution of ***(±)-127*** (1 eq, 0.874 mmol, 410 mg) in dry CH_2Cl_2 (20 mL) were added TBSOTf (3 eq, 2.62 mmol, 0.6 mL) and 2,6-lutidine (6 eq, 5.24 mmol, 0.61 mL), and stirring was continued at 0°C for 1.5 h. The reaction mixture was poured into a saturated NaCl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4

and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (20:1) gave ***(±)-146*** (90%, 0.79 mmol, 459 mg, colorless needles).

General Data: $C_{32}H_{62}O_5Si_2$; FW: 582.41; TLC: R_f = 0.9 (hexane//EtOAc 7:1); UV (-); Vanillin: black; Mp 90-93 °C.

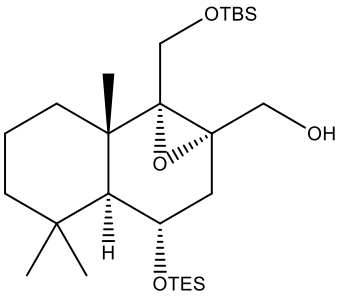
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.40 (d, *J* = 12.3 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 3.93-4.02 (m, 2H), 3.41 (d, *J* = 11.5 Hz, 1H), 2.18-2.28 (m, 1H), 1.99 (dd, *J* = 15.3, 8.4 Hz, 1H), 1.71 (d br, *J* = 12.0 Hz, 1H), 1.45-1.58 (m, 4H), 1.27-1.36 (m, 2H), 1.24 (s, 9H), 1.19 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H),0.96 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.62 (q, *J* = 7.7 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 178.5, 71.1, 68.7, 67.4, 62.9, 62.7, 48.6, 43.5, 39.1, 39.0, 37.5, 36.3, 35.8, 33.2, 27.4, 26.0, 22.6, 19.0, 18.4, 18.2, 7.2, 5.7, -5.5, -5.6.

IR (neat): 2954 (m), 2926 (m), 1724 (m), 1463 (m), 1166 (m), 1080 (s), 835 (s), 724 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{32}H_{62}O_5Si_2Na[M+Na]^+$: 605.4033; found: 605.4029.

(7b-(((tert-butyldimethylsilyl) oxy) methyl) -4,4,7a-trimethyl-3-((triethylsilyl)oxy) octahydronaphtho[1,2-b] oxiran-1a(2H)-yl) methanol:



(±)-147

To a solution of ***(±)-146*** (1 eq, 1.37 mmol, 800 mg) in dry THF (20 mL) was added 1 M DIBAL-H in hexane (4.0 eq, 5.48 mmol, 5.5 mL) dropwise under argon at 0°C, and the mixture was stirred at 0°C for 3 h. The reaction mixture was quenched with MeOH, poured into a saturated aqueous Rochelle's salt solution and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (25:1), yielding ***(±)-147*** (70%, 0.96 mmol, 479 mg) as oil.

General Data: $C_{27}H_{54}O_4Si_2$; FW: 498.36; TLC: R_f = 0.65 (hexane/EtOAc 7:1); UV (+); Vanillin: brown.

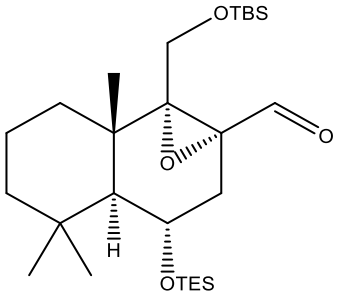
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.24 (d, *J* = 11.3 Hz, 1H), 3.91-4.00 (m, 1H), 3.31-3.59 (m, 2H), 2.88 (d br, *J* = 8.9 Hz, 1H), 2.55 (dd, *J* = 15.5, 7.5 Hz, 1H), 1.84 (dd, *J* = 14.6, 8.9 Hz, 1H), 1.40-1.58 (m, 5H), 1.27-1.36 (m, 2H), 1.15 (s, 3H), 1.08 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 12H), 0.88 (s, 9H), 0.63 (q, *J* = 7.7 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 71.2, 67.7, 66.3, 64.9, 64.2, 48.9, 43.5, 38.8, 38.0, 36.3, 36.1, 33.3, 26.0, 22.6, 19.0, 18.4, 18.3, 7.2, 5.7, -5.4. -5.7.

IR (neat): 3321 (br), 2952 (m), 2926 (m), 2857 (m), 1463 (m), 1255 (m) 1166 (m), 1083 (s), 1043 (s), 836 (s), 740 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{58}NO_4Si_2[M+NH_4]^+$: 516.3905; found: 516.3906.

7b-(((tert-butyldimethylsilyl) oxy) methyl)-4,4,7a-trimethyl-3-((triethylsilyl) oxy) octahydronaphtho[1,2-b] oxirane-1a(2H)-carbaldehyde:



(±)-148

To a stirred solution of ***(±)-147*** (1 eq, 1.84 mmol, 920 mg) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (2.3 eq, 4.23 mmol, 1.80 g) at 0°C, and stirring was continued at room temperature overnight. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (25:1) gave the corresponding aldehyde ***(±)-148*** (96%, 1.77 mmol, 831 mg, sticky oil).

General Data: $C_{27}H_{52}O_4Si_2$; FW: 496.34; TLC: R_f = 0.9 (hexane/EtOAc 7:1); UV (+); Vanillin: brown.

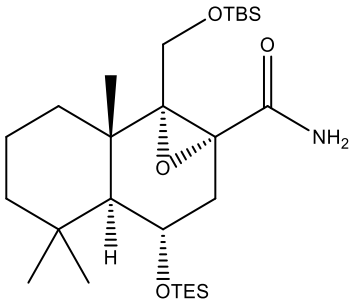
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 9.30 (s, 1H), 3.88-4.00 (m, 2H), 3.71 (q, *J* = 12.1 Hz, 1H), 2.81 (q, *J* = 15.3, 7.2 Hz, 1H), 2.10-2.28 (m, 1H), 1.40-1.60 (m, 5H), 1.27-1.36 (m, 2H), 1.15 (s, 3H), 1.08 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 12H), 0.88 (s, 9H), 0.63 (q, *J* = 7.7 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 199.1, 75.2, 67.3, 66.9, 61.0, 57.0, 43.2, 38.9, 37.7, 36.2, 36.0, 33.1, 25.9, 22.4, 18.8, 18.3, 18.2, 7.1, 5.5, -5.8, -5.6.

IR (neat): 2952 (m), 2926 (m), 2856 (m), 1715 (w), 1607 (w), 1363 (w), 1254 (m), 1086 (s), 1006 (m), 835 (s), 740 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{53}O_4Si_2$ $[M+H]^+$: 497.3482; found: 497.3490.

7b-(((tert-butyldimethylsilyl) oxy) methyl)-4,4,7a-trimethyl-3-((triethylsilyl) oxy) octahydronaphtho[1,2-b] oxirane-1a(2H)-carboxamide:



(±)-150

$NaClO_2$ (2 eq, 2.42 mmol, 221 mg) and NaH_2PO_4 (4 eq, 4.84 mmol, 755 mg) were dissolved in water (1.5 mL) at 0 °C and stirred for 1 h. Compound ***(±)-148*** (1 eq, 1.21 mmol, 600 mg) was dissolved in *t*-BuOH 5 mL) and 2-methyl-2-butene (8.1 eq, 9.80 mmol, 1 mL). The system was stirred for half an hour, then the aqueous $NaClO_2$/ NaH_2PO_4 aqueous was added slowly over 15 min at 0 °C. After the reaction was kept for 2 h at this temperature, saturated NH_4Cl was poured into the system. The aqueous layer was extracted with Et_2O, then the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford in quantitative yield the oxidized product ***(±)-149*** (1.20 mmol, 614 mg).

Carboxylic acid ***(±)-149*** was dissolved in THF (20 mL), cooled to 0 °C and ethyl chloroformate (1.3 eq, 1.56 mmol, 150 µL) was added dropwise, followed by NEt_3 (1.4 eq, 1.68 mmol, 230 µL). The mixture was stirred for 30 min at 0 °C and then 25% aqueous NH_4OH solution (0.7 mL) was added. The mixture was stirred for 30 min at 0 °C and for 1 h at room temperature. The solution

was washed with H_2O and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to afford in 99% yield the amide as colorless oil ***(±)-150*** (1.20 mmol, 613 mg), which was used for the next step without further purification.

General Data: $C_{27}H_{53}NO_4Si_2$; FW: 511.35; TLC: R_f = 0.4 (hexane/EtOAc 7:1); UV (-); Vanillin: brown; Mp 170-173 °C.

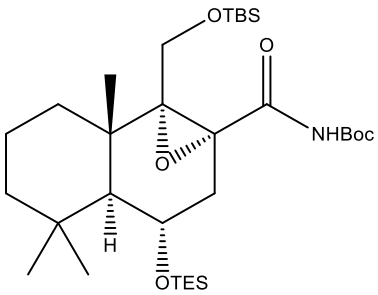
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.29 (s br, 1H), 5.61 (s br, 1H), 3.98-4.06 (m, 1H), 3.77 (s, 1H), 2.86 (q, *J* = 15.0, 6.3 Hz, 1H), 1.86 (q, *J* = 14.6, 6.8 Hz, 1H), 1.80 (d br, *J* = 13.6 Hz, 1H), 1.42-1.59 (m, 5H), 1.23-1.36 (m, 2H), 1.18 (s, 3H), 1.06 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 12H), 0.86 (s, 9H), 0.62 (q, *J* = 7.7 Hz, 6H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 172.3, 72.4, 66.9, 65.6, 60.7, 49.7, 43.4, 38.8, 36.4, 36.1, 35.6, 33.4, 26.0, 22.6, 19.5, 18.4, 18.3, 7.2, 5.6, -5.65, -5.4.

IR (neat): 3415 (s), 2926 (m), 2856 (m), 2322 (w),1671 (s), 1463 (m), 1081 (s), 835 (s), 721 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{57}N_2O_4Si_2$ $[M+NH_4]^+$: 529.3857; found: 529.3853.

tert-butyl (7b-(((tert-butyldimethylsilyl) oxy) methyl)-4,4,7a-trimethyl-3-((triethylsilyl)oxy) decahydronaphtho[1,2-b] oxirane-1a-carbonyl) carbamate:



(±)-151

To a solution of ***(±)-150*** (1 eq, 0.88 mmol, 450 mg) in dry CH_2Cl_2 (2 mL) was added DMAP (0.1 eq, 0.088 mmol, 11 mg), NEt_3 (2 eq, 1.758 mmol, 0.25 mL) and Boc_2O (2 eq, 1.758 mmol, 0.40 mL) at 0°C, and stirring was continued at room temperature for 1 h. The reaction mixture was poured into a saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was

washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (40:1) afforded ***(±)-151*** (80%, 0.703 mmol, 430.4 mg) as a sticky oil.

General Data: $C_{32}H_{61}NO_6Si_2$; FW: 611.40; TLC: R_f = 0.9 (hexane/EtOAc 8:1); UV (+); Vanillin: brown.

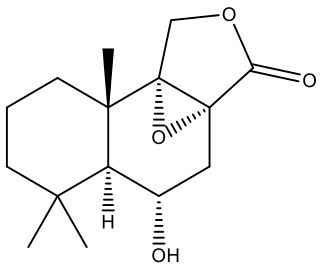
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.03- 4.15 (m, 1H), 3.84 (d, *J* = 12.5 Hz, 1H), 3.70 (d, *J* = 12.0 Hz, 1H), 2.39 (dd, *J* = 14.5, 6.6 Hz, 1H), 1.98 (dd, *J* = 14.5, 9.2 Hz, 1H), 1.83 (d br, *J* = 12.7 Hz, 1H), 1.53 (s, 9H), 1.33-1.47 (m, 4H), 1.29 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.87 (s, 9H), 0.60 (q, *J* = 7.7 Hz, 6H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.5, 149.2, 84.5, 73.0, 67.4, 66.3, 61.3, 48.9, 43.5, 39.7, 38.2, 36.6, 36.4, 33.2, 27.8, 26.2, 22.7, 18.9, 18.6, 18.3, 7.2, 5.6, -5.4, -5.5.

IR (neat): 2953 (m), 2928 (m), 2857 (m), 1782 (m), 1649 (s), 1251 (s), 1119 (s), 837 (s), 739 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{32}H_{61}NO_6Si_2Na$ [*M*+Na]$^+$: 634.3934; found: 634.3938.

5-hydroxy-6,6,9a-trimethyloctahydro-1H,3H-3a,9b-epoxynaphtho[1,2-c] furan-3-one:



(±)-152

Procedure	***reagent***	***solvent***	***conditions***	***time***	***Result***
Method A	TBAF (1M)	THF	0°C	3 h	Cleavage of silyl-groups and closing of the ring; yield: 40%.
Method B	HF•Py	THF/Py	0°C-rt	ON	Cleavage of silyl-groups and closing of the ring; yield: 35%.

Method A*:* To a solution of ***(±)-151*** (1 eq, 0.08 mmol, 50 mg) in THF (2 mL) at 0°C, TBAF (1M in THF, 1 eq, 0.08 mmol, 80 µL) was added and the stirring was continued at the same temperature. After 3 h, the reaction mixture was poured into a saturated solution of NH_4Cl

and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified with flash chromatography (pentane/Et_2O 1:1) to afford ***(±)-152*** (40%, 0.032 mmol, 8.5 mg) as sticky oil.

Method B: A solution of ***(±)-151*** (1 eq, 0.08 mmol, 50 mg) in THF (0.3 mL) and pyridine (0.1 mL) was cooled at 0°C and 60 µL of HF•Py complex (~70%) was added dropwise. The reaction was stirred for 30 min at the same temperature and then was poured into a saturated solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, then dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography. Elution pentane/Et_2O (1:1) afforded ***(±)-152*** (35%, 0.028 mmol, 7.5 mg, sticky oil).

General Data: $C_{15}H_{22}O_4$; FW: 266.15; TLC: R_f = 0.2 (hexane/EtOAc 3:1); UV (-); Vanillin: brown.

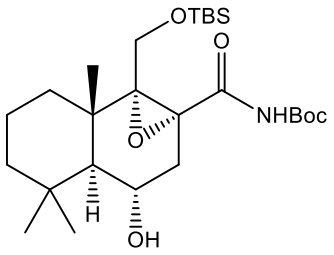
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.31 (q, *J* = 9.9 Hz, 2H), 3.92-3.97 (m, 1H), 2.66 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.11 (dd, *J* = 15.9, 7.0 Hz, 1H), 1.61 (d, *J* = 10.3 Hz, 1H), 1.50-1.55 (m, 2H), 1.41-1.49 (m, 3H), 1.24-1.30 (m, 2H), 1.22 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 172.1, 72.7, 67.1, 66.1, 58.2, 50.4, 43.0, 36.3, 36.1, 36.0, 33.3, 30.5, 22.4, 19.4, 18.0.

IR (neat): 3526 (br), 2980 (m), 1705 (w), 1072 (w), 950 cm^{-1}.

HRMS (ESI): calculated for $C_{15}H_{23}O_4$ [*M*+H]$^+$: 267.1596; found: 267.1580.

tert-butyl (7b-(((tert-butyldimethylsilyl) oxy) methyl)-3-hydroxy-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxirane-1a-carbonyl) carbamate:



(±)-152b

Procedure	Reagent	Solvent	Conditions	Time	Result
Method A	PPTS	ETOH	0°C-rt	24 h	Cleavage of TES-group; yield: 50%.
Method B	CSA	CH_2Cl_2/ MeOH	0°C-rt	24 h	Cleavage of TES-group; yield: 40%.

Method A: To a solution of ***(±)-151*** (1 eq, 0.08 mmol, 50 mg) in EtOH (2.5 mL) was added PPTS (0.2 eq, 0.02 mmol, 4 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (9:1) gave ***(±)-152b*** (50%, 0.04 mmol, 20 mg, sticky oil).

Method B: To a solution of ***(±)-151*** (1 eq, 0.08 mmol, 50 mg) in CH_2Cl_2/MeOH (2 mL/ 2 mL) was added CSA (0.5 eq, 0.025 mmol, 6 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 9:1) to afford ***(±)-152b*** (40%, 0.032 mmol, 16 mg, sticky oil).

General Data: $C_{26}H_{47}NO_6Si$; FW: 497,32; TLC: R_f = 0.5 (hexane/EtOAc 8:1); UV (+); Vanillin: brown.

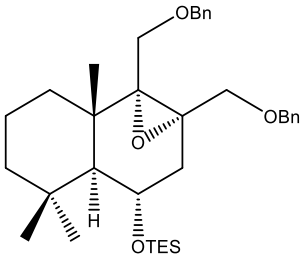
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.25-4.40 (m, 1H), 3.91 (d, *J* = 12.5 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 2.68 (dd, *J* = 14.4, 6.7 Hz, 1H), 2.36 (dd, *J* = 14.6, 9.4 Hz, 1H), 1.83 (d br, *J* = 12.7 Hz, 1H), 1.52 (s, 9H), 1.33-1.47 (m, 4H), 1.29 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.9, 149.5, 85.0, 72.6, 66.0, 61.0, 55.6, 53.6, 42.1, 38.4, 38.4, 36.6, 34.2, 34.1, 27.8, 26.1, 22.6, 18.7, 18.6, 18.5, -5.4, -5.5.

IR (neat): 3425 (br), 2950 (m), 2926 (m), 1784 (m), 1648 (s), 1250 (s), 1117 (s), 837 (s), 739 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{47}NO_6SiNa$ $[M+Na]^+$: 520.3070; found: 520.3076.

((1a,7b-bis((benzyloxy)methyl)-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxiran-3-yl) oxy) triethylsilane:



(±)-153

To a stirred suspension of NaH (3 eq, 3.90 mmol, 94 mg, 60 % dispersion in mineral oil) in DMF (5 mL) at 0 °C was added dropwise a solution of ***(±)-126*** (1 eq, 1.30 mmol, 500 mg) in DMF (20 mL) dropwise. Effervescence was observed and after stirring for 30 min BnBr (2.5eq, 3.25 mmol, 320 µL) was added dropwise. After stirring at room temperature for 5 h, TLC indicated complete consumption of starting material. The mixture was added to an Et_2O/H_2O bilayer and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (20:1), yielding the desired compound ***(±)-153*** in 99% yield (3.86 mmol, 2.18 g) as an oil.

General Data: $C_{35}H_{52}O_4Si$; FW: 564.36; TLC: R_f = 0.75 (hexane/EtOAc 5:1); UV (+); Vanillin: black.

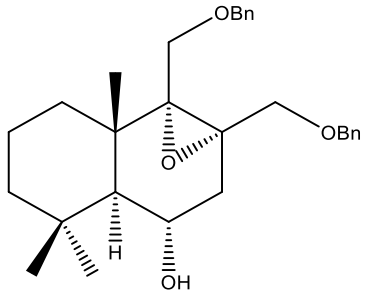
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.26-7.34 (m, 10H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 3.34 Hz, 1H), 4.43 (d, *J* = 3.53 Hz, 1H), 4.38 (d, *J* = 12.1 Hz, 1H), 3.95-4.00 (m, 1H), 3.82 (d, *J* = 11.4 Hz, 1H), 3.72 (d, *J* = 10.9 Hz, 1H), 3.37 (d, *J* = 11.2 Hz, 1H), 3.31 (d, *J* = 10.8 Hz, 1H), 2.43 (dd, *J* = 15.4, 7.0 Hz, 1H), 1.99 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.70 (d br, *J* = 13.3 Hz, 1H), 1.50-1.58 (m, 2H), 1.41- 1.47 (m, 1H), 1.24-1.36 (m, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.97 (t, *J* = 7.63 Hz, 9H), 0.62 (q, *J* = 8.1 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 138.5, 137.9, 128.5, 128.4, 128.0, 127.8, 127.6, 73.4, 73.1, 72.9, 69.5, 68.8, 67.6, 63.9, 49.0, 43.5, 38.9, 37.4, 36.2, 35.8, 33.3, 22.6, 18.7, 18.4, 7.3, 5.7.

IR (neat): 2924 (m), 1726 (w), 1455 (m), 1361 (w), 1084 (s), 1006 (m), 734 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{35}H_{53}O_4Si$ $[M+H]^+$: 565.3713; found: 565.3698.

1a,7b-bis((benzyloxy)methyl)-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxiran-3-ol:



(±)-154

To a solution of ***(±)-153*** (1 eq, 2.66 mmol, 1.50 g) in EtOH (80 mL) was added PPTS (0.1 eq, 0.27 mmol, 68 mg) at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (3:1) gave ***(±)-154*** (95%, 2.53 mmol, 1.14 g, oil).

General Data: $C_{29}H_{38}O_4$; FW: 450.28; TLC: R_f = 0.3 (hexane/EtOAc 5:1); UV (+); Vanillin: black.

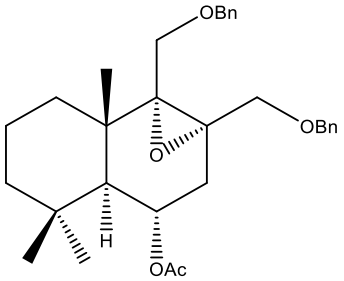
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.26-7.34 (m, 10H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 3.33 Hz, 1H), 4.43 (d, *J* = 3.53 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 3.71-3.76 (m, 1H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.69 (d, *J* = 10.7 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.37 (d, *J* = 10.8 Hz, 1H), 2.58 (dd, *J* = 15.4, 7.0 Hz, 1H), 1.99 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.84 (d br, *J* = 13.3 Hz, 1H), 1.50-1.58 (m, 2H), 1.41-1.47 (m, 1H), 1.24-1.36 (m, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 138.2, 137.9, 128.5, 128.4, 127.8, 127.7, 127.6, 73.5, 73.1, 71.5, 68.6, 68.5, 66.4, 63.8, 55.3, 42.2, 38.0, 36.1, 35.8, 34.4, 34.0, 22.5, 18.9, 18.7.

IR (neat):) 3459 (br), 2926 (m), 1453 (m), 1074 /s), 750 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{29}H_{39}O_4$ $[M+H]^+$: 451.2848; found: 451.2844.

1a,7b-bis((benzyloxy)methyl)-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxiran-3-yl acetate:



(±)-155

To a solution of ***(±)-154*** (1 eq, 2.66 mmol, 1.2 g) in CH_2Cl_2 (15 mL) were added at room temperature DMAP (0.1 eq, 0.27 mmol, 33 mg), pyridine (4.5 eq, 12 mmol, 1 mL) and Ac_2O (3 eq, 8.0 mmol, 756 µL) and the mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into a 1M HCl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 4:1), yielding ***(±)-155*** in 99% yield (2.63 mmol, 1.3 g) as oil.

General Data: $C_{31}H_{40}O_5$; FW: 492.29; TLC: R_f = 0.45 (hexane/EtOAc 5:1); UV (+); Vanillin: black.

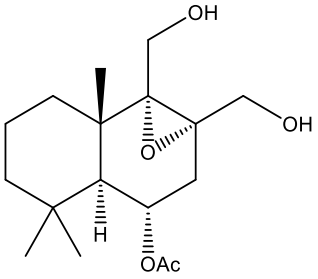
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.27-7.34 (m, 10H), 4.99-5.03 (m, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 3.30 Hz, 1H), 4.43 (d, *J* = 3.53 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 3.85 (d, *J* = 11.2 Hz, 1H), 3.67 (d, *J* = 10.6 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.37 (d, *J* = 10.7 Hz, 1H), 2.58 (dd, *J* = 15.4, 7.0 Hz, 1H), 2.22 (s, 3H), 1.99 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.84 (d br, *J* = 13.3 Hz, 1H), 1.50-1.58 (m, 2H), 1.41- 1.47 (m, 1H), 1.24-1.36 (m, 3H), 1.15 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.8, 138.2, 137.9, 128.5, 127.8, 127.8, 127.7, 127.7, 73.4, 73.1, 72.1, 69.9, 68.8, 67.8, 63.3, 48.1, 42.3, 38.0, 35.7, 34.5, 33.7, 32.8, 22.5, 22.0, 18.8, 18.5.

IR (neat): 2926 (m), 1728 (s), 1365 (m), 1246 (s), 1074 (m), 750 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{41}O_5$ $[M+H]^+$: 493.2954; found: 493.2948.

1a,7b-bis(hydroxymethyl)-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxiran-3-yl acetate:



(±)-156

10% Pd/C (0.6 eq, 0.462 mmol, 50 mg) was added to a solution of ***(±)-155*** (1 eq, 0.77 mmol, 380 mg) in MeOH (8 mL). After two vacuum/H_2 cycles to remove air from the reaction flask, the reaction mixture was stirred under hydrogen atmosphere at room temperature for 24 h. Filtration through a Celite pad to remove catalyst and evaporation of solvent gave ***(±)-156*** in quantitative yield (0.760 mmol, 238 mg, sticky oil).

General Data: $C_{17}H_{28}O_5$; FW: 312.19; TLC: R_f = 0.1 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

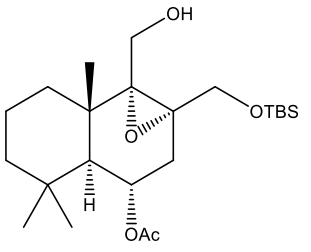
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.95-5.05 (m, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 3.59-3.78 (m, 3H), 2.71 (dd, *J* = 15.4, 7.0 Hz, 1H), 2.03 (s, 3H), 1.88 (dd, *J* = 14.8, 7.0 Hz, 1H), 1.79 (d br, *J* = 13.3 Hz, 1H), 1.45-1.66 (m, 4H), 1.24- 1.44 (m, 4H), 1.20 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.8, 70.5, 68.8, 66.0, 65.6, 64.4, 47.5, 42.5, 38.1, 35.5, 35.1, 33.5, 33.4, 22.5, 21.9, 18.7, 18.3.

IR (neat): 3433 (br), 2927 (m), 1714 (s), 1245 (s), 1204 (s), 753 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_5$ $[M+H]^+$: 313.2015; found: 313.2000.

1a-(((tert-butyldimethylsilyl) oxy) methyl)-7b-(hydroxymethyl)-4,4,7a-trimethyldecahydronaphtho[1,2-b] oxiran-3-yl acetate:



(±)-157

To a stirred solution of ***(±)-156*** (1 eq, 0.64 mmol, 200 g) in DMF (7 mL) was added imidazole (4 eq, 2.56 mmol, 174 mg) at 0°C. After the reaction mixture has been stirred at 0°C for 10 min, TBSCl (1.3 eq, 0.83 mmol, 125 mg) was added portion wise at 0°C. The reaction mixture was allowed to warm to 20°C. After 1 h, H_2O and Et_2O were added and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Elution with pentane/Et_2O (6:1) afforded ***(±)-157*** (80%, 0.51 mmol, 218.5 mg, colorless oil) together with a 10% yield (0.06 mmol, 34 mg) of the di-TBS product.

General Data: $C_{23}H_{42}O_5Si$; FW: 426.28; TLC: R_f = 0.55 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

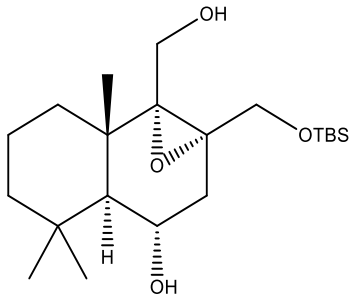
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.96-5.01 (m, 1H), 3.89-3.96 (m, 1H), 3.59-3.78 (m, 3H), 2.70 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.57 (s br, 1H), 2.03 (s, 3H), 1.87 (dd, *J* = 14.7, 7.1 Hz, 1H), 1.45-1.66 (m, 4H), 1.24- 1.44 (m, 2H), 1.19 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.8, 70.1, 68.9, 66.3, 64.4, 60.6, 47.9, 42.4, 37.8, 35.6, 34.7, 33.7, 33.3, 25.9, 22.5, 22.0, 18.8, 18.4, 18.2, -5.3, -5.4.

IR (neat): 3505 (br), 2929 (m), 1732 (m), 1465 (w), 1245 (s), 1026 (m), 836 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{43}O_5Si$ $[M+H]^+$: 427.2880; found: 427.2875.

1a-(((tert-butyldimethylsilyl) oxy) methyl)-7b-(hydroxymethyl)-4,4,7a trimethyldecahydronaphtho[1,2-b] oxiran-3-ol:



(±)-158

To a solution of ***(±)-157*** (1 eq, 0.70 mmol, 300 g) in dry THF (9 mL) was added 1.0 M DIBAL-H in hexane (2.10 mmol, 2.10 mL) dropwise under argon at 0°C, and the mixture was stirred at 0°C for 3 h. The reaction mixture was quenched with MeOH, poured into a saturated aqueous Rochelle's salt solution and extracted with Et_2O. The organic layer was washed with brine,

dried over anhydrous Na_2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (5:1) and yielding ***(±)-158*** (80%, 0.56 mmol, 215 mg) as oil.

General Data: $C_{21}H_{40}O_4Si$; FW: 384.27; TLC: R_f = 0.4 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

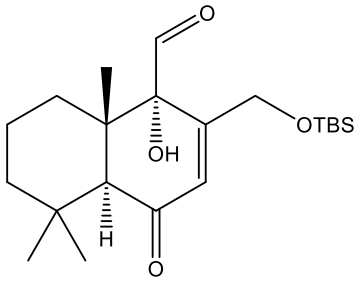
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 3.95 (d, *J* = 12.7 Hz, 1H), 3.65-3.80 (m, 4H), 2.58 (dd, *J*= 15.6, 7.5 Hz, 1H), 1.97 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.91 (d br, *J* = 12.7 Hz, 1H), 1.45-1.66 (m, 4H), 1.24-1.44 (m, 2H), 1.16 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 70.8, 66.6, 66.4, 66.0, 53.9, 42.5, 38.0, 36.9, 36.0, 34.9, 34.3, 33.9, 25.9, 22.5, 18.8, 18.6, 18.2, -5.3, -5.4.

IR (neat): 3440 (br), 2925 (s), 1462 (m), 1255 (m), 1053 (m), 838 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{41}O_4Si$ $[M+H]^+$: 385.2774; found: 385.2765.

2-(((tert-butyldimethylsilyl) oxy) methyl)-1-hydroxy-5,5,8a-trimethyl-4-oxo-1,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde:



(±)-160

To a stirred solution of ***(±)-158*** (1 eq, 1.43 mmol, 550 g) in CH_2Cl_2 (25 mL) was added Dess-Martin periodinane (4.6 eq, 6.58 mmol, 2.79 mg) at 0°C, and stirring was continued at room temperature for 2.5 h. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (10:1) gave the corresponding ketoaldehyde ***(±)-159*** (80%, 1.14 mmol, 435 mg) and ***(±)-160*** (10%, 0.14 mmol, 54 mg). Compound ***(±)-159*** was dissolved in toluene (25 mL) and DBU (0.1 eq, 0.13 mmol, 21 µL) was added at 0°C. After stirring the solution for 1 h, the reaction mixture was poured into a saturated aqueous NaCl solution and extracted with Et_2O. The organic layer was washed with

brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography using pentane/Et_2O (8:1), yielding ***(±)-160*** as colorless needles (80% based on ***(±)-159***, 0.92 mmol, 350 mg, for a total yield of 90% of ***(±)-160***).

General Data: $C_{21}H_{36}O_4Si$; FW: 380.24; TLC: R_f = 0.78 (hexane/EtOAc 4:1); UV (-); Vanillin: green; Mp 128-130 °C.

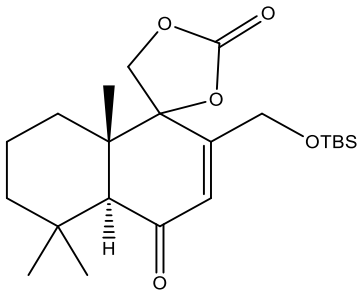
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 9.90 (s, 1H), 5.95 (s, 1H), 4.17-4.19 (m, 2H), 2.8 (s, 1H), 1.46-1.64 (m, 5H), 1.33-1.38 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 202.7, 199.7, 151.4, 128.7, 80.7, 63.4, 55.6, 45.2, 42.5, 33.8, 32.5, 32.4, 25.9, 21.9, 19.3, 18.4, 17.5, -5.5, -5.6.

IR (neat): 3372 (br), 2925 (m), 2322 (w), 1712 (m), 1662 (s), 1106 (m), 836 (s), 784 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{37}O_4Si$ $[M+H]^+$: 381.2461; found: 381.2450.

2-(((tert-butyldimethylsilyl) oxy) methyl)-5,5,8a-trimethyl-4a,5,6,7,8,8a-hexahydro-4H-spiro[naphthalene-1,4'-[1,3] dioxolane]-2',4-dione:



(±)-162

To a stirred solution of ***(±)-160*** (1 eq, 0.66 mmol, 250 mg) in MeOH (16 mL) was added $NaBH_4$ (4 eq, 2.64 mmol, 100 mg) at 0°C, and stirring was continued at room temperature for 1 h. The reaction mixture was poured in water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue (crude ***(±)-161*** was taken up in toluene (8 mL), CDI (1.6 eq, 1.04 mmol, 169 mg) was added and the mixture was stirred at reflux. After 2 h, the solvent was evaporated and crystallization in hexane afforded ***(±)-162*** in 70 % yield over two steps (0.46 mmol, 189 mg, yellow powder).

General Data: $C_{22}H_{36}O_4Si$; FW: 408.23; TLC: R_f = 0.45 (hexane/EtOAc 4:1); UV (+); Vanillin: blue; Mp 130-135 °C.

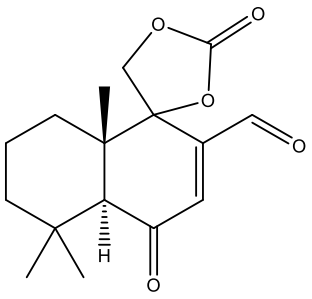
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.09 (s, 1H), 4.25-4.43 (m, 2H), 2.8 (s, 1H), 1.44-1.60 (m, 8H), 1.18 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 198.5, 154.1, 147.9, 131.4, 85.8, 66.3, 62.8, 56.8, 44.5, 42.3, 33.2, 32.6, 32.1, 25.9, 21.5, 18.5, 18.1, 17.4, -5.3, -5.4.

IR (neat): 2927 (m), 2322 (w), 1703 (m), 1602 (s), 1006 (m), 830 (s), 780 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{37}O_4Si$ $[M+H]^+$: 409.2410; found: 409.2417.

5,5,8a-trimethyl-2',4-dioxo-4a,5,6,7,8,8a-hexahydro-4H-spiro [naphthalene-1,4'- [1,3] dioxolane]-2-carbaldehyde:



(±)-164

To a stirred solution of ***(±)-162*** (1 eq, 0.25 mmol, 100 mg) in CH_2Cl_2/MeOH (4mL/4mL), CSA (0.1 eq, 0.03 mmol, 6 mg) was added at 0°C and the stirring was continued at room temperature for 16 h. The reaction mixture was poured in saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude allyl alcohol ***(±)-163*** was dissolved in 5 mL of CH_3CN and oxidized by adding manganese dioxide (25 eq, 6.25 mmol, 543 mg) at 0°C. The stirring was continued for 2 h at this temperature. Filtration of the reaction mixture through a short pad of silica with ether gave in quantitative yield over two steps compound ***(±)-164*** (72 mg, sticky oil).

General Data: $C_{16}H_{20}O_5$; FW: 292.12; TLC: R_f = 0.45 (hexane/EtOAc 2:1); UV (+); Vanillin: blue.

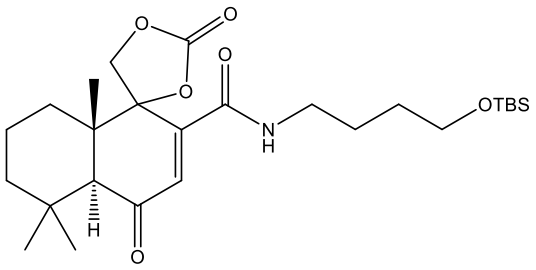
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 9.75 (s, 1H), 6.63 (s, 1H), 4.70 (d, *J* = 9.0 Hz, 1H), 4.41 (d, *J* = 8.8 Hz, 1H), 2.8 (s, 1H), 1.44-1.60 (m, 6H), 1.18 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 198.6, 193.1, 152.0, 144.4, 127.8, 82.5, 66.7, 58.0, 43.3, 42.0, 32.9, 31.8, 29.6, 21.5, 18.4, 18.0.

IR (neat): 2817 (m), 2622 (w), 1778 (m), 1622 (s), 1086 (m), 830 (s), 780 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{16}H_{21}O_5$ $[M+H]^+$: 292.1389; found: 292.1396.

N-(4-((tert-butyldimethylsilyl) oxy) butyl)-5,5,8a-trimethyl-2',4-dioxo-4a,5,6,7,8,8a-hexahydro-4H-spiro [naphthalene-1,4'- [1,3] dioxolane]-2-carboxamide:



(±)-166

$NaClO_2$ (2 eq, 3.24 mmol, 313 mg) and NaH_2PO_4 (4 eq, 6.84 mmol, 1.08 g) were dissolved in water (2 mL) at 0 °C and stirred for 1 h. Compound ***(±)-164*** (1 eq, 1.71 mmol, 500 mg) was dissolved in *t*-BuOH (7.5 mL) and 2-methyl-2-butene (8.1 eq, 13.85 mmol, 1.47 mL). The system was stirred for half an hour, then the aqueous $NaClO_2$/ NaH_2PO_4 aqueous was added slowly over 15 min at 0 °C. After the reaction was kept for 2 h at this temperature, saturated NH_4Cl was poured into the system. The aqueous layer was extracted with Et_2O, then the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford in quantitative yield the oxidized product ***(±)-165*** (1.69 mmol, 527 mg).

The crude ***(±)-165*** compound was dissolved in DMF (40 mL) and cooled to 0°C. DIPEA (5 eq, 8.45 mmol, 1.47 mL), HATU (1.5 eq, 2.54 mmol, 964 mg), and ***136*** (1 eq, 1.69 mmol, 344 mg) were added and the reaction mixture was stirred at room temperature for 3 h. The solution was poured in the water and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification with flash chromatography (pentane/Et_2O 1:1) gave ***(±)-166*** (60% over two steps, 1.01 mmol, 499 mg) as oil.

General Data: $C_{26}H_{43}NO_6Si$; FW: 493.29; TLC: R_f = 0.4 (hexane/EtOAc 2:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

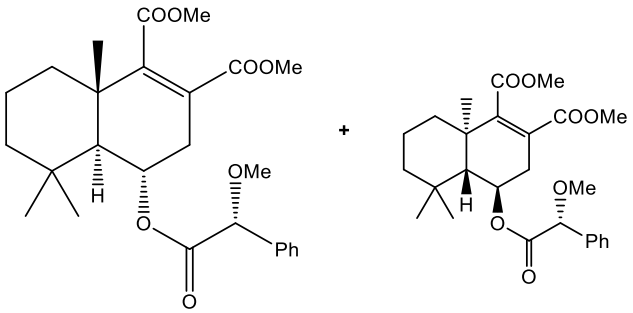
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.45 (t, *J* = 5.7 Hz, 1H), 6.12 (s, 1H), 4.63 (d, *J* = 9.44 Hz, 1H), 4.41 (d, *J* = 9.44 Hz, 1H), 3.67 (t, *J* = 5.9 Hz, 2H), 3.42-3.51 (m, 1H), 3.25-3.35 (m, 1H), 2.7 (s, 1H), 2.11-2.27 (m, 1H), 1.92-2.06 (m, 2H), 1.44-1.67 (m, 7H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 198.3, 165.5, 153.9, 144.1, 131.8, 84.2, 67.5, 62.8, 57.3, 44.2, 42.1, 39.8, 33.0, 32.5, 30.3, 29.9, 26.2, 26.1, 21.5, 18.5, 18.1, 17.3, -5.1, -5.2.

IR (neat): 2903 (m), 2122 (w), 1713 (s), 1654 (s), 1206 (s), 865 (m), 780 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{43}NO_6SiNa$ $[M+Na]^+$: 516.2757; found: 516.2762.

dimethyl 4-(2-methoxy-2-phenylacetoxy)-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate:



(+)-170 ***(–)-171***

To a stirred solution of the racemic mixture of compound ***(±)-123*** (1 eq, 12.06 mmol, 3.74 g) in CH_2Cl_2 (236 mL) was added (*R*)-(−)-α-methoxyphenylacetic acid (2 eq, 23.12 mmol, 4 g), EDC·HCl (2 eq, 23.12 mmol, 4.62 g), and DMAP (0.2 eq, 2.41 mmol, 294 mg) at 23 °C. After 3 h, water (~100 mL) was added to the reaction mixture, and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography using hexane/EtOAc (5:1), affording the diastereoisomers ***(+)-170*** (39%, 4.70 mmol, 2.16 g, oil) and ***(–)-171*** (29%, 3.50 mmol, 1.60 g, oil).

General Data *(+)-170*: $C_{26}H_{34}O_7$; FW: 458.23; TLC: R_f = 0.35 (hexane/EtOAc 4:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ =+9.5 (c 0.76, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.30-7.44 (m, 5H), 5.37 (dt, *J* = 10.9, 6.9 Hz, 1H), 4.74 (s, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.43 (s, 3H), 2.77 (dd, *J* = 18.4, 7.0 Hz, 1H), 2.04 (dd, *J* = 18.5, 6.7 Hz, 1H), 1.39-1.60 (m, 7H), 1.27 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.3, 168.9, 166.0, 152.7, 135.9, 128.8, 128.7, 127.2, 123.9, 83.0, 70.7, 57.6, 52.2, 52.1, 52.0, 42.9, 39.8, 36.3, 35.4, 33.7, 32.1, 22.2, 20.6, 18.2.

IR (neat): 3523 (w), 2931 (w), 1723 (s), 1424 (m), 1249 (s), 1172 (m), 1203 (m), 1066 (m), 697 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{35}O_7$ $[M+H]^+$: 476.2648; found: 476.2646.

General Data *(+)-171*: $C_{26}H_{34}O_7$; FW: 458.23; TLC: R_f = 0.25 (hexane/EtOAc 4:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = -89.2 (c 0.66, $CHCl_3$).

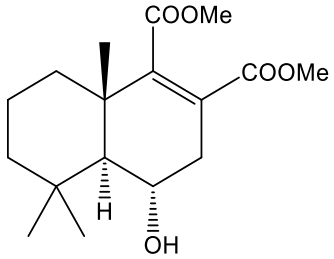
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.20-7.34 (m, 5H), 5.18 (dt, *J* = 10.8, 6.8 Hz, 1H), 4.58 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.28 (s, 3H), 2.87 (dd, *J* = 18.3, 7.0 Hz, 1H), 2.31 (dd, *J* = 18.4, 6.6 Hz, 1H), 1.39-1.57 (m, 7H), 1.14 (s, 3H), 0.51 (s, 3H), 0.40 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.3, 168.9, 166.1, 152.9, 135.4, 129.2, 128.8, 128.2, 124.0, 83.2, 71.3, 57.2, 52.3, 52.1, 52.0, 42.5, 39.9, 36.3, 34.5, 33.3, 32.7, 21.7, 20.5, 18.1.

IR (neat): 3518 (w), 2940 (w), 1720 (s), 1515 (w), 1396 (m), 1259 (s), 1168 (m), 1210 (m), 1067 (m), 684 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{26}H_{35}O_7$ $[M+H]^+$: 476.2648; found: 476.2651.

Dimethyl (4S,4aS,8aS)-4-hydroxy-5,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate:



(+)-123

Compound ***(+)-170*** (1 eq, 4.11 mmol, 1.90 g) was dissolved in was dissolved in MeOH (50 mL), and finely powdered K_2CO_3 (1 eq, 4.11 mmol, 568 mg) was added. The mixture was stirred at room temperature for 16 h, then it was partitioned between Et_2O and H_2O, and the aqueous layer was extracted with Et_2O. The combined organic extracts were passed through a plug of silica/Na_2SO_4, and the solvents were evaporated. Compound ***(+)-123*** (85 %, 3.50 mmol, 1.08 g) was obtained as a colorless oil.

General Data: $C_{17}H_{26}O_5$; FW: 310.18; TLC: R_f = 0.4 (hexane/EtOAc 2:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = +71.94 (*c* = 0.36, $CHCl_3$).

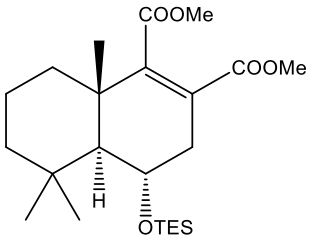
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 4.16-4.23 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.85 (dd, *J* = 18.2, 6.7 Hz, 1H), 2.37 (dd, *J* = 18.3, 8.1 Hz, 1H), 1.35-1.59 (m, 6H), 1.33 (d, *J* = 11.04 Hz, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 169.3, 166.6, 152.9, 124.5, 67.7, 55.1, 52.3, 52.1, 43.3, 40.5, 37.4, 36.6, 36.2, 34.0, 22.2, 21.2, 18.5.

IR (neat): 3523 (br), 2931 (m), 1712 (s), 1644 (w), 1424 (m), 1246 (s), 1203 (m), 1069 (m), 837 (w), 758 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{27}O_5$ $[M+H]^+$: 311.1858; found: 311.1858.

Dimethyl (4S,4aS,8aS)-5,5,8a-trimethyl-4-((triethylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate:



(+)-124

To a solution of ***(+)-123*** (1 eq, 8.05 mmol, 2.5 g) in dry DMF (40 mL) with imidazole (6 eq, 48.30 mmol, 3.3 g) was added TESCl (3 eq, 24.15 mmol, 4.1 mL) at 0°C and the reaction was stirred for 2 h at this temperature. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in

vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (10:1), yielding ***(+)-124*** (99%, 7.97 mmol, 3.4 g) as a sticky oil.

General Data: $C_{23}H_{40}O_5Si$; FW: 424,26; TLC: R_f = 0.8 (hexane/EtOAc 4:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = +61.5 (*c* = 0.4, $CHCl_3$).

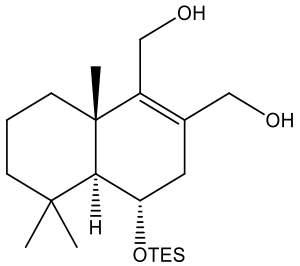
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.24 (ddd, *J* = 10.7, 8.7, 6.2 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.73 (dd, *J* = 18.0, 6.2 Hz, 1H), 2.37 (dd, *J* = 18.1, 8.9 Hz, 1H), 1.14-1.58 (s, 6H), 1.37 (d, *J* = 10.7 Hz, 1H), 1.27 (s, 3H), 1.14 (s, 3H), 1.03 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.66 (q, *J* = 8 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 169.4, 166.7, 152.5, 124.8, 68.2, 54.7, 52.3, 52.0, 43.7, 40.4, 38.0, 37.0, 36.1, 33.8, 22.2, 21.5, 18.4, 7.2, 5.6.

IR (neat): 1724 (s), 1649 (w), 1246 (s), 1086 (m), 1006 (m), 818 (w), 726 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{44}NO_5Si$ $[M+NH_4]^+$: 442.2989; found: 442.2987.

((4S,4aS,8aS)-5,5,8a-trimethyl-4-((triethylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-diyl) dimethanol:



(+)-125

To a solution of ***(+)-124*** (1 eq, 12.7 mmol, 5.4 g) in dry THF (200 mL) was added 1M DIBAL-H in hexane (6 eq, 76.2 mmol, 76.2 mL) dropwise at 0°C for 3 h. The reaction mixture was quenched with MeOH, poured into a saturated aqueous Rochelle's salt solution, and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (2:1) gave ***(+)-125*** (68%, 8.64 mmol, 3.2 g) as a sticky oil.

General Data: $C_{21}H_{40}O_3Si$; FW: 368.27; TLC: R_f = 0.2 (hexane/EtOAc 2:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$= +83.0 (*c* = 0.46, $CHCl_3$).

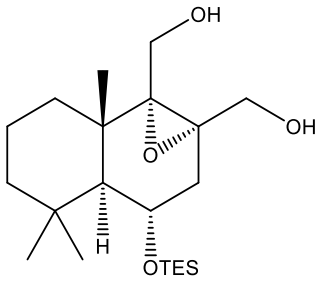
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.00-4.20 (m, 5H), 2.52 (dd, *J* = 17.4, 5.9 Hz, 1H), 2.29 (dd, *J* = 17.4, 9.2 Hz, 1H), 2.04 (s, 1H), 1.80 (d, *J* = 12.7 Hz, 1H), 1.12-1.64 (m, 5H), 1.31 (d, *J* =10.7 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.98 (t, *J* = 8 Hz, 9H), 0.65 (q, *J* = 7.6 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 146.0, 134.1, 69.0, 63.6, 57.9, 56.2, 43.8, 43.0, 41.0, 36.9, 36.2, 33.6, 22.3, 21.8, 18.8, 7.3, 5.7.

IR (neat): 3321 (br), 2929 (m), 1121 (m), 1085 (s), 1001 (s), 981 (s), 834 (m), 724 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{41}O_3Si$ $[M+H]^+$: 369.2825; found: 369.2817.

((1aS,3S,3aS,7aS,7bR)-4,4,7a-trimethyl-3-((triethylsilyl)oxy) octahydronaphtho[1,2-b] oxirane-1a,7b-diyl) dimethanol:



(+)-126

To a stirred solution of ***(+)-125*** (1 eq, 18.4 mmol, 6.8 g) in CH_2Cl_2 (260 mL) was added 1 eq of m-CPBA (ca. 77%, 18.4 mmol, 4.12 g), and stirring was continued at 0°C for 3 h. The reaction mixture was poured into a 5% aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (2:1) gave ***(+)-126*** (99%, 18.2 mmol, 7 g, white powder).

General Data: $C_{21}H_{40}O_4Si$; FW: 384.27; TLC: R_f = 0.4 (hexane/EtOAc 2:1); UV (-); Vanillin: brown; $[\alpha]_D^{20}$= +37.2 (*c* = 0.44, $CHCl_3$); Mp 85-90°C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.09 (d, *J* = 11.6 Hz, 1H), 3.99 (ddd, *J* = 10.7, 8.9, 6.9 Hz, 1H), 3.67 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 11.8 Hz, 1H), 3.55 (d, *J* = 11.3 Hz, 1H), 2.46 (dd, *J* =

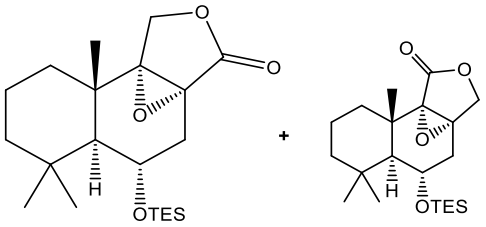
14.7, 6.8 Hz, 1H), 1.87 (dd, *J* = 14.9, 8.9 Hz, 1H), 1.70 (d br, *J* = 12.7 Hz, 1H), 1.18-1.59 (m, 5H), 1.48 (d, *J* = 10.6 Hz, 1H), 1.17 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.64 (q, *J* = 8 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 71.4, 67.6, 65.8, 64.8, 61.8, 49.0, 43.5, 38.8, 37.9, 36.3, 35.6, 33.2, 22.6, 18.5, 18.3, 7.2, 5.6.

IR (neat): 3344 (br), 2927 (s), 1458 (m), 1239 (m), 1117 (m), 1086 (s), 1016 (s), 838 (m), 723 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{41}O_4Si$ $[M+H]^+$: 385.2774; found: 385.2769.

(3aR,5S,5aS,9aS,9bR)-6,6,9a-trimethyl-5-((triethylsilyl)oxy) octahydro-1H,3H-3a,9b-epoxynaphtho[1,2-c] furan-3-one:



(+)-111 ***(–)-111b***

Compound ***(+)-126*** (1 eq, 0.52 mmol, 200 mg) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. TEMPO (0.1 eq, 0.05 mmol, 8 mg) and $PhI(OAc)_2$ (2 eq, 1.04 mmol, 335 mg) were added and the reaction mixture was continued at this temperature. After 24 h, saturated aqueous $Na_2S_2O_3$ was added for quenching. The reaction was stirred for 15 min and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc (30:1), yielding the desired compound ***(+)-111*** (75%, 0.40 mmol, 148.4 mg, light-yellow powder) and its regioisomer ***(–)-111b*** (8%, 0.04 mmol, 16 mg, colorless sticky oil).

General Data *(+)-111*: $C_{21}H_{36}O_4Si$; FW: 380.24; TLC: R_f = 0.64 (hexane/EtOAc 4:1); UV (-); Vanillin: brown**;** $[\alpha]_D^{20}$ = +37.0 (*c* = 0.3, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.30 (d, *J* = 10.7 Hz, 1H), 4.25 (d, *J* = 10.7 Hz, 1H), 4.02 (ddd, *J* = 10.6, 8.9, 6.9 Hz, 1H), 2.57 (dd, *J* = 15.4, 7.0 Hz, 1H), 2.00 (dd, *J* = 15.3, 8.9 Hz, 1H),

1.66 (d, *J* = 10.7 Hz, 1H), 1.45-1.58 (m, 4H), 1.35-1.40 (m, 1H), 1.19-1.24 (m, 1H), 1.26 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.9 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 172.5, 73.0, 67.2, 67.1, 58.3, 48.1, 43.7, 37.1, 36.4, 36.1, 33.1, 30.8, 22.4, 19.8, 17.9, 7.1, 5.5.

IR (neat): 2915 (s), 1776 (s), 1091 (s), 1075 (s), 1017 (s), 811 (m), 800 (m), 743 (m), 724 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{37}O_4Si$ $[M+H]^+$: 381.2461; found: 381.2455.

General Data *(–)-111b*: $C_{21}H_{36}O_4Si$; FW: 380.24; TLC: R_f = 0.84 (hexane/EtOAc 4:1); UV (-); Vanillin: blue**;** $[\alpha]_D^{20}$ = -7.4 (*c* = 0.8, $CHCl_3$).

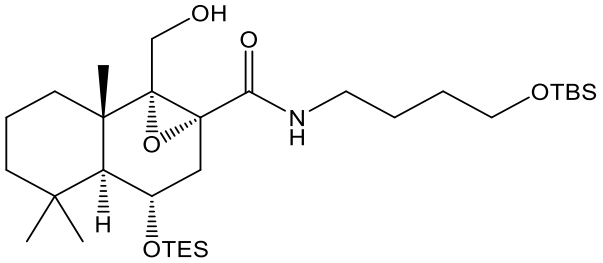
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.33 (d, *J* = 10.8 Hz, 1H), 4.07-4.13 (m, 1H), 4.04 (d, *J* = 11.0 Hz, 1H), 2.33 (d br, 1H), 2.30 (dd, *J* = 15.0, 6.8 Hz, 1H), 2.10 (dd, *J* = 14.7, 9.2 Hz, 1H), 1.60 (d, *J* = 10.6 Hz, 2H), 1.45-1.53 (m, 1H), 1.39-1.44 (m, 1H), 1.32-1.38 (m, 1H), 1.28 (s, 3H), 1.22-1.27 (m, 1H), 1.10 (s, 3H), 1.01 (s, 3H), 0.98 (t, *J* = 8.1 Hz, 9H), 0.63 (q, *J* = 8.1 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.8, 70.3, 67.2, 65.0, 64.2, 48.7, 43.9, 36.2, 35.0, 34.6, 33.8, 33.2, 22.4, 18.3, 17.7, 7.2, 5.6.

IR (neat): 2980 (s), 1770 (s), 1075 (s), 1063 (s), 1016 (s), 824 (m), 800 (m), 737 (m), 723 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{37}O_4Si$ $[M+H]^+$: 381.2461; found: 381.2463.

(1aR,3S,3aS,7aS,7bR)-N-(4-((tert-butyldimethylsilyl) oxy) butyl)-7b-(hydroxymethyl)-4,4,7a-trimethyl-3-((triethylsilyl)oxy) octahydronaphtho[1,2-b] oxirane-1a(2H)-carboxamide:



(+)-110

To a solution of ***(+)-111*** (1 eq, 0.33 mmol, 124 mg) in toluene (4.8 mL), TBD (0.1 eq, 0.03 mmol, 5 mg) and compound ***136*** (2 eq, 0.66 mmol, 134 mg) were added and the reaction mixture was refluxed at 110°C. After 24 h, the solvent was evaporated and the crude was partitioned between brine and Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 4:1) to afford ***(+)-110*** (80%, 0.26 mmol, 154 mg) as a sticky oil.

General Data: $C_{31}H_{61}NO_5Si_2$; FW: 583.40; TLC: R_f = 0.36 (hexane/EtOAc 4:1); UV (-); Vanillin: brown; $[\alpha]_D^{20}$ = +21.4 (*c* = 0.28, $CHCl_3$).

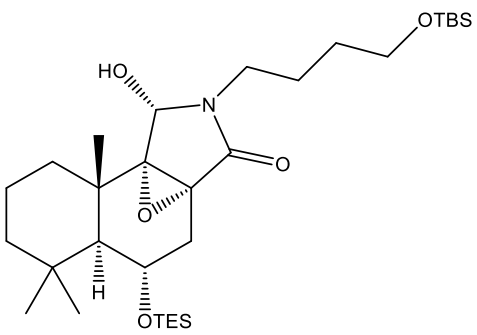
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.46 (t, *J* = 6.1 Hz, 1H), 4.00-4.10 (m, 1H), 3.56-3.73 (m, 2H), 3.18-3.38 (m, 2H), 2.77 (dd, *J* = 15.1, 7.1 Hz, 1H), 1.85 (dd, *J* = 15.1, 7.6 Hz, 1H), 1.78 (d, *J* = 12.2 Hz, 1H), 1.46-1.61 (m, 6H), 1.12-1.39 (m, 6H), 1.21 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.96 (t, *J* = 9 Hz, 9H), 0.89 (s, 9H), 0.63 (q, *J* = 8 Hz, 6H), 0.05 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.2, 72.7, 67.0, 66.9, 62.8, 60.8, 49.4, 43.5, 39.1, 38.7, 36.2, 36.1, 36.0, 33.3, 30.1, 26.2, 26.1, 22.5, 19.0, 18.5, 18.2, 7.2, 5.6, -5.2.

IR (neat): 3456 (br), 2928 (m), 1637 (s), 1462 (w), 1079 (s), 1006 (m), 853 (s), 721 (s), 618 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{62}NO_5Si_2$ $[M+H]^+$: 584.4166; found: 584.4169.

(1S,3aR,5S,5aS,9aS,9bS)-2-(4-((tert-butyldimethylsilyl) oxy) butyl)-1-hydroxy-6,6,9a-trimethyl-5-((triethylsilyl)oxy) decahydro-3H-3a,9b-epoxybenzo[e]isoindol-3-one:



(+)-172

To a stirred solution of ***(+)-110*** (1 eq, 0.21 mmol, 121 mg) in CH_2Cl_2 (4.2 ml) was added Dess-Martin periodinane (2 eq, 0.42 mmol, 178 mg) at 0°C, and stirring was continued at room

temperature for 1 h. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (5:1) gave ***(+)-172*** (75%, 0.16 mmol, 93 mg) as a clear -sticky oil.

General Data: $C_{31}H_{59}NO_5Si_2$; FW: 581.39; TLC: R_f = 0.58 (hexane/EtOAc 4:1); UV (-); Vanillin: violet; $[\alpha]_D^{20}$ = +22.94 (*c* = 0.34, $CHCl_3$).

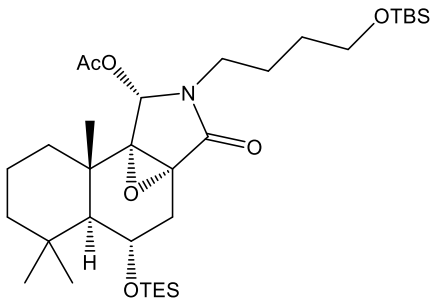
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.98 (d, *J* = 13.0 Hz, 1H), 3.93- 4.00 (m, 1H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.30-3.38 (m, 1H), 3.06-3.13 (m, 1H), 2.58 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.55 (d, *J* = 12.9 Hz, 1H), 1.96 (dd, *J* = 15.4, 8.9 Hz, 1H), 1.82 (d br, *J* = 12.1 Hz, 1H), 1.41-1.65 (m, 7H), 1.22-1.37 (m, 3H), 1.21 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.64 (q, *J* = 8.1 Hz, 6H), 0.04 (s, 6H).

^{13}C-NMR (151MHz, $CDCl_3$): δ (ppm): 169.7, 78.5, 70.9, 67.2, 62.9, 62.7, 48.6, 43.8, 39.7, 36.4, 36.3, 35.9, 33.2, 30.8, 30.3, 26.1, 24.2, 22.4, 19.3, 18.5, 17.9, 7.8, 5.5, -5.2.

IR (neat): 3258 (br), 2929 (m), 1668 (s), 1460 (w), 1252 (w), 1083 (s), 1006 (m), 853 (s), 729 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{31}H_{60}NO_5Si_2$ $[M+H]^+$: 582.4010; found: 582.4015.

(1S,3aR,5S,5aS,9aS,9bS)-2-(4-((tert-butyldimethylsilyl) oxy) butyl)-6,6,9a-trimethyl-3-oxo-5-((triethylsilyl) oxy) decahydro-1H-3a,9b-epoxybenzo[e]isoindol-1-yl acetate:



(+)-173

To a solution of ***(+)-172*** (1 eq, 0.53 mmol, 310 mg) in CH_2Cl_2 (7 mL) were added at 0°C NEt_3 (3 eq, 1.60 mmol, 220 µL). Ac_2O (3 eq, 1.60 mmol, 150 µL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into a saturated NH_4Cl solution and

extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel using pentane/Et_2O (8:1), yielding the desired compound ***(+)-173*** as a sticky oil in 99% yield (0.52 mmol, 327 mg).

General Data: $C_{33}H_{61}NO_6Si_2$; FW: 623.40; TLC: R_f = 0.69 (hexane/EtOAc 4:1); UV (-); Vanillin: brown; $[\alpha]_D^{20}$ = +25.45 (*c* = 0.33, $CHCl_3$).

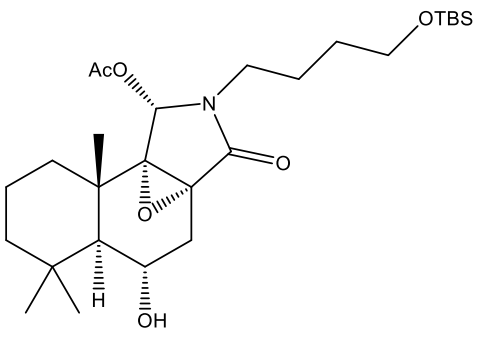
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.40 (s, 1H), 3.97 (ddd, *J* = 10.4, 9.02, 6.9 Hz, 1H), 3.58 (td, *J* = 7.7, 6.1, 1.6 Hz, 2H), 3.29-3.39 (m, 1H), 2.83-2.92 (m, 1H), 2.57 (dd, *J* = 15.2, 6.9 Hz, 1H), 2.14 (s, 3H), 1.99 (dd, *J* = 15.6, 9.1 Hz, 1H), 1.61 (d, *J* = 10.8 Hz, 1H), 1.28-1.59 (m, 10H), 1.24 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.87 (s, 9H), 0.64 (q, *J* = 7.5 Hz, 6H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.6, 170.0, 77.4, 68.3, 67.1, 62.7, 60.6, 48.4, 43.6, 40.2, 36.4, 36.2, 35.7, 33.1, 30.5, 30.2, 26.1, 24.3, 22.4, 21.2, 19.5, 18.5, 17.9, 7.2, 5.5, -5.2.

IR (neat): 2929 (m), 2321 (w), 1721 (s), 1419 (w), 1218 (m), 1096 (s), 1014 (s), 853 (s), 724 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{33}H_{62}NO_6Si_2$ $[M+H]^+$: 624.4115; found: 624.4118.

(1S,3aR,5S,5aS,9aS,9bS)-2-(4-((tert-butyldimethylsilyl) oxy) butyl)-5-hydroxy-6,6,9a-trimethyl-3-oxodecahydro-1H-3a,9b-epoxybenzo[e]isoindol-1-yl acetate:



(+)-174

To a solution of ***(+)-173*** (1 eq, 0.10 mmol, 60 mg) in THF (1.7 mL) at 0°C, TBAF (1M in THF, 1 eq, 0.10 mmol, 100 µL) was added and the stirring was continued at the same temperature. After 1 h, the reaction mixture was poured into a saturated solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated

in vacuo. The crude was purified by flash chromatography. Elution with hexane/EtOAc (3:1) afforded in 99% yield the deprotected compound ***(+)-174*** (0.10 mmol, 51 mg) as a sticky oil.

General Data: $C_{27}H_{47}NO_6Si$; FW: 509.32; TLC: R_f = 0.35 (hexane/EtOAc 3:1); UV (-); Vanillin: green; $[\alpha]_D^{20}$ = +20.93 (*c* = 0.33, $CHCl_3$).

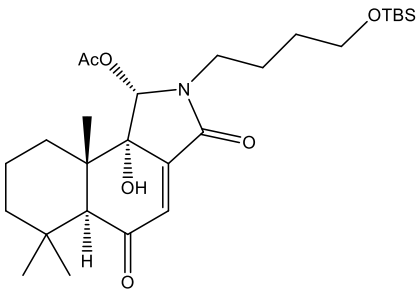
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.43 (s, 1H), 3.89 (ddd, *J* = 15.6, 8.5, 6.9 Hz, 1H), 3.58 (td, *J* = 8.9, 6.3, 2.7 Hz, 2H), 3.33-3.39 (m, 1H), 2.84-2.91 (ddd, *J* = 13.57.7, 5.1 Hz, 1H), 2.63 (dd, *J* = 16.7, 7.1 Hz, 1H), 2.16 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.15 (s, 3H), 1.56 (d, *J* = 9.6 Hz, 1H), 1.21-1.52 (m, 10H), 1.19 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 170.5, 169.6, 76.7, 68.0, 66.0, 62.6, 60.5, 51.3, 42.8, 40.1, 36.1, 35.9, 35.0, 33.4, 30.2, 30.1, 26.1, 24.2, 22.4, 21.1, 19.2, 18.5, 18.0, -5.2.

IR (neat): 3458 (br), 2929 (m), 1713 (s), 1423 (m), 1217 (s), 1017 (s), 835 (s), 755 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{48}NO_6Si$ $[M+H]^+$: 510.3251; found: 510.3248.

(1S,5aS,9aS,9bS)-2-(4-((tert-butyldimethylsilyl) oxy) butyl)-9b-hydroxy-6,6,9a-trimethyl-3,5-dioxo-2,3,5,5a,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-1-yl acetate:



(+)-176

To a stirred solution of ***(+)-174*** (1 eq, 1.0 mmol, 510 mg) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (2 eq, 2 mmol, 849 mg) at 0°C, and stirring was continued at room temperature for 2 h. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (5:1) gave ***(+)-175*** (85%, 0.85 mmol, 432 mg) and ***(+)-176*** (10%, 0.10 mmol, 51 mg). Compound ***(+)-175*** was dissolved in toluene (20 mL) and DBU (0.1 eq, 0.2 mmol, 25 µL) was added at 0°C. After stirring the solution for 1

h, the solvent was evaporated under vacuum, the reaction mixture was poured into a saturated aqueous NaCl solution and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to afford ***(+)-176*** (80%, 0.7 mmol, 345 mg, white needles based on ***(+)-175***; for a total yield of 90% of ***(+)-176***).

General Data: $C_{27}H_{45}NO_6Si$; FW: 507.30; TLC: R_f = 0.38 (hexane/EtOAc 3:1); UV (+); Vanillin: green; $[\alpha]_D^{20}$ = +12.60 (*c* = 0.23, $CHCl_3$); Mp 136-138 °C.

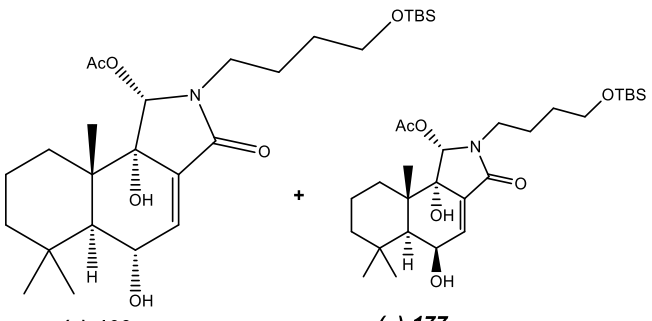
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 6.48 (s, 1H), 6.37 (s, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 3.04-3.14 (m, 2H), 2.25 (s, 3H), 1.59 (s, 1H), 1.34-1.80 (m, 8H), 1.06-1.23 (m, 2H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 199.8, 168.9, 164.8, 145.7, 127.1, 78.8, 74.6, 62.5, 56.1, 45.6, 42.8, 40.8, 33.7, 32.4, 30.8, 30.2, 26.1, 24.3, 21.5, 21.1, 19.2, 18.5, 17.4, -5.2.

IR (neat): 3245 (w), 2928 (m), 1752 (m), 1687 (s), 1219 (s), 1044 (s), 939 (w), 836 (s), 774 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{46}NO_6Si$ $[M+H]^+$: 508.3094; found: 508.3096.

(1S,5S,5aS,9aS,9bS)-2-(4-((tert-butyldimethylsilyl) oxy) butyl)-5,9b-dihydroxy-6,6,9a-trimethyl-3-oxo-2,3,5,5a,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-1-yl acetate:



(–)-109 ***(–)-177***

To a solution of ***(+)-176*** (1 eq, 0.2 mmol, 100 mg) in MeOH (2 mL) was added $CeCl_3 \cdot 7H_2O$ (2 eq, 0.4 mmol, 150 mg) and $NaBH_4$ (3 eq, 0.6 mmol, 23 mg) at 0 °C. After stirring the mixture at this temperature for 1 h, the reaction mixture was poured into a saturated NH_4Cl solution, extracted with Et_2O. The organic layer was washed with a saturated $NaHCO_3$ aqueous solution

and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification with flash chromatography (hexane/ EtOAc 2:1, then 1:1) of the residue afforded ***(–)-109*** (48%, 0.1 mmol, 51 mg, colorless oil) and ***(–)-177*** (45%, 0.09 mmol, 46 mg, white powder).

General Data *(–)-109*: $C_{27}H_{47}NO_6Si$; FW: 509.32; TLC: R_f = 0.32 (hexane/EtOAc 1:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = -25.8 (*c* = 0.2, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.99 (d, *J* = 1.9 Hz, 1H), 6.55 (s, 1H), 4.70 (dd, *J* = 10.2, 2.4 Hz, 1H), 3.58-3.63 (m, 2H), 3.01-3.07 (m, 2H), 2.62 (d, *J* = 9.8 Hz, 1H), 2.20 (s, 3H), 1.21-1.62 (m, 10H), 1.19 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

IR (neat): 3442 (br), 2926 (s), 1661 (s), 1461 (m), 1253 (m), 1076 (s), 834 (s), 773 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{47}NO_6SiNa$ $[M+Na]^+$: 532.3070; found: 532.3068.

General Data *(–)-181*: $C_{27}H_{47}NO_6Si$; FW: 509.32; TLC: R_f = 0.48 (hexane/EtOAc 1:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; Mp 133-135 °C; $[\alpha]_D^{20}$ = -65.2 (*c* = 0.2, $CHCl_3$).

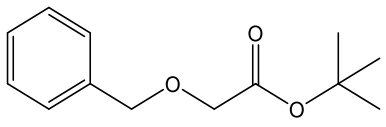
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.99 (d, *J* = 4.0 Hz, 1H), 6.57 (s, 1H), 4.75 (dt, *J* = 4.6, 4.0 Hz, 1H), 3.56-3.64 (m, 2H), 3.01-3.06 (m, 2H), 2.21 (s, 3H), 2.20 (d, *J* = 4.5 Hz, 1H), 1.20-1.56 (m, 10H), 1.19 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

IR (neat): 3445 (br), 2944 (s), 1610 (s), 1452 (m), 1222 (m), 1078 (s), 835 (s), 777 (s) cm^{-1}.

HRMS (ESI): calculated for $C_{27}H_{47}NO_6SiNa$ $[M+Na]^+$: 532.3070; found: 532.3072.

5.1.2. Synthesis of the linker: from compound *186* to *(–)-198*

Tert-butyl 2-(benzyloxy)acetate:



186

To a stirred suspension of NaH (1.1 eq, 4.58 mmol, 110 mg, 60 % dispersion in mineral oil) in DMF (30 mL) was added at 0 °C dropwise *tert-butyl glycolate* (1 eq, 4.16 mmol, 534 µL). Effervescence was observed and after stirring for 30 min BnBr (1.1 eq, 4.58 mmol, 450 µL) was added dropwise. After stirring at room temperature for 5 h, TLC indicated complete consumption of starting material. The mixture was added to an Et_2O/H_2O bilayer and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (6:1) gave ***186*** in 99% yield (4.12 mmol, 916 mg, oil).

General Data: $C_{13}H_{18}O_3$; FW: 222.13; TLC: R_f = 0.75 (hexane/EtOAc 3:1); UV (+); Vanillin: green.

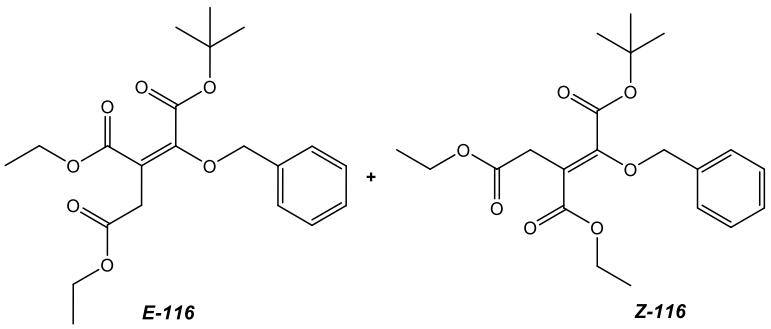
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.33-7.39 (m, 4H), 7.28-7.31 (m, 1H), 4.62 (s, 2H), 3.99 s, (s, 2H), 1.49 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.0, 137.5,128.6, 128.2, 127.0, 81.7, 73.3, 67.9, 28.2.

IR (neat): 1743 (s), 1225 (m), 1160 (m), 1122 (s), 736 (m), 698 (m) cm^{-1}.

HRMS (ESI): calculated for $C_{13}H_{22}NO_3$ $[M+NH_4]^+$: 240.1600; found: 240.1591.

1-(tert-butyl) 2,3-diethyl (Z)-1-(benzyloxy) prop-1-ene-1,2,3-tricarboxylate:



E-116 + ***Z-116***

Compound ***186*** (1 eq, 0.68 mmol, 151 mg) was dissolved in 2.5 mL of dry Et_2O, and the solution was cooled to -78°C. LDA (1.2 eq, 0.82 mmol, 410 µL) was added dropwise and the mixture was stirred for 1 h at this temperature. After adding dropwise diethyl oxalate ***187*** (1 eq, 0.68 mmol, 100 µM) at - 78°C, the stirring was continued at room temperature for 16 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution, and the organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude ***(±)-117*** was used for the next step without purification. The crude product ***(±)-117*** (1 eq, 0.54 mmol, 175 mg) was added to a solution of triphenylphosphonium ethoxycarbonylmethylide (***118***) (1.5 eq, 0.81 mmol, 282 mg) in 2.5 mL of CH_3CN. The solution was heated to 55°C for 1h. After the mixture was cooled to room temperature, the acetonitrile was removed in vacuo and the residue was diluted with Et_2O. The solution was filtered through a silica plug and eluted with additional Et_2O. Purification of the crude oil by flash chromatography (pentane/Et_2O 7:1) yielded the ***E-116*** (60% over 2 steps, 0.41 mmol, 160 mg) and ***Z-116*** (10% over 2 steps, 0.07 mmol, 27 mg).

General Data *E-116*: $C_{21}H_{28}O_7$; FW: 392.18; TLC: R_f = 0.25 (pentane/Et_2O 6:1; UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.28-7.39 (m, 5H), 5.00 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 2H), 1.56 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.9, 166.3, 162.4, 157.3, 135.8, 128.7, 128.6, 127.8, 106.7, 84.1, 71.9, 60.8, 60.7, 31.3, 28.0, 14.4, 14.3.

IR (neat): 2979 (w), 1728 (s), 1716 (s), 1369 (m), 1307 (m), 1150 (s), 1108 (s), 1027 (m), 843 (w), 698 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{29}O_7$ $[M+H]^+$: 393.1913; found: 393.1906.

General Data *Z-116:* $C_{21}H_{28}O_7$; FW: 392.18; TLC: R_f = 0.16 (pentane/Et_2O 6:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

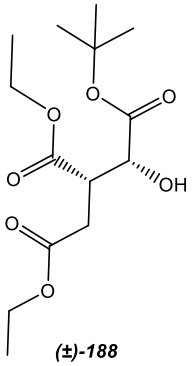
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.28-7.43 (m, 5H), 4.93 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.55 (s, 2H), 1.52 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 170.5, 167.0, 162.4, 151.6, 136.5, 128.5, 128.3, 128.0, 117.2, 83.9, 74.1, 61.2, 61.1, 34.5, 28.1, 14.3, 14.2.

IR (neat): 2970 (w), 1728 (s), 1700 (s), 1350 (m), 1312 (m), 1148 (s), 1106 (s), 1015 (m), 843 (w), 690 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{29}O_7$ $[M+H]^+$: 393.1913; found: 393.1909.

1-(tert-butyl) 2,3-diethyl 1-hydroxypropane-1,2,3-tricarboxylate:



(±)-188

E-116 (1 eq, 0.51 mmol, 200 mg) was added to a mixture of 10% Pd/C (1.2 eq, 0.61 mmol, 65 mg) in MeOH (5 mL) under N_2. After two vacuum/H_2 cycles to remove air from the reaction flask, the reaction was stirred under hydrogen atmosphere at room temperature for 24 h. The reaction mixture was filtered through a Celite pad with CH_2Cl_2 to remove catalyst and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc 10:1) to afford the racemic ***(±)-188*** in 99% yield (0.61 mmol, 154 mg, oil).

General Data: $C_{14}H_{24}O_7$; FW: 304.15; TLC: R_f = 0.4 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

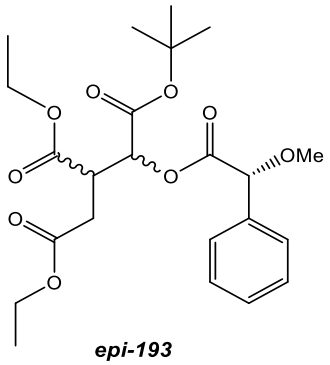
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.25 (d, *J* = 2.7 Hz, 1H), 4.12-4.17 (m, 4H), 3.42-3.46 (m, 1H), 2.85 (dd, *J* = 16.9, 8.9 Hz, 1H), 2.57 (dd, *J* = 16.8, 5.6 Hz, 1H), 1.50 (s, 9H), 1.21-1.27 (m, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 172.2, 172.0, 170.9, 83.5, 70.9, 61.3, 60.9, 45.1, 32.4, 28.0, 14.3, 14.2.

IR (neat): 3025 (br), 1723 (s), 1156 (s), 1108 (s), 1096 (s), 1027 (m), 846 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{14}H_{24}O_7Na$ $[M+Na]^+$: 327.1419; found: 327.1414.

1-(tert-butyl) 2,3-diethyl 1-((R)-2-methoxy-2-phenylacetoxy) propane-1,2,3-tricarboxylate:



epi-193

To a stirred solution of the racemic mixture of compound ***(±)-188*** (1 eq, 0.66 mmol, 200 mg) in CH_2Cl_2 (12 mL) was added (*R*)-(−)-α-methoxyphenylacetic acid (2 eq, 1.32 mmol, 220 mg), EDC·HCl (2 eq, 1.32 mmol, 253 g), and DMAP (0.2 eq, 0.13 mmol, 17 mg) at room temperature. After 16 h, water was added to the reaction mixture, and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography using hexane/EtOAc (10:1), which afforded an inseparable mixture of diastereoisomers ***epi-193*** (80%, 0.53 mmol, 239 mg, oil).

General Data: $C_{23}H_{32}O_9$; FW: 452.20; TLC: R_f = 0.43 (hexane/EtOAc 3:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

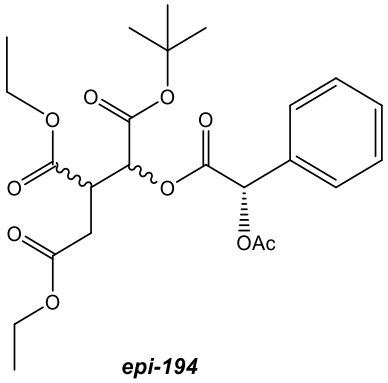
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.41-7.74 (m, 4H), 7.30-7.39 (m, 6H), 5.28 (d, *J* = 3.6 Hz, 1H), 5.23 (d, *J* = 3.72 Hz, 1H), 4.86 (s, 1H), 4.82 (s, 1H), 4.05-4.18 (m, 8H), 3.50-3.55 (m, 1H), 3.48 (s, 3H), 3.44 (s, 3H), 3.39-3.43 (m, 1H), 2.75 (dd, *J* = 16.9, 9.7 Hz, 1H), 2.50 (dd, *J* = 16.9, 9.6 Hz, 1H), 2.42 (dd, J = 16.8, 4.8 Hz, 1H), 2.16 (dd, *J* = 17.0, 5.1 Hz, 1H), 1.44 (s, 9H), 1.33 (s, 9H), 1.19-1.28 (m, 12H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.3, 171.2, 170.0, 169.9, 169.8, 166.2, 165.9, 136.0, 135.9, 129.0, 128.9, 128.8, 128.7, 127.4, 127.3, 83.4, 83.2, 82.5, 82.2, 72.4, 72.2, 61.6, 61.5, 61.1, 61.0, 57.8, 57.7, 43.0, 42.8, 32.1, 31.9, 28.0, 27.9, 14.3, 14.2, 14.1, 14.0.

IR (neat): 2981 (w), 1734 (s), 1455 (w), 1370 (m), 1230 (m), 1150 (s), 1113 (s), 1028 (m), 844 (w), 732 (w), 698 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{33}O_9$ $[M+H]^+$: 453.2124; found: 453.2126.

1-(tert-butyl) 2,3-diethyl 1-((S)-2-acetoxy-2-phenylacetoxy) propane-1,2,3-tricarboxylate:



epi-194

To a stirred solution of the racemic mixture of compound ***(±)-188*** (1 eq, 0.33 mmol, 100 mg) in CH_2Cl_2 (6 mL) was added (*S*)-O-Acetylmandelic acid (2 eq, 0.66 mmol, 128 mg), EDC· HCl (2 eq, 0.66 mmol, 127 g), and DMAP (0.2 eq, 0.1 mmol, 8 mg) at room temperature. After 3 h, water was added to the reaction mixture, and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography. Elution with pentane/Et_2O (3:1) afforded a mixture of diastereoisomers ***epi-194*** (70%, 0.23 mmol, 111 mg, oil) inseparable via flash chromatography.

General Data: $C_{24}H_{32}O_{10}$; FW: 480.20; TLC: R_f = 0.37 (hexane/EtOAc 3:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

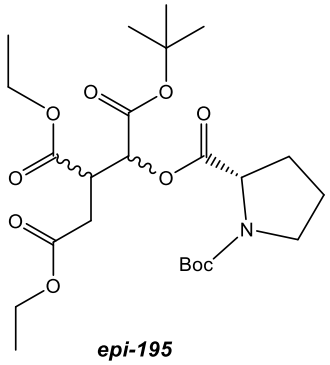
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 7.46-7.51 (m, 4H), 7.36-7.41 (m, 6H), 6.04 (s, 1H), 6.00 (s, 1H), 5.28 (d, *J* = 3.6 Hz, 1H), 5.24 (d, *J* = 3.6 Hz, 1H), 4.01-4.17 (m, 8H), 3.54-3.59 (m, 1H), 3.45-3.49 (m, 1H), 2.81 (dd, *J* = 17.7, 10.7 Hz, 1H), 2.60 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.44 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.22 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.19 (s, 6H), 1.43 (s, 9H), 1.32 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 6H), 1.23 (t, *J* = 4.0 Hz, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.4, 171.2, 170.3, 170.2, 169.9, 169.8, 167.9, 167.8, 165.8, 165.6, 133.7, 133.2, 129.5, 129.4, 129.0, 128.8, 128.0, 127.9, 83.4, 83.1, 74.4, 74.2, 72.9, 72.6, 61.5, 61.5, 61.1, 61.0, 43.0, 42.9, 32.1, 32.0, 28.0, 27.8, 22.8, 20.8, 14.2, 14.2, 14.1, 14.0.

IR (neat): 2920(w), 1735 /s), 1457 (w), 1370 (m), 1227 (s), 1204 (m), 1154 (s), 1084 (m), 1029 (m), 912 (m), 843 (w), 731 (s), 696 (m), 648 (w), 521 (w) m^{-1}.

HRMS (ESI): calculated for $C_{24}H_{33}O_{10}$ $[M+H]^+$: 481.2073; found: 481.2075.

1-(tert-butyl) 2,3-diethyl 1-(((tert-butoxycarbonyl)-L-prolyl) oxy) propane-1,2,3-tricarboxylate:



epi-195

To a stirred solution of the racemic mixture of compound ***(±)-188*** (1 eq, 0.16 mmol, 50 mg) in CH_2Cl_2 (3 mL) was added Boc-Pro-OH (2 eq, 0.32 mmol, 70 mg), EDC· HCl (2 eq, 0.32 mmol, 50 mg), and DMAP (0.2 eq, 0.03 mmol, 4 mg) at room temperature. After 1 h, water was added to the reaction mixture, and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography using pentane/Et_2O (3:1), yielding an inseparable mixture of diastereoisomers ***epi-195*** (60%, 0.1 mmol, 48 mg, oil).

General Data: $C_{24}H_{39}NO_{10}$; FW: 501.26; TLC: R_f = 0.35 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

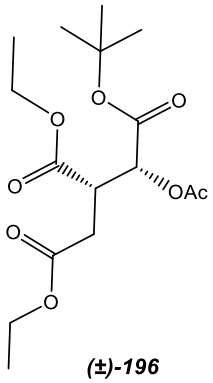
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.26 (d, *J* = 3.4 Hz, 1H), 5.21 (d, *J* = 3.5 Hz, 1H), 4.01-4.17 (m, 8H), 4.20-4.41 (m, 4H), 3.46-3.59 (m, 4H), 3.31-3.45 (m, 4H), 3.23-3.30 (m, 4H), 1.77-2.10 (m, 4H), 1.42 (s, 18H), 1.32 (s, 18H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.23 (t, *J* = 4.1 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 178.4, 177.7, 171.9, 171.7, 171.4, 171.2, 166.3, 166.0, 159.3, 155.8, 83.1, 83.0, 79.9, 79.8, 79.4, 79.1, 71.9, 70.7, 61.4, 61.1, 61.0, 60.8, 58.5, 58.3, 36.6, 35.0, 31.2, 30.6, 30.1, 29.6, 28.5, 28.4, 28.3, 27.9, 24.4, 23.4, 15.6, 15.3, 14.2, 14.1.

IR (neat): 2926 (w), 1738 (m), 1645 (m), 1393 (s), 1368 (s), 1255 (m), 1158 (s), 1123 (m), 1088 (m), 806 (w), 732 (m), 597 (w), 513 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{40}NO_{10}$ $[M+H]^+$: 502.2652; found: 502.2656.

1-(tert-butyl) 2,3-diethyl 1-acetoxypropane-1,2,3-tricarboxylate:



(±)-196

To a solution of ***(±)-188*** (1 eq, 1 mmol, 300 mg) in CH_2Cl_2 (13 mL) were added at 0°C NEt_3 (3 eq, 3 mmol, 420 µL), DMAP (0.05 eq, 0.05 mmol, 6mg) and Ac_2O (3 eq, 3 mmol, 300 µL) and the mixture was stirred at room temperature for 5 h. The reaction mixture was poured into a 1M HCl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 3:1) to afford ***(±)-196*** (80%, 0.8 mmol, 277 mg) as a sticky oil.

General Data: $C_{16}H_{26}O_8$; FW: 346.16; TLC: R_f = 0.6 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue.

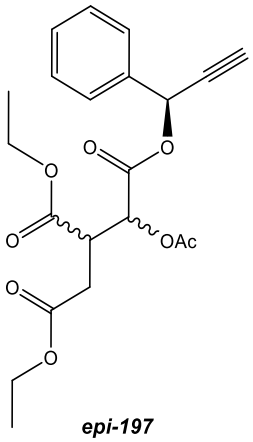
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.30 (d, *J* = 3.5 Hz, 1H), 4.12-4.20 (m, 4H), 3.46-3.53 (m, 1H), 2.78 (dd, *J* = 17.2, 9.3 Hz, 1H), 2.50 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.12 (s, 3H), 1.45 (s, 9H), 1.26 (td, *J* = 8.8, 7.1, 1.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.1, 170.5, 169.7, 166.2, 83.0, 71.6, 61.4, 61.0, 42.7, 32.0, 28.0, 20.6, 14.2, 14.1.

IR (neat): 1723 (s), 1708 (s), 1152 (s), 1201 (s), 1063 (s), 1015 (m), 843 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{16}H_{27}O_8$ $[M+H]^+$: 347.1706; found: 347.1709.

2,3-diethyl 1-((R)-1-(2-methoxyphenyl) prop-2-yn-1-yl) 1-acetoxypropane-1,2,3-tricarboxylate:



epi-197

Compound ***(±)-196*** (1 eq, 0.9 mmol, 300 mg) was dissolved in CH_2Cl_2 (1.5 mL) followed by slow addition of 250 µL of TFA. After complete consumption of starting material as followed by TLC, the reaction was diluted with toluene and the solvent together with TFA were removed by evaporation. The crude as oil was used for next step without purification.

To a stirred solution of the crude residue in CH_2Cl_2 (5 mL) was added (*R*)-1-Phenylpropargyl alcohol (1 eq, 0.9 mmol, 118 mg), EDC· HCl (1.5 eq, 1.35 mmol, 260 g), and DMAP (0.05 eq, 0.045 mmol, 6 mg) at room temperature. After 3 h, water was added to the reaction mixture, and the layers were separated. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude residue was purified by flash chromatography using pentane/Et_2O (3:1), yielding an inseparable mixture of diastereoisomers ***epi-197*** in 80% yield (0.72 mmol, 292 mg, oil).

General Data: $C_{21}H_{24}O_8$; FW: 404.15; TLC: R_f = 0.5 (hexane/EtOAc 2:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue.

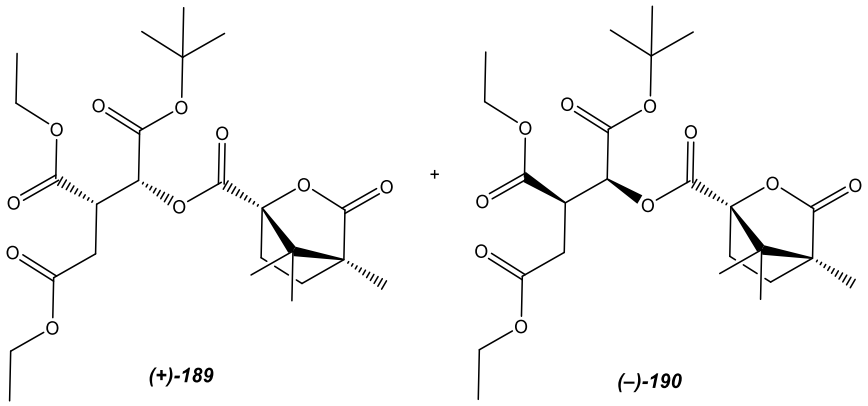
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.49-7.54 (m, 4H), 7.36-7.41 (m, 6H), 6.47 (d, *J* = 2.23 Hz, 1H), 6.44 (d, *J* = 2.30, 1H), 5.44 (dd, *J* = 5.2, 3.5 Hz, 2H), 4.09-4.19 (m, 8H), 4.01-4.08 (m, 1H), 3.90-3.99 (m, 1H), 3.55-3.65 (m, 2H), 2.89 (dd, *J* = 16.9, 9.4 Hz, 1H), 2.75 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.70 (dd, *J* = 3.0, 2.3 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 6H), 1.10 (t, *J* = 6.9 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.3, 171.2, 170.0, 169.9, 169.8, 169.7, 166.8, 166.8, 135.7, 135.6, 129.5, 129.4, 128.9, 128.8, 128.1, 127.9, 79.4, 79.3, 76.6, 76.4, 71.4, 71.3, 67.2, 66.9, 61.7, 61.6, 61.1, 61.1, 42.8, 42.7, 32.2, 32.1, 20.6, 20.5, 14.1, 14.0.

IR (neat): 3268 (w), 2981 (w), 1733 (s), 1455 (w), 1373 (m), 1189 (s), 1177 (s), 1076 (m), 1028 (m), 910 (w), 858 (w), 733 (m), 698 (m), 649 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{25}O_8$ $[M+H]^+$: 405.1549; found: 405.1543.

1-(tert-butyl) 2,3-diethyl (1R,2S)-1-(((1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo [2.2.1] heptane-1-carbonyl) oxy) propane-1,2,3-tricarboxylate:



To a stirred solution of ***(±)-188*** (1 eq, 1.31 mmol, 400 mg) in CH_2Cl_2 (10 mL) with NEt_3 (4.5 eq, 6.00 mmol, 0.8 mL) and DMAP (0.35 eq, 0.46 mmol, 56 mg), (–)-(1*S*,4*R*)-camphanic chloride (2 eq, 2.63 mmol, 570 mg) was added at 0°C. The stirring was continued overnight at room temperature. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 1:1) affording ***(+)-189*** in 45% yield (0.59 mmol, 286 mg, sticky oil) and ***(–)-190*** in 40% yield (0.52 mmol, 254 mg, clear oil).

General Data *(+)-189:* $C_{24}H_{36}O_{10}$; FW: 484.23; TLC: R_f = 0.45 (pentane/Et_2O 1:1); UV (-); Vanillin: light-blue; $[\alpha]_D^{20}$ = +2.8 (*c* = 1.45, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.36 (d, *J* = 3.6 Hz, 1H), 4.12-4.17 (m, 4H), 3.55-3.59 (m, 1H), 2.81 (dd, *J* = 16.7, 9.7 Hz, 1H), 2.51 (dd, *J* = 17.1, 5.0 Hz, 1H), 2.44-2.49 (m, 1H), 2.03-2.08 (m, 1H), 1.88-1.94 (m, 1H), 1.65-1.71 (m, 1H), 1.47 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 6H), 1.11 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 178.2, 171.2, 169.8, 166.7, 165.7, 91.1, 83.6, 72.9, 61.7, 61.2, 55.1, 54.6, 42.8, 32.1, 30.8, 28.9, 28.0, 16.8, 16.7, 14.3, 14.2, 9.9.

IR (neat): 2978 (w), 1791 (m), 1735 (s), 1252 (m), 1229 (m), 1156 (s), 1105 (s), 1061 (s), 1019 (m), 934 (w), 843 (w), 735 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{37}O_{10}$ $[M+H]^+$: 485.2386; found: 485.2384.

General Data *(–)-190*: $C_{24}H_{36}O_{10}$; FW: 484.23; TLC: R_f = 0.35 (pentane/Et_2O 1:1); UV (-); Vanillin: light-blue; $[\alpha]_D^{20}$ = -12.4 (*c* = 0.8, $CHCl_3$).

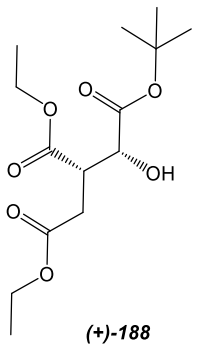
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 5.33 (d, *J* = 3.6 Hz, 1H), 4.14-4.19 (m, 4H), 3.55-3.59 (m, 1H), 2.81 (dd, *J* = 16.9, 9.6 Hz, 1H), 2.47 (dd, *J* = 16.9, 4.9 Hz, 1H), 2.39-2.44 (m, 1H), 2.04-2.10 (m, 1H), 1.90-1.96 (m, 1H), 1.67-1.73 (m, 1H), 1.48 (s, 9H), 1.26 (td, *J* = 8.5, 7.1, 1.3 Hz, 6H), 1.11 (s, 3H), 1.10 (s, 3H), 1.03 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 178.0, 171.2, 169.9, 166.4, 165.7, 91.0, 83.7, 72.7, 61.7, 61.2, 55.0, 54.8, 42.8, 32.4, 30.8, 29.2, 28.1, 16.6, 16.4, 14.3, 14.2, 9.8.

IR (neat): 2978 (w), 1786 (m), 1730 (s), 1253 (m), 1245 (m), 1140 (s), 1102 (s), 1052 (s), 1018 (m), 935 (w), 843 (w), 736 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{24}H_{37}O_{10}$ $[M+H]^+$: 485.2386; found: 485.2383.

1-(tert-butyl) 2,3-diethyl (1R,2S)-1-hydroxypropane-1,2,3-tricarboxylate:



(+)-188

Compound ***(+)-189*** (1 eq, 0.10 mmol, 50 mg) was dissolved in was dissolved in EtOH (2 mL), and finely powdered K_2CO_3 (1 eq, 0.10 mmol, 14 mg) was added. The mixture was stirred at room temperature for 4 h, then it was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined organic extracts were passed through a plug of silica/Na_2SO_4. The solvents were evaporated, and the residue was purified by flash

chromatography (hexane/EtOAc 15:1), yielding compound ***(+)-188*** (60%, 0.06 mmol, 18 mg) as a colorless oil.

General Data: $C_{14}H_{24}O_7$; FW: 304.15; TLC: R_f = 0.4 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = +32 (*c* = 0.10, $CHCl_3$).

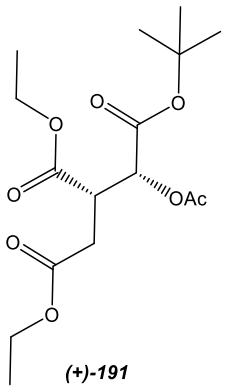
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 4.25 (d, *J* = 2.7 Hz, 1H), 4.12-4.17 (m, 4H), 3.42-3.46 (m, 1H), 2.85 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.57 (dd, *J* = 16.8, 5.5 Hz, 1H), 1.49 (s, 9H), 1.21-1.26 (m, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.9, 171.6, 170.8, 83.5, 70.8, 61.3, 60.9, 45.1, 32.3, 28.0, 14.3, 14.2.

IR (neat): 3015 (br), 1723 (s), 1156 (s), 1108 (s), 1096 (s), 1027 (m), 846 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{14}H_{24}O_7Na$ $[M+Na]^+$: 327.1419; found: 327.1414.

1-(tert-butyl) 2,3-diethyl (1R,2S)-1-acetoxypropane-1,2,3-tricarboxylate:



(+)-191

To a solution of ***(+)-188*** (1 eq, 0.164 mmol, 50 mg) in CH_2Cl_2 (2.5 mL), NEt_3 (3 eq, 0.5 mmol, 70 µL), DMAP (0.05 eq, 0.01 mmol, 1 mg), and Ac_2O (3 eq, 0.5 mmol, 50 µL) were added at 0°C. The mixture was stirred at room temperature for 5 h. The reaction mixture was poured into a 1M HCl solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 3:1), yielding the desired compound ***(+)-191*** (80%, 0.131 mmol, 45 mg, sticky oil).

General Data: $C_{16}H_{26}O_8$; FW: 346.16; TLC: = 0.6 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = +11.8 (*c* = 1.4, $CHCl_3$).

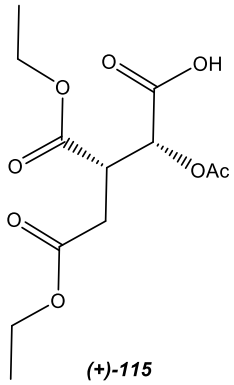
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.30 (d, *J* = 3.5 Hz, 1H), 4.13-4.20 (m, 4H), 3.47-3.54 (m, 1H), 2.78 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.50 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.12 (s, 3H), 1.46 (s, 9H), 1.26 (td, *J* = 8.8, 7.2, 1.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 171.1, 170.4, 169.7, 166.2, 83.0, 71.6, 61.4, 61.0, 42.8, 32.0, 28.0, 20.6, 14.2, 14.1.

IR (neat): 1721 (s), 1703 (s), 1152 (s), 1107 (s), 1063 (s), 1014 (m), 846 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{16}H_{26}O_8Na$ $[M+Na]^+$: 369.1525; found: 369.1524.

(2R,3S)-2-acetoxy-5-ethoxy-3-(ethoxy carbonyl)-5-oxopentanoic acid:



(+)-115

Compound ***(+)-191*** (1 eq, 0.144 mmol, 50 mg) was dissolved in CH_2Cl_2 (0.5 mL), followed by slow addition of 100 µL of TFA. After complete consumption of starting material, as monitored by TLC, the reaction was diluted with toluene, and the solvent along with TFA were removed by evaporation. The resulting crude product ***(+)-115,*** yielded in 90% (0.143 mmol, 41 mg) a colorless oil, was used for next step without purification.

General Data: $C_{12}H_{18}O_8$; FW: 290.10; TLC: = 0.1 (hexane/EtOAc 3:1); UV (-); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = +6.0 (*c* = 1.05, $CHCl_3$). 3.42-3.46 (m, 1H)

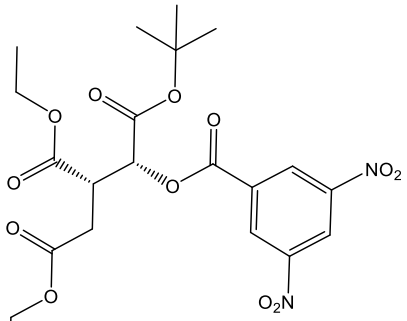
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 5.42 (d, *J* = 3.6 Hz, 1H), 4.12-4.17 (m, 4H), 3.60-3.66 (m, 1H), 2.86 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.54 (dd, *J* = 16.9, 5.4 Hz, 1H), 2.14 (s, 3H), 1.23-1.27 (m, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm): 173.0, 171.3, 170.6, 170.0, 71.3, 61.9, 61.2, 42.8, 32.4, 20.6, 14.2, 14.0.

IR (neat): 2982 (br), 1730 (s), 1446 (w), 1373 (m), 1216 (s), 1176 (s), 1027 (m), 956 (w), 857 (w), 734 (w), 615 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{12}H_{18}O_8Na$ $[M+Na]^+$: 313.0899; found: 313.0891.

1-(tert-butyl) 2,3-diethyl (1R,2S)-1-((3,5-dinitrobenzoyl) oxy) propane-1,2,3-tricarboxylate:



(–)-198

To a solution of ***(+)-188*** (1 eq, 0.164 mmol, 50 mg) in CH_2Cl_2 (3 mL), NEt_3 (3 eq, 0.5 mmol, 70 µL) and DMAP (0.1 eq, 0.02 mmol, 2 mg) were added at 0°C. Subsequently, 3,5-dinitrobenzoyl chloride (2 eq, 0.33 mmol, 76 mg) was added, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (5:1) gave ***(–)-198*** in 60% yield (0.1 mmol, 49 mg) as sticky oil.

General Data: $C_{21}H_{26}N_2O_{12}$; FW: 498.15; TLC: = 0.5 (hexane/EtOAc 3:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; con spot down $[\alpha]_D^{20}$ = -4.3 (*c* = 0.45, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm): 9.20 (t, *J* = 2.1 Hz, 1H), 9.10 (t, *J* = 2.1 Hz, 2H), 5.30 (d, *J* = 3.2 Hz, 1H), 4.08-4.17 (m, 4H), 3.64-3.69 (m, 1H), 2.90 (dd, *J* = 17.2, 8.6 Hz, 1H), 2.54 (dd, *J* = 17.1, 8.6 Hz, 1H), 1.44 (s, 9H), 1.26 (t, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 7.3 Hz, 3H).

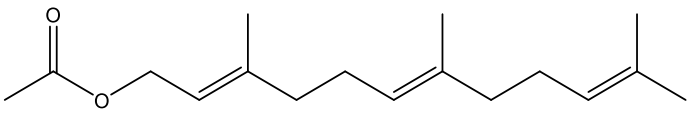
^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm): 171.1, 170.5, 169.8, 165.7, 148.9, 133.1, 129.8, 129.7, 123.0, 84.3, 74.0, 61.4, 62.0, 42.9, 32.5, 28.0, 14.3, 14.2.

IR (neat): 3600 (m), 1723 (s), 1523 (s), 1406 (s), 1156 (s), 1108 (s), 1096 (s), 1027 (m), 1108 (m), 846 (w), 713 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{26}N_2O_{12}Na$ $[M+Na]^+$: 521.1383; found: 521.1384.

5.1.3. Synthesis of (±)-albicanol: from compound *200* to *(±)-203*

(2E,6E) -3,7,11-trimethyldodeca-2,6,10-trien-1-yl acetate:



200

All-trans-Farnesol ***199*** (1 eq, 11.24 mmol, 2.82 mL) was dissolved in CH_2Cl_2 (60 mL) at room temperature. Pyridine (4 eq, 45 mmol, 3.6 mL), Ac_2O (6 eq, 67.44 mmol, 6.4 mL), and DMAP (0.05 eq, 0.56 mmol, 69 mg) were added sequentially. The mixture was stirred for 1 h at this temperature, after which 1 M HCl solution was added, and the layers were separated. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 75:1) to afford *all-trans*-Farnesyl Acetate ***200*** in 99% yield (11.13 mmol, 2943 mg) as a colorless oil.

General Data: $C_{17}H_{28}O_2$; FW: 264.21; TLC: R_f = 0.7 (hexane/EtOAc 9:1); UV (+); Vanillin: brown.

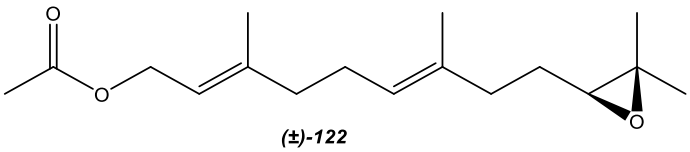
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm): 5.33 (tq, *J* = 7.1, 1.3 Hz, 1H), 5.07-5.10 (m, 2H), 4.58 (d, *J* = 7.1 Hz, 2H), 2.08-2.13 (m, 2H), 2.04 (s, 3H), 2.02-2.07 (m, 4H), 1.95-1.98 (m, 2H), 1.69-1.71 (m, 3H), 1.66-1.68 (m, 3H), 1.57-1.60 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ (ppm): 171.2, 142.4, 135.6, 131.4, 124.4, 123.7, 118.4, 61.5, 39.8, 39.7, 26.8, 26.3, 25.8, 21.2, 17.8, 16.6, 16.1.

IR (neat): 2920 (w), 1739 (s), 1443 (w), 1366 (w), 1229 (s), 1022 (m), 954 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_2$ $[M+H]^+$: 265.2167; found: 265.2162.

(2E,6E) -9-(3,3-dimethyloxiran-2-yl) -3,7-dimethylnona-2,6-dien-1-yl acetate:



(±)-122

N-bromosuccinimide (1.2 eq, 46.80 mmol, 8.3 g) was added to an ice-cooled solution of trans,trans-farnesyl acetate ***200*** (1 eq, 39 mmol, 10.2 g) in a mixture of THF/H_2O (225 mL/ 75 mL). The mixture was stirred at this temperature for 3h. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude material was used for next step without purification. The crude residue was dissolved in THF (130 mL) and cooled to 0°C. DBU (1.3 eq, 50.70 mmol, 7.6 mL) was then added, and the reaction was stirred at this temperature for 3h. H_2O was added, and the reaction mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with pentane/Et_2O (16:1) gave the desired compound ***(±)-122*** in 75% yield (29.3 mmol, 8.2 g) as a colorless oil.

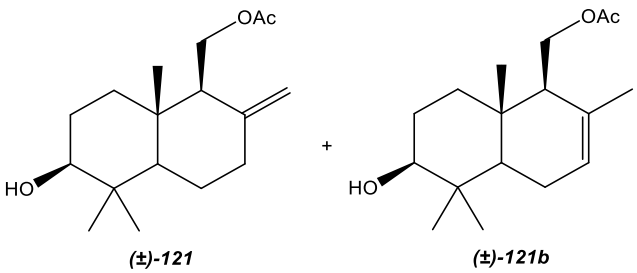
General Data: $C_{17}H_{28}O_3$; FW: 280.20; TLC: R_f = 0.6 (hexane/EtOAc 4:1); UV (+); Vanillin: brown. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm): 5.32 (tq, *J* = 7.2, 1.2 Hz, 1H), 5.13 (tq, *J* = 6.9, 1.2 Hz, 1H), 4.56 (d, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.04-2.14 (m, 5H), 2.03 (s, 4H), 1.66-1.70 (m, 3H), 1.54-1.66 (m, 5H), 1.28 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 171.2, 142.2, 134.7, 124.4, 118.5, 64.2, 61.5, 58.4, 39.5, 36.4, 27.6, 26.3, 25.0, 21.2, 18.9, 16.6, 16.1.

IR (neat): 3022 (w), 2921 (m), 2850 (w), 1738 (s), 1445 (w), 1337 (w), 1229 (s), 1022 (m), 733 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_3$ $[M+H]^+$: 281.2116; found: 281.2097.

(6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) methyl acetate:



(±)-121 ***(±)-121b***

A mixture of Mn dust (8 eq, 11.44 mmol, 629 mg) and Cp_2TiCl_2 (0.2 eq, 0.29 mmol, 71 mg) was suspended in THF (20 mL) at room temperature. After 15–20 min, the color of the reaction mixture changed from reddish to greenish. A solution of trimethylsilyl chloride (4.5 eq, 6.44 mmol, 0.82 mL) in THF (1 mL) and a solution of 2,4,6-collidine (7 eq, 10 mmol, 1.32 mL) in THF (0.5 mL) were added simultaneously. After 5 min, compound ***(±)-122*** (1 eq, 1.43 mmol, 400 mg) was added, and the mixture was stirred for 20 h. Excess Mn was dissolved by adding HCl (2M, 1.5 mL). H_2O was added, and the reaction mixture was extracted with Et_2O. The combined organic extracts were evaporated, and the resulting highly viscous, brownish oil was dissolved in CH_3CN (1.5 mL), and HF (40% in H_2O; 0.1 mL) was added. After 1 h, $KHCO_3$ (2 eq, 2.86 mmol, 286 mg) and H_2O (0.5 mL) were slowly added. The mixture was partitioned between CH_2Cl_2 and H_2O, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (pentane/Et_2O 40:1) yielding ***(±)-121*** (37%, 0.53 mmol, 148 mg) and ***(±)-121b*** (5%, 0.1 mmol, 20 mg), both oily and colorless.

General Data *(±)-121*: $C_{17}H_{28}O_3$; FW: 280.20; TLC: R_f = 0.7 (hexane/EtOAc 3:1); UV (+); Vanillin: green.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 4.86 (d, *J* =1.4 Hz, 1H), 4.55 (d, *J* = 1.5 Hz, 1H), 4.33 (dd, *J* = 11.2, 3.8 Hz, 1H), 4.17 (dd, *J* = 11.3, 8.9 Hz, 1H), 3.23 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.40 (ddd, *J* = 13.0, 4.2, 2.3 Hz, 1H), 2.00-2.01 (m, 2H), 1.74-2.00 (m, 4H), 1.67-1.72 (m, 2H), 1.35 -1.57 (m, 3H), 1.10 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.98 (s, 3H), 0.75 (s, 3H), 0.74 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 171.0, 145.9, 107.0, 78.8, 60.9, 54.0, 53.9, 39.0, 38.9, 37.0, 36.5, 28.1, 27.6, 23.2, 20.7, 15.4, 14.7.
IR (neat): 3105 (br), 2952 (w), 1739 (s), 1610 (m), 1443 (w), 1367 (m), 1239 (s), 1095 (s), 893 (s), 838 (s), 749 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_3$ $[M+H]^+$: 281.2116; found: 281.2105.

General Data *(±)-121b*: $C_{17}H_{28}O_3$; FW: 280.20; TLC: R_f = 0.75 (hexane/EtOAc 3:1); UV (+); Vanillin: blue.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.40 (t, *J* = 1.5 Hz, 1H), 4.35 (dd, *J* = 11.0, 3.6 Hz, 1H), 4.17 (dd, *J* = 11.1, 7.6 Hz, 1H), 3.12 (dd, *J* = 11.2, 3.9 Hz, 1H), 2.31 (ddd, *J* = 13.1, 4.2, 2.0 Hz, 1H),

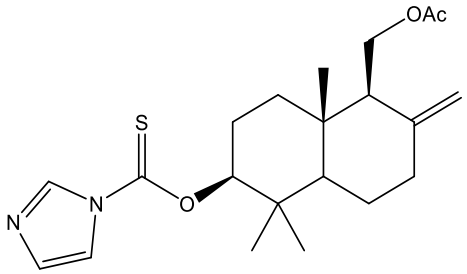
1.91-1.97 (m, 2H), 1.70-2.00 (m, 4H), 1.68 (s, 3H), 1.35 -1.57 (m, 3H), 1.10 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.98 (s, 3H), 0.75 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 171.2, 132.4, 123.3, 79.4, 61.5, 54.1, 54.4, 39.0, 38.9, 36.5, 28.0, 27.6, 23.2, 21.2, 20.7, 15.4, 14.7.

IR (neat): 3100 (br), 2955 (w), 1712 (s), 1588 (m), 1414 (w), 1337 (s), 1096 (s), 890 (s), 837 (s), 743 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_3$ $[M+H]^+$: 281.2116; found: 281.2111.

(6-((1H-imidazole-1-carbonothioyl) oxy)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) methyl acetate:



(±)-201

Compound ***(±)-121*** (1 eq, 0.52 mmol, 146 mg) was dissolved in toluene (12 mL), and TCDI (2.7 eq, 1.40 mmol, 250 mg) and DMAP (1.1 eq, 0.57 mmol, 70 mg) were added at room temperature. The reaction mixture was stirred at 80 °C for 48 h. The mixture was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1, then 1:1) to afford ***(±)-201*** in 80% yield (0.42 mmol, 162 mg) as a light-yellow crystalline solid.

General Data: $C_{21}H_{30}O_3N_2S$; FW: 390.20; TLC: R_f = 0.6 (hexane/EtOAc 3:2); UV (+); Vanillin: black; Mp 110-115 °C.

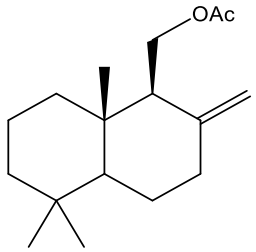
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.4 (s, 1H), 7.6 (d, *J* = 1.5 Hz, 1H), 7.2 (d, *J* = 1.5 Hz, 1H), 5.26 (dd, *J* = 11.9, 4.2 Hz, 1H), 4.88 (d, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 1.5 Hz, 1H), 4.29 (dd, *J* = 11.5, 4.3 Hz, 1H), 4.17 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.42 (ddd, *J* =13.0, 4.0, 2.2 Hz, 1H), 2.03-2.05 (m, 4H), 2.00 (s, 3H), 1.82 (ddd, *J* = 13.1, 3.6 Hz, 1H), 1.30-1.74 (m, 4H), 0.98 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 181.4, 171.4, 145.4, 135.0, 132.6, 118.6, 108.5, 93.2, 61.4, 54.5, 54.3, 39.0, 38.6, 37.2, 36.5, 28.5, 23.2, 23.0, 21.2, 17.6, 15.2.

IR (neat): 2942 (w), 1735 (s), 1370 (m), 1228 (s), 1099 (w), 1030 (w), 896 (w), 730 (s), 644 (w), 606 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{31}O_3N_2S$ $[M+H]^+$: 391.2055; found: 391.2056.

(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) methyl acetate:



(±)-202

Thiocarbamate ***(±)1-201*** (1 eq, 0.51 mmol, 200 mg), Bu_3SnH (3 eq, 1.53 mmol, 0.4 mL), and AIBN (0.2 eq, 0.10 mmol, 17 mg) were dissolved in toluene (75 mL). The reaction mixture was stirred at 160 °C for 3 h, then the oil-bath temperature was reduced to 125°C, and stirring continued for an additional 2 h. The mixture was cooled to room temperature using a water bath, then all the

volatiles were evaporated. The crude product was purified by flash chromatography (pentane/Et_2O 20:1), yielding ***(±)-202*** (85%, 0.43 mmol, 115 mg) as a colorless oil.

General Data: $C_{17}H_{28}O_2$; FW: 264.21; TLC: R_f = 0.8 (hexane/EtOAc 3:1); UV (-); Vanillin: black.

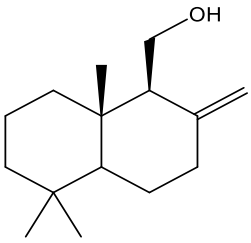
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 4.85 (d, *J* = 1.4 Hz, 1H), 4.48 (d, *J* = 1.5 Hz, 1H), 4.33 (dd, *J* = 11.3, 3.8 Hz, 1H), 4.19 (dd, *J* = 11.3, 9.1 Hz, 1H), 2.40 (ddd, *J* = 13.1, 4.1, 2.2 Hz, 1H), 2.03-2.06 (m, 2H), 2.01 (s, 3H), 1.73-1.76 (m, 1H), 1.12-1.72 (m, 8H), 0.88 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 171.4, 145.4, 108.5, 61.4, 54.5, 54.3, 42.1, 39.1, 39.0, 37.2, 33.8, 33.7, 23.2, 21.2, 19.3, 17.6, 15.2.

IR (neat): 2952 (m), 1739 (s), 1610 (m), 1443 (w), 1367 (w), 1230 (s), 1095 (m), 1031 (m), 893 (m), 838 (s), 749 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{17}H_{29}O_2$ $[M+H]^+$: 265.2167; found: 265.2151.

(5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl) methanol:



(±)-203

Finely powdered K_2CO_3 (2.5 eq, 0.85 mmol, 118 mg) was added to a solution of Albicanyl acetate ***(±)-202*** (1 eq, 0.34 mmol, 90 mg) in MeOH (4 mL), and the reaction was stirred at room temperature overnight. The mixture was partitioned between Et_2O and H_2O, the aqueous layer was extracted with Et_2O, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (pentane/Et_2O 10:1) afforded compound ***(±)-203*** (90 %, 0.31 mmol, 68 mg) as a colorless oil.
General Data: $C_{15}H_{26}O$; FW: 222.20; TLC: R_f = 0.4 (hexane/EtOAc 3:1); UV (-); Vanillin: brown.

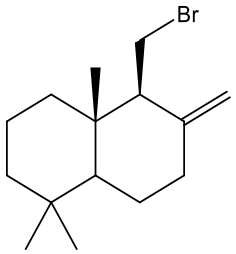
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 4.94 (d, *J* = 1.4 Hz, 1H), 4.64 (d, *J* = 1.5 Hz, 1H), 3.83 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.75 (dd, *J* = 11.0, 9.7 Hz, 1H), 2.42 (ddd, *J* = 12.9, 4.5, 2.5 Hz, 1H), 2.02 (td, *J* = 18.4, 13.0, 5.0 Hz, 2H), 1.72-1.77 (m, 2H), 1.64-1.68 (m, 2H), 1.45-1.58 (m, 2H), 1.30-1.44 (m, 2H), 1.10-1.14 (m, 1H), 0.87 (s, 3H), 0.80 (s, 3H),0.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 148.1, 106.5, 59.3, 59.0, 55.3, 42.1, 39.1, 39.0, 38.0, 33.8, 33.6, 24.4, 21.9, 19.4, 15.4.

IR (neat): 3353 (br), 2919 (s), 2846 (m), 1458 (m), 1384 (m), 1363 (w), 1113 (w), 1088 (w), 1023 (s), 969 (s), 913 (s), 822 (w), 770 (w), 674 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{15}H_{27}O$ $[M+H]^+$: 223.2062; found: 223.2057.

(4aS,5S)-5-(bromomethyl)-1,1,4a-trimethyl-6-methylenedecahydronaphthalene:



(±)-120

To a solution of ***(±)-203*** (1 eq, 0.03 mmol, 6 g) in dry THF (0.65 mL) was added PBr_3 (1.5 eq, 0.05 mmol, 5 µL) at 0°C, and the reaction was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo.

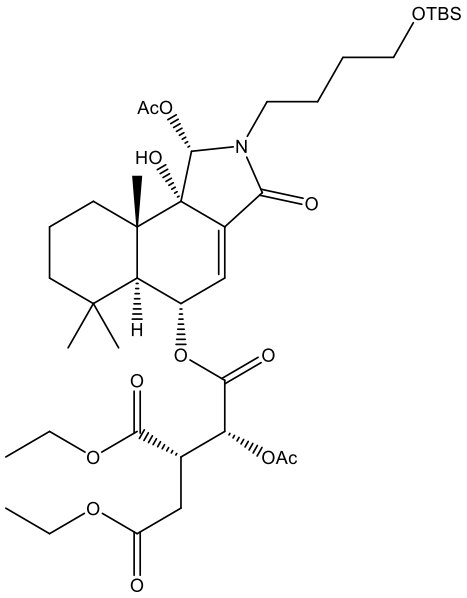
General Data: $C_{15}H_{25}Br$; FW: 284.11; TLC: R_f = 0.3 (hexane); UV (-); Vanillin: black.

HRMS (ESI): calculated for $C_{15}H_{25}$ $[M\text{-}Br]^+$: 205.1951; found: 205.1953.

HRMS (ESI): calculated for $C_{15}H_{26}Br$ $[M+H]^+$: 285.1218; found: 285.1226.

5.1.4. Coupling reaction: from compound *(–)-205* to *(–)-207*

1-((1S,5S,5aS,9aS,9bS)-1-acetoxy-2-(4-((tert-butyldimethylsilyl) oxy) butyl) -9b-hydroxy-6,6,9a-trimethyl-3-oxo-2,3,5,5a,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-5-yl) 2,3-diethyl (1R,2S)-1-acetoxypropane-1,2,3-tricarboxylate:



(–)-205

The crude acid ***(+)-115*** (1.5 eq, 0.03 mmol, 9mg) was dissolved in THF (0.3 mL) and treated at room temperature with NEt_3 (6 eq, 0.12 mmol, 17 µL) and 2,4,6-trichlorobenzoyl chloride (4 eq, 0.08 mmol, 12 µL). The turbid solution was stirred for 2 h at room temperature and then diluted with toluene (0.3 mL) and added dropwise to a solution of alcohol ***(–)-109*** (1 eq, 0.02 mmol, 10 mg) and DMAP (6 eq, 0.12 mmol, 15 mg) in toluene (0.5 mL). The mixture was stirred 3 h at room temperature and then quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with Et_2O. The organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 1:1) to afford ***(–)-205*** (60%, 0.12 mmol, 9 mg) as a sticky yellow oil.

General Data: $C_{39}H_{63}NO_{13}Si$; FW: 781.41; TLC: R_f = 0.45 (hexane/EtOAc 1:1); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = -24 (*c* = 0.25, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.99 (d, *J* = 2.0 Hz, 1H), 6.50 (s, 1H), 5.40 (d, *J* = 3.7 Hz, 1H), 5.36 (dd, *J* = 9.8, 2.3 Hz, 1H), 4.05-4.19 (m, 4H), 3.55-3.76 (m, 3H), 2.70-2.81 (m, 3H), 2.60 (d, *J* = 9.6 Hz, 1H), 2.51 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.12 (s, 3H), 2.12 (s, 3H), 1.34-1.80 (m, 6H),

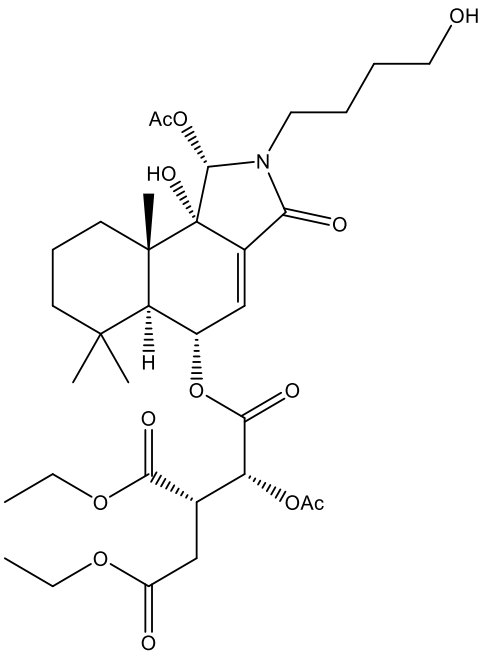
1.26 (t, *J* = 7.2 Hz, 6H), 1.06-1.23 (m, 4H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.6, 171.4, 170.8, 170.1, 170.0, 167.4, 140.5, 135.3, 87.3, 71.8, 71.5, 65.8, 61.8, 61.2, 61.1, 48.7, 45.9, 42.9, 40.2, 36.0, 34.4, 34.2, 34.1, 32.3, 30.5, 25.8, 22.8, 21.6, 20.7, 20.6, 19.2, 18.4, 17.6, 14.3, 14.0, -5.2.

IR (neat): 3380 (br), 2987 (w), 2931 (w), 2853 (w), 1730 (s), 1547 (m), 1373 (m), 1216 (m), 1162 (m), 1123 (m), 1027 (m), 843 (s), 820 (m), 803 (m), 734 (w), 537 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{39}H_{64}NO_{13}Si$ $[M+H]^+$: 782.4147; found: 782.4148.

1-((1S,5S,5aS,9aS,9bS)-1-acetoxy-9b-hydroxy-2-(4-hydroxybutyl)-6,6,9a-trimethyl-3-oxo-2,3,5,5a,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-5-yl) 2,3-diethyl (1R,2S)-1-acetoxypropane-1,2,3-tricarboxylate:



(–)-206

To a solution of ***(–)-205*** (1 eq, 0.012 mmol, 9 mg) in THF (2 mL) TBAF (1M in THF, 1 eq, 0.08 mmol, 80 µL) was added at 0°C and the stirring was continued at the same temperature. After 3 h, the reaction mixture was poured into a saturated solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and

concentrated in vacuo. The crude material was purified with flash chromatography (hexane/EtOAc 1:2) to afford ***(–)-206*** in quantitative yield (0.012 mmol, 8 mg) as sticky oil.

General Data: $C_{33}H_{49}NO_{13}$; FW: 667.32; TLC: R_f = 0.40 (hexane/EtOAc 1:2); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = -16 (*c* = 0.2, $CHCl_3$).

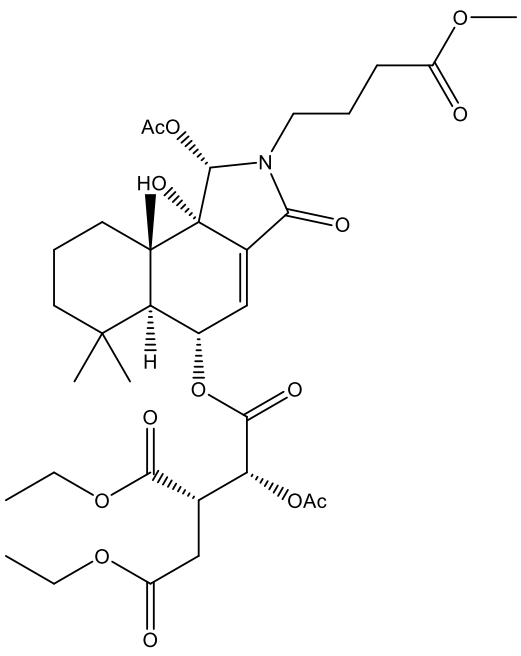
^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.99 (d, *J* = 2.1 Hz, 1H), 6.51 (s, 1H), 5.38 (d, *J* = 3.7 Hz, 1H), 5.36 5.36 (dd, *J* = 9.5, 2.2 Hz, 1H), 4.04-4.19 (m, 4H), 3.58-3.76 (m, 3H), 2.75-2.81 (m, 3H), 2.60 (d, *J* = 9.6 Hz, 1H), 2.50 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 1.34-1.82 (m, 6H), 1.26 (t, *J* = 7.2 Hz, 6H), 1.06-1.20 (m, 4H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.6, 171.4, 170.8, 170.1, 170.0, 167.4, 140.5, 135.3, 87.3, 71.8, 71.5, 65.8, 62.6, 61.2, 61.1, 48.7, 45.9, 42.9, 41.7, 36.0, 34.4, 34.2, 34.1, 31.9, 31.0, 30.5, 21.6, 20.7, 20.6, 19.2, 17.6, 14.3, 14.0.

IR (neat): 3412 (br), 2980 (w), 2929 (w), 2880 (m), 2453 (w), 1690 (s), 1545 (m), 1363 (m), 1210 (m), 1153 (m), 1123 (m), 1027 (m), 843 (s), 803 (m), 734 (w), 535 (w) cm^{-1}.

HRMS (ESI): calculated for $C_{33}H_{53}N_2O_{13}$ $[M+NH_4]^+$: 685.3548; found: 685.3546.

1-((1S,5S,5aS,9aS,9bS)-1-acetoxy-9b-hydroxy-2-(4-methoxy-4-oxobutyl)-6,6,9a-trimethyl-3-oxo-2,3,5,5a,6,7,8,9,9a,9b-decahydro-1H-benzo[e]isoindol-5-yl) 2,3-diethyl (1R,2S)-1-acetoxypropane-1,2,3-tricarboxylate:



(–)-207

To a stirred solution of ***(-)-206*** (1 eq, 0.012 mmol, 8 mg) in CH_2Cl_2 (40 mL) was added Dess-Martin periodinane (2 eq, 0.024 mmol, 10 g) at 0°C, and stirring was continued at room temperature 3 h. The white solution was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was used without further purification.

$NaClO_2$ (2 eq, 0.024 mmol, 2 mg) and NaH_2PO_4 (4 eq, 0.05 mmol, 6 g) were dissolved in water (15 µL) at 0 °C and stirred for 1 h. The crude aldehyde (1 eq, 0.012 mmol, 8 mg) was dissolved in *t*-BuOH (50 µL) and 2-methyl-2-butene (8.1 eq, 0.1 mmol, 10 µL). The system was stirred for half an hour, then the aqueous $NaClO_2$/ NaH_2PO_4 solution was added slowly over 15 min at 0 °C. After the reaction was kept for 1 h at this temperature, saturated NH_4Cl was poured into the system. The aqueous layer was extracted with Et_2O, then the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford in quantitative yield the oxidized product. The residue was dissolved in ether (0.2 mL) and the solution was cooled to 0 °C. A 2.0 M ethereal solution of diazomethane (1.5 eq, 0.015 mmol, 7.5 µL) was added and the reaction was stirred for 30 min. The reaction was quenched by the dropwise addition of acetic acid (5 µL), followed by the subsequent addition of saturated aqueous $NaHCO_3$.The who phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography on silica gel (hexane/EtOAc 1:2) afforded ***(-)-207*** as sticky oil in 65% yield over 3 steps (0.01 mmol, 7 mg).

General Data: $C_{34}H_{49}NO_{14}$; FW: 695.32; TLC: R_f = 0.45 (hexane/EtOAc 1:2); UV (+); Cerium-Molybdate Phosphoric acid reagent: blue; $[\alpha]_D^{20}$ = -19.5 (*c* = 0.20, $CHCl_3$).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm): 6.69 (d, *J* = 7.8 Hz, 1H), 6.40 (s, 1H), 5.40 (d, *J* = 3.7 Hz, 1H), 5.28-5.36 (m, 1H), 4.05-4.19 (m, 4H), 3.65 (s, 3H), 3.49-3.52 (m, 1H), 2.75-2.81 (m, 3H), 2.51 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.12 (s, 3H), 2.12 (s, 3H), 2.01 (d, *J* = 6.3 Hz, 1H), 1.34-1.82 (m, 6H), 1.26 (t, *J* = 7.2 Hz, 6H), 1.06-1.23 (m, 4H), 1.20 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H).

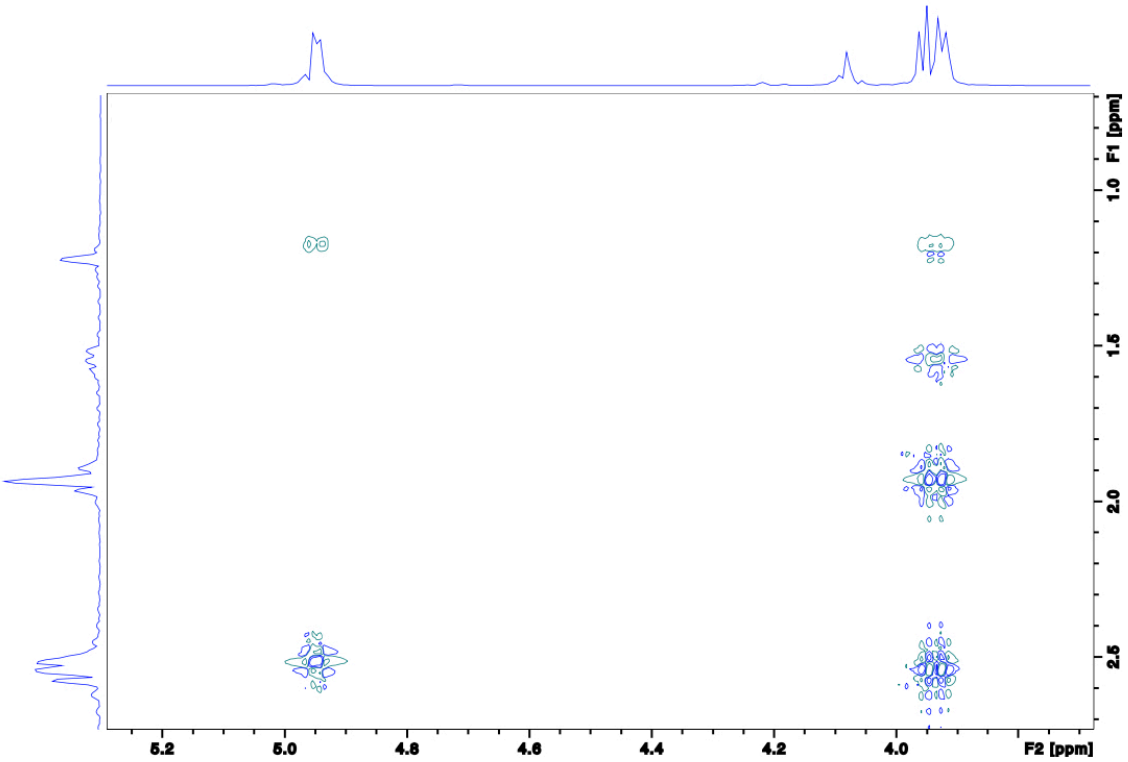
^{13}C-NMR (151 MHz, $CDCl_3$): δ (ppm): 171.5, 171.4, 170.7, 170.2, 170.0, 167.5, 166.5, 140.7, 135.3, 87.4, 71.8, 71.5, 65.9, 62.5, 61.2, 61.1, 48.8, 46.0, 43.0, 41.7, 36.0, 34.3, 34.3, 34.1, 31.9, 31.0, 30.6, 21.6, 20.7, 20.6, 19.1, 17.6, 14.3, 14.1.

IR (neat): 3420 (br), 2981 (w), 2930 (w), 2880 (m), 2453 (w), 1690 (s), 1756 (s), 1545 (m), 1365 (m), 1222 (m), 1170 (m), 1125 (m), 1027 (m), 843 (s), 803 (m), 734 (w) cm^{-1}.

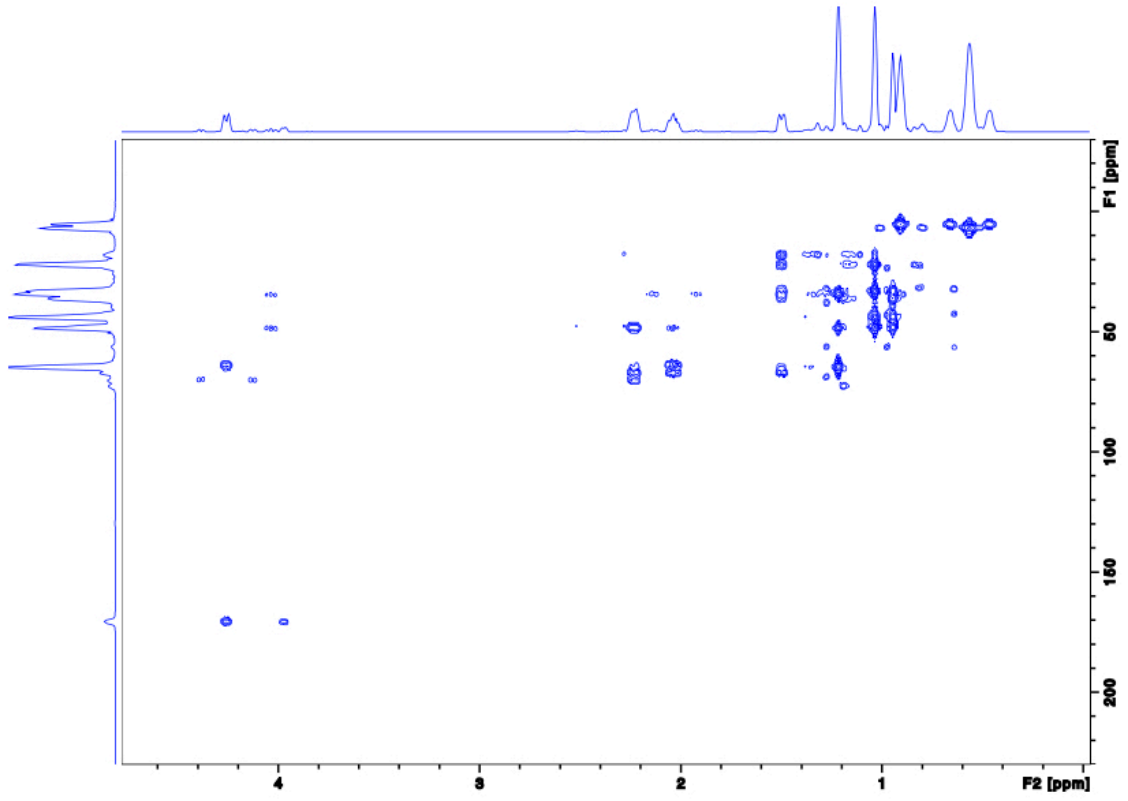
HRMS (ESI): calculated for $C_{34}H_{49}N_2O_{14}Na$ $[M+Na]^+$: 718.3050; found: 718.3051.

5.2. Appendix – NOESY NMR and HMBC NMR spectra for confirmation of stereochemistry

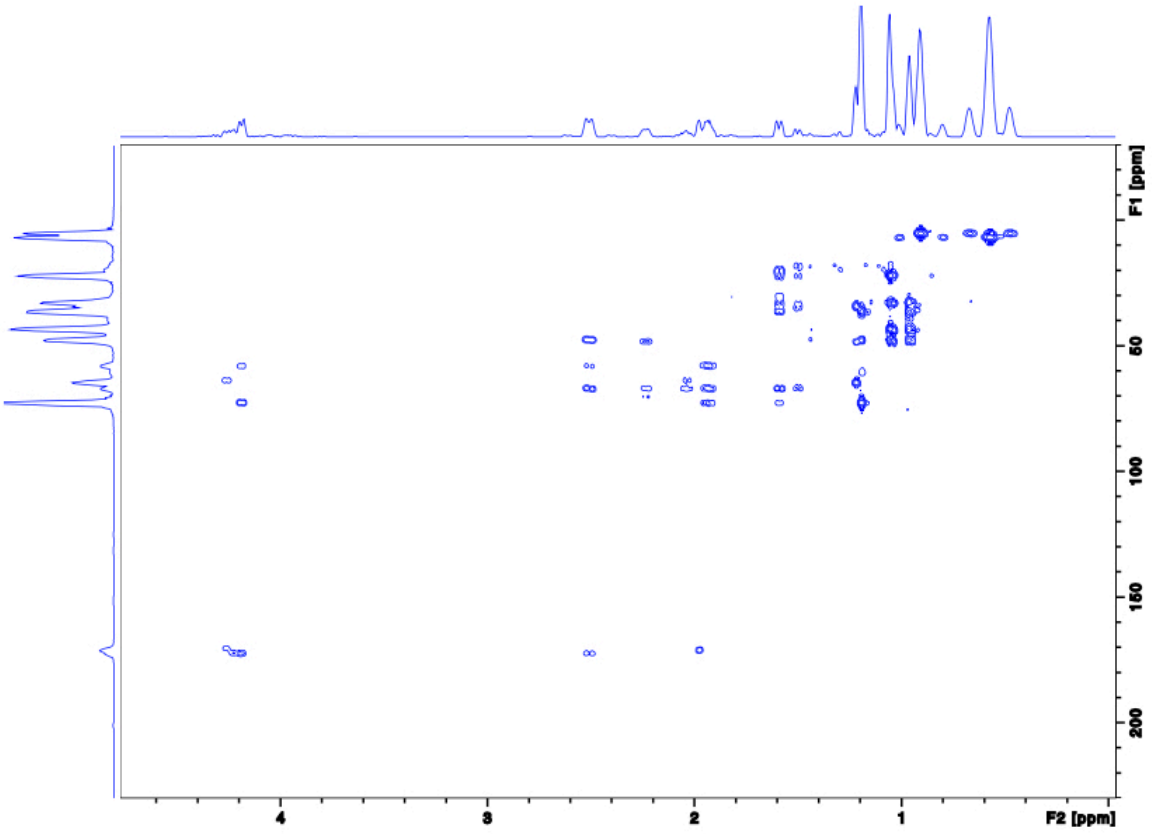
- Compound ***(±)-172***



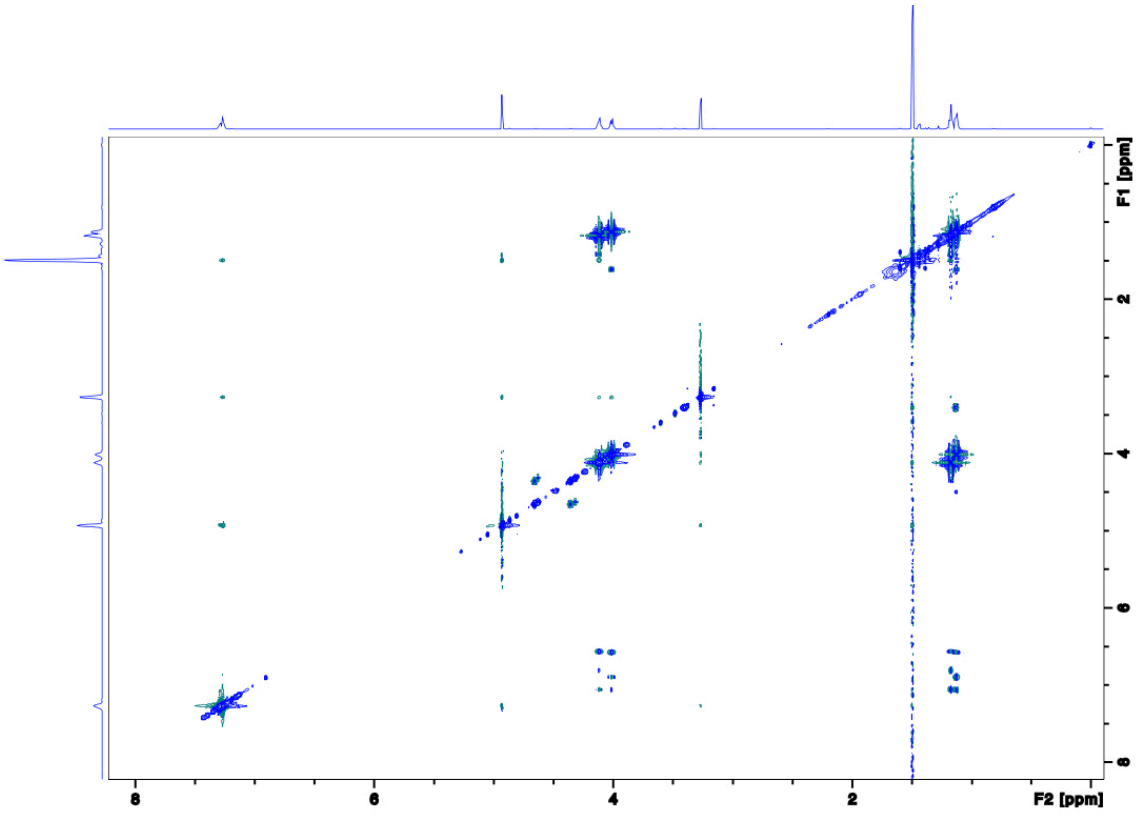
- Compound ***(–)-111b***



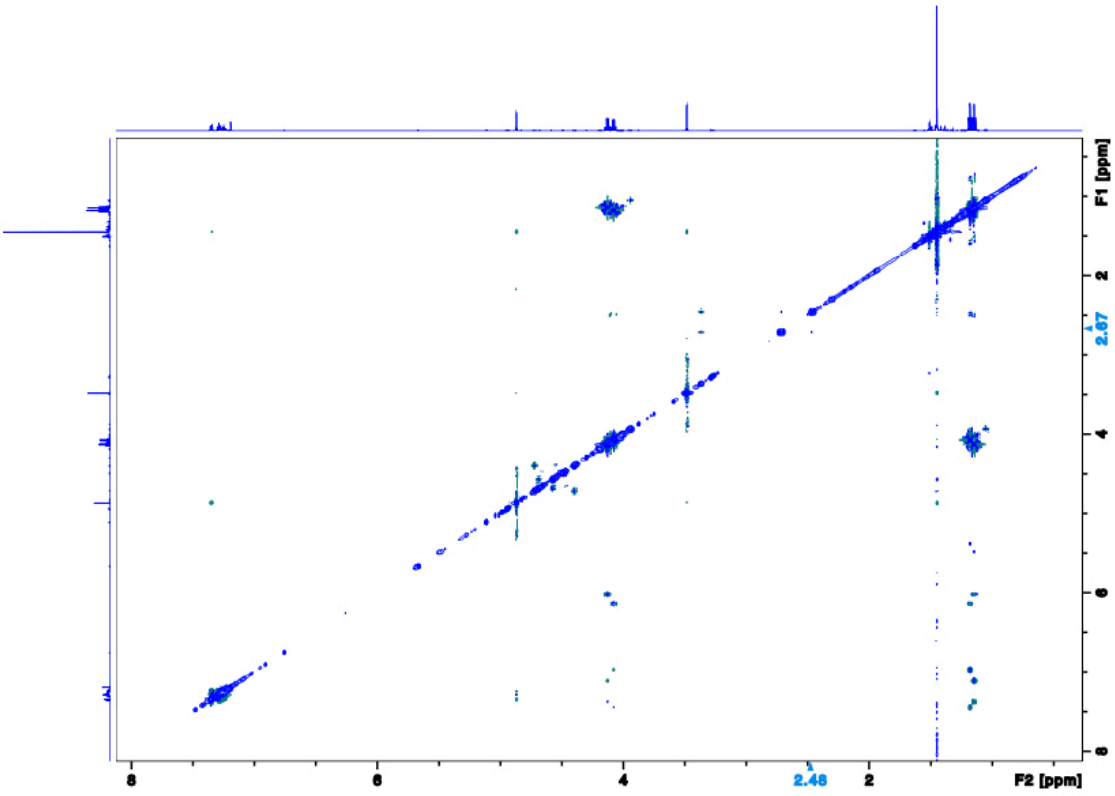
- Compound ***(+)-111***



- Compound ***E-116***



- Compound ***Z-116***



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