Sclareolide as a building block for natural product syntheses

and

Mechanistic studies on the α-chlorination of aldehydes

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by
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from Berlin

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I hereby declare that the submitted thesis is my own work and was prepared autonomously without the aid of other sources than the ones cited and acknowledged. The work was not submitted to any other prior doctoral procedure.

Martina Menger Berlin, 14.09.2018

The following thesis was carried out under the supervision of Prof. Dr. Mathias Christmann from November 2014 until September 2018 at the Department of Biology, Chemistry, and Pharmacy of Freie Universität Berlin.

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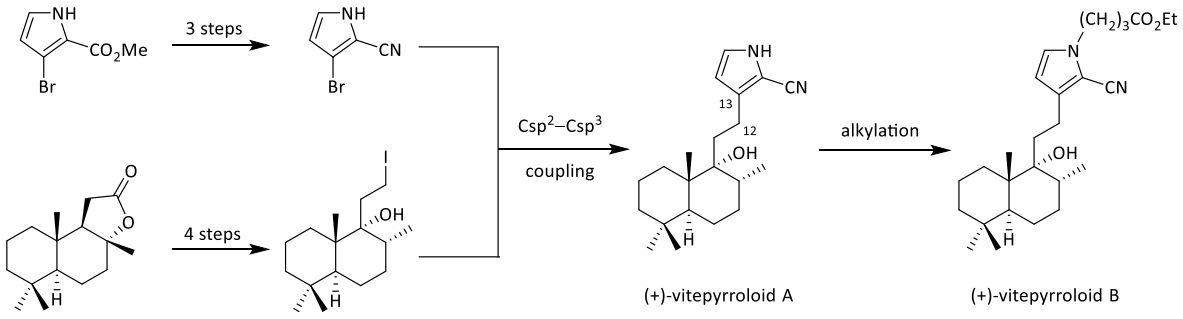
ABSTRACT

In the following thesis, the syntheses of two natural products and of a natural products' skeleton starting from (+)-sclareolide are presented. The second part of this thesis deals with the mechanistic studies on the organocatalytic α-chlorination of aldehydes.

The first synthesis of (+)-vitepyrroloid A and B, which are labdane-type diterpene alkaloids isolated from the dried leaves of the shrub *Vitex trifolia* L. in 2017, is outlined. The natural products share an unprecedented 2-cyanopyrrole labdane core but differ in the substitution pattern of the pyrrole ring. Furthermore, (+)-vitepyrroloid A displayed an interesting biological activity. The low isolation yield prompted the development of an efficient synthesis. Therefore, the natural product was divided into two fragments.

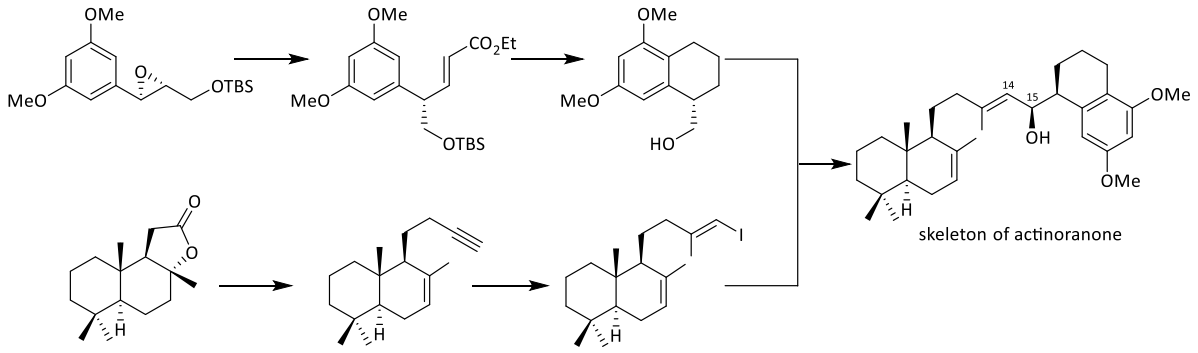
(+)-Sclareolide formed the base for the four-step synthesis of the alkyl iodide, which featured simultaneous methanolysis and tertiary alcohol elimination. The aryl bromide was synthesized starting from 3-bomopyrrole-2-carboxylic acid in three steps. The key step was the Csp^2–Csp^3 cross-electrophile coupling of both fragments in a concise and protecting-group-free manner. This cross-coupling illustrates a rare application of this method in natural product synthesis. In the end, (+)-vitepyrroloid B was accessible by late-stage *N*-alkylation of its congener.



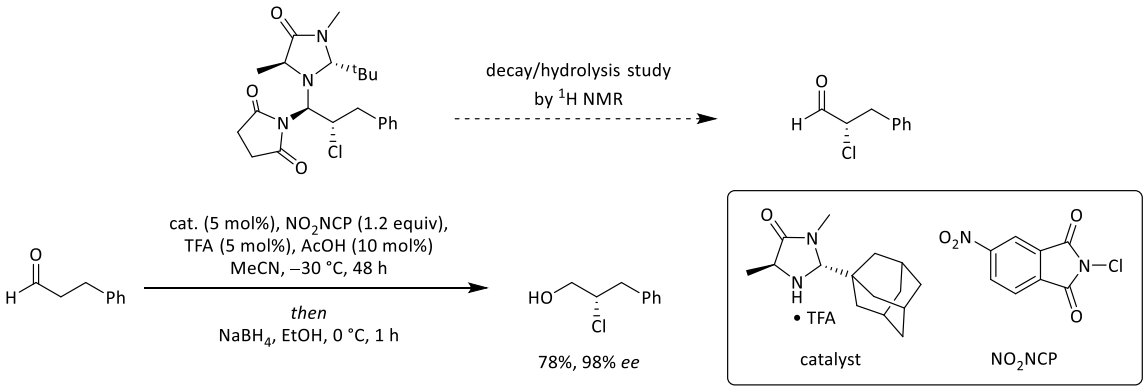
The second project comprises the formal synthesis of actinoranone, a meroterpenoid isolated from the marine actinomycete strain CNQ-027 in 2013. This natural product constitutes of a tetralone-type polyketide connected with a bicyclic diterpenoid fragment and displayed a cytotoxicity against HCT-116 human colon carcinoma. This work addressed a new and more efficient formal synthesis in comparison to the two recently published synthesis routes.

3,5-Dimethoxybenzaldehyde and (+)-sclareolide served as starting points for the two fragments envisioned by the disconnection between C14 and C15 of actinoranone. The first fragment, a vinyl iodide, was obtained in a concise five-step route featuring NEGISHI's zirconium-catalyzed carboalumination/iodination sequence as the main step. The key step of

the tetralone fragment synthesis featured a LEWIS acid-mediated rigorous chirality transfer of the previously synthesized epoxy silyl ether to the β-siloxy aldehyde *via* a rearrangement inspired by YAMAMOTO. Subsequent WITTIG olefination led to the conjugated ester. The last steps to the actinoranone skeleton were similar to the already published routes.



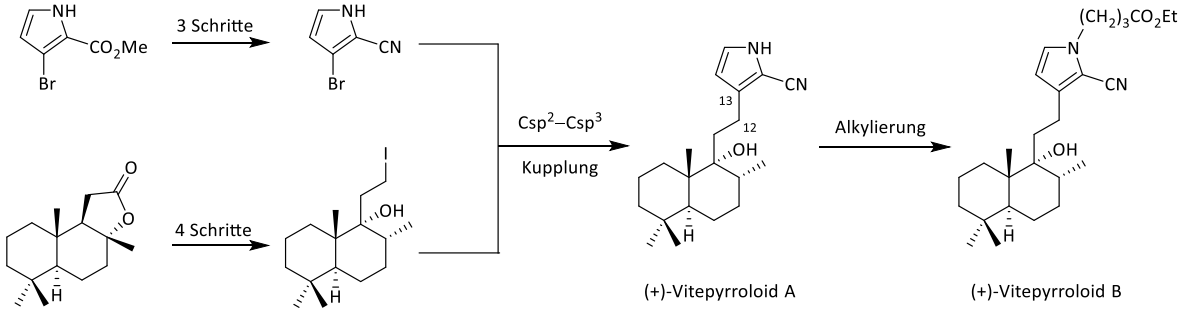
In the second part of this thesis, the mechanistic investigation of the organocatalytic α-chlorination of aldehydes is discussed. Preliminary studies revealed a high catalyst loading in a procedure using *N*-chlorosuccinimide and MACMILLAN's imidazolidinone catalyst. In this study, the α-chlorination of hydrocinnamaldehyde served as a model reaction. An unusual aminal intermediate, consisting of the substrate, the catalyst, and the chlorinating agent, was isolated and fully characterized. This work aimed at a deeper understanding of the aminal formation and its decay with the aid of ^{1}H MR measurements. The results enabled the optimization of the α-chlorination by suppressing the aminal accumulation and enhancing the turnover by applying an improved reaction system (yields up to 87%, >99% *ee*).



KURZFASSUNG

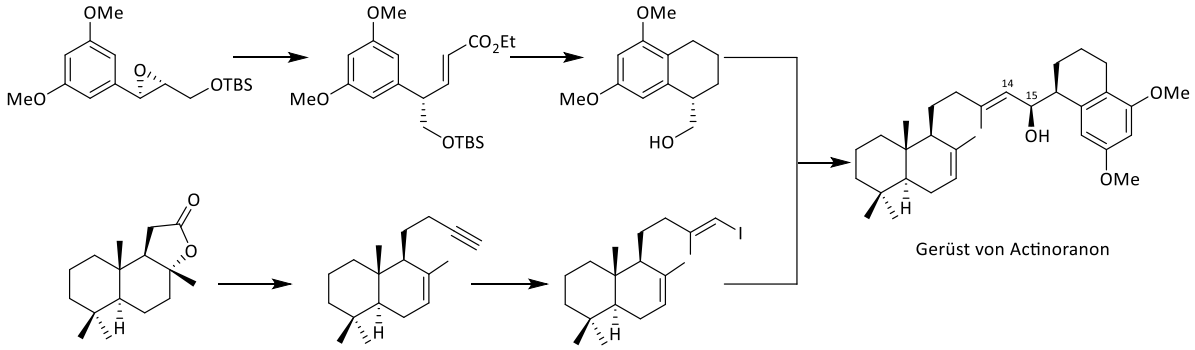
In der vorliegenden Arbeit sind die Synthesen von zwei Naturstoffen und von einem Naturstoffgerüst ausgehend von Sclareolid beschrieben. Der zweite Teil der Arbeit beinhaltet die mechanistische Untersuchung der organokatalysierten α-Chlorierung von Aldehyden.

Die erste Synthese von (+)-Vitepyrroloid A und B, zwei 2017 aus den getrockneten Blättern des *Vitex trifolia* L. Busches isolierte Labdan-artigen Diterpenalkaloide, ist beschrieben. Sie besitzen einen beispiellosen 2-Cyanopyrrollabdankern, unterscheiden sich jedoch im Substitutionsmuster des Pyrrolringes. Darüber hinaus wurde eine interessante biologische Aktivität von (+)-Vitepyrroloid A festgestellt. Die geringe Isolationsmenge spornte uns für die Entwicklung einer effizienten Synthese an. Dafür wurde der Naturstoff in zwei Fragmente unterteilt. (+)-Sclareolid diente als Ausgangsverbindung für die vierstufige Synthese des Alkyliodides, welche eine Methanolyse und gleichzeitige Eliminierung des entstehenden tertiären Alkohols aufwies. Das Arylbromid wurde in drei Stufen ausgehend von 3-Brompyrrol-2-carboxylsäuremethylester aufgebaut. Der Schlüsselschritt der Synthese war die präzise und schutzgruppenfreie kreuzelektrophilen Kupplung der beiden Fragmente. Die Csp^2–Csp^3-Kreuzkupplung stellt ein seltenes Beispiel dieser Methode in der Naturstoffsynthese dar. (+)-Vitepyrroloid B konnte durch eine Alkylierung des Stickstoffatoms von (+)-Vitepyrroloid A dargestellt werden.

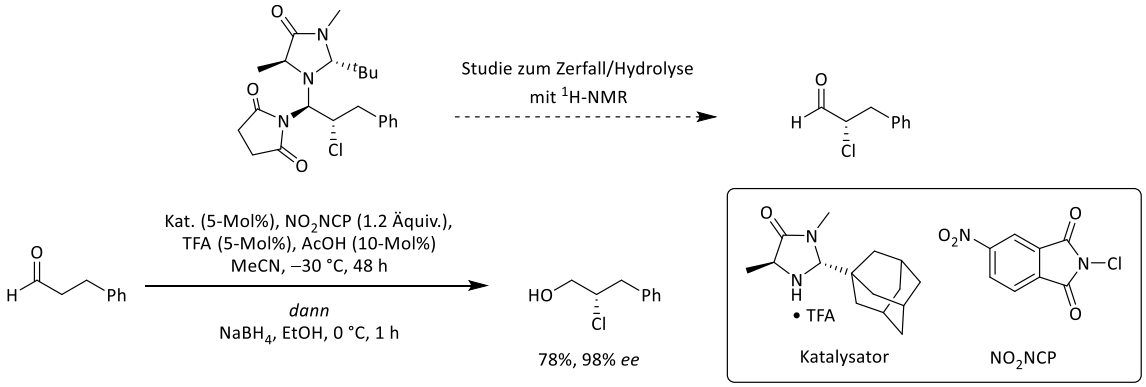


Das zweite Projekt beinhaltet die Formalsynthese von Actinoranon, ein Meroterpenoid, welches aus dem marinen Actinomycetstrang CNQ-027 2013 isoliert wurde. Dieser Naturstoff ist aus einem tetralon-artigen Polyketid verbunden mit einem bizyklischen Diterpen aufgebaut und besitzt eine Cytotoxizität gegenüber HCT-116 humanen Darmkrebs. Es wurde auf eine neue und effizientere Route zu diesem Naturstoff im Vergleich zu den beiden kürzlich veröffentlichten Routen abgezielt. 3,5-Dimethoxybenzaldehyd und (+)-Sclareolid bildeten die Ausgangsverbindungen für die Synthese der Fragmente von Actinoranon, welche durch den

retrosynthetischen Schnitt zwischen C14 und C15 entstanden. Das Vinyliodidfragment wurde durch eine fünfstufige Route kennzeichnend durch NEGISHI's Zirconium-katalysierte Carboaluminierung/Iodierungssequenz erhalten. Der Schlüsselschritt der Tetralonsynthese war der durch Lewissäure unterstützte rigorose Chiralitätstransfer von dem dargestellten Epoxysilylether auf den β-Siloxyaldehyd durch eine von YAMAMOTO inspirierte Umlagerung. Der Aldehyd wurde sofort mittels WITTIG-Reaktion zum ungesättigten Ester umgesetzt. Die abschließenden Schritte zum Actinoranongerüst waren ähnlich den bereits veröffentlichten Routen.



Der zweite Teil dieser Arbeit handelt von mechanistischen Untersuchungen der organokatalytischen α-Chlorierungen von Aldehyden. In einer vorausgehenden Studie wurden hohe Katalysatorbeladungen bei der Verwendung von *N*-Chlorsuccinimid und MACMILLAN's Imidazolidinonkatalysator beobachtet. In dieser Studie diente die α-Chlorierung von Hydrozimtaldehyd als Modellreaktion. Ein ungewöhnliches Aminal-Intermediat, bestehend aus dem Substrat, dem Katalysator und dem Chlorierungsmittel, wurde isoliert und charakterisiert. Die Untersuchungen mittels ^{1}H-NMR Spektroskopie zielten auf die Bildung und den Zerfall des Aminals ab. Die Ergebnisse dieser Untersuchungen führten zu einem optimierten System mit erhöhter Reaktionsrate und verminderter Katalysatorbeladung (Ausbeuten bis zu 87%, >99% *ee*).



ABBREVIATIONS

API	active pharmaceutical ingredient
9-BBN	9-borabicyclo[3.3.1]nonane
BCE	before common era
bpy	bipyridine
CE	common era
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	discrete Fourier transform
FDA	Food and Drug Administration
GC-MS	gas chromatography-mass spectrometry
GGPP	geranylgeranyl pyrophosphate
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzym-A
HTS	high-throughput screening
HV	high vacuum
IC_{50}	median inhibitory concentration
LD_{50}	median lethal dose
LLS	longest linear sequence
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
ROESY	rotating-frame nuclear Overhauser effect
SAR	structure-activity relationship
SOMO	single occupied molecular orbital
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
UV	ultraviolet

TABLE OF CONTENT

Part A

Sclareolide as a building block for natural product syntheses

1) INTRODUCTION

1.1 General aspects of natural products

1.1.1 The origin of natural products

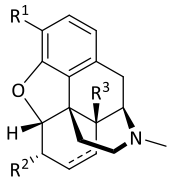
For centuries, humans relied on nature to provide for their basic needs, whether it was for the production of shelters and clothing, fertilizers, flavors and fragrances, and not at last, nutritional or medical purposes.[1-2] In particular, the discovery and utilization of biogenic compounds led to major advances in the health and nutrition sector over the last century. Especially, the supplementation of vitamins, the identification of natural toxins, and the introduction of drugs based on natural products in modern medicine improved life in terms of expectancy and quality.[3]

Nature is an enormous source of small molecules, which are defined by a molecular weight smaller than 1 000 Da and have attained massive success related to health problems of our society (e.g., diabetes, cancer, obesity). Due to their small size, they are capable to pass the cell membrane and then affect or complement biological targets such as proteins and hence might regulate biological processes. With their inherent diversity, they are distinct from macromolecules such as proteins, nucleic acids, and most polysaccharides and serve as a tool proofing biological functions as well as promising leads for the development of therapeutic agents.[4] The naturally occurring small molecules are produced by living organisms such as plants, animals, or microorganisms.[5] The term “natural product” is mostly used to describe secondary metabolites which, in contrast to the primary ones like carbohydrates, lipids, proteins, and nucleic acids, are not essential for the normal growth, development, or reproduction of an organism. Secondary metabolites provide the general maintenance and homeostasis of an organism.[6] They can contribute to the organism’s survival by providing specific responses to competitors, pathogens, or predators; in the competition for environment and nutriments; in the inter- and intraspecies communication for mating, or for hunting and quorum signaling.[5] These selected natural substances are binding to protein receptors and thereby initiate a cascade process, which leads to the modulation of specific functions. Additional hypotheses for the origin of natural products have been proposed: secondary metabolites might have had a former functional role. They could have been products of accidental mutations or formed as by-products of the organism’s response to an external stimulus such as infestation.[2, 6] Naturally occurring small molecules are generally

divided into different classes of compounds: alkaloids, terpenoids, phenolics, polyketides, lipids, glycosides, nonribosomal peptides, phenanzines, and tetrapyrroles. They not only affect their actual target in animals, plants, or microorganisms but may also influence human cells.[7] They feature complex and diverse molecular structures which have been applied as medicines, flavorings, or recreational drugs.[8] In ancient times, indigenous tribes used natural substances for hunting, religious purposes, and medicaments. Not without a reason, it is told that nature is an ancient pharmacy. Owing to this, the pharmacological active natural products can be of therapeutic benefit for treating human diseases. The two main sources, namely plants and marine organisms, for these biologically active compounds are discussed in the following subchapter.

1.1.2 Plant- and marine-derived natural products – a historical perspective

Plants for medical treatment have been already used 60 000 years ago and still remain one of the main sources for pharmacologically active compounds in drug discovery.[9-10] Over 1 000 plant-derived formulations were documented in Mesopotamia medicine and some of the used oils are still employed today for coughs and colds in the Egyptian medicine.[11] Around 700 medicaments from plant origin were recorded in the Ebers Papyrus dating from 1 500 BCE in Egypt.[2] Other prominent examples are the herbals in Chinese medicine or the Indian Ayurvedic system.[11] The rational development of herbal drugs in the ancient Western world was driven by the Greeks and Romans around 100 CE. Finally, the Arabs combined the Greco-Roman expertise with the knowledge about Chinese and Indian herbs in the Early Middle Ages.[2] Still today, the plant-based medicine continues to play an essential role in healthcare. This is highlighted by the fact that around 65% of the world population relies on plant-derived traditional medicine for primary health care as estimated by the World Health Organization (WHO) in 2002.[12] The evolution from herbal remedies to potent clinical drugs and therefore to active pharmaceutical ingredients (API) was a slow and gradual process that started in 1804. In this year, the German pharmacist F. SERTÜRNER isolated a highly potent alkaloid, which is nowadays still used as a painkiller, from the opium poppy *Papaver somniferum* (Figure 1) and named after the Greek god of dreams, morphine.[7] This first-time isolated natural product was the basis for many synthetic and natural analogs with similar relevant analgesic properties such as heroin, codeine, and oxycodone (Figure 1).



morphine: R^1, R^2 = OH, R^3 = H
double bond
heroin: R^1, R^2 = OAc, R^3 = H
double bond
codeine: R^1 = OMe, R^2 = OH, R^3 = H
double bond
oxycodone: R^1 = OMe R^2 = CO, R^3 = OH
single bond

Figure 1: Structure of morphine, its direct derivatives, and opium poppy flower. Reprinted with permission of P. Robot.[13]

In the last century, the receptor theory of drug action in which certain chemical compounds in extracts of plants specifically interact with the biological macromolecules in human bodies remodeled the way of thinking towards drugs as individual active substances instead of plants as remedies.[14] Thus, the active compounds of several traditional medicinal plants were elucidated. For instance, in 1820, French pharmacists isolated the antimalarial drug quinine from the bark of *Cinchona* species.[1] Before, it has already been used by indigenous groups in the Andes and later by the Spanish conquerors for the treatment of fevers. With the isolation and also the proper administration, quinine became the antimalarial treatment of choice over the powdered bark treatment; however, the structure has not been elucidated until 1908 (Figure 2).[10] Another example of plant-derived medicine is the cardiotonic agent digoxin. It was elucidated from the extracted of foxglove, *Digitalis purpurea*, which was commonly used for the treatment of heart diseases (Figure 2).[1, 14]

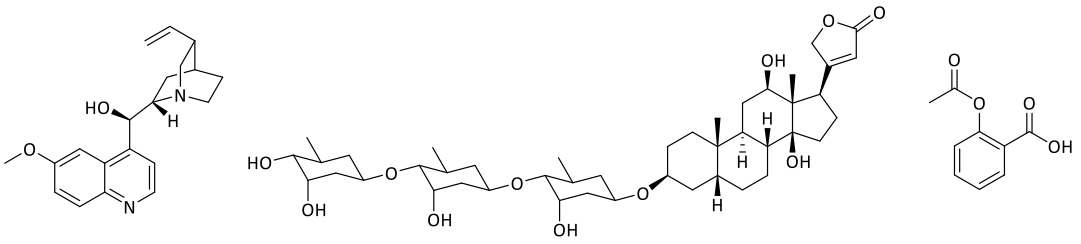


Figure 2: Structures of digoxin, quinine, and Aspirin®.

The Greek physician Hippocrates already used willow trees and other plants for pain relieve at childbirth, but not until the 19th century the acidic component of the willow tree extracts, salicylic acid, was isolated. This natural product was optimized in terms of the pharmacological profile leading to the popular drug acetylsalicylic acid (Aspirin®) by Bayer in 1897 (Figure 2).[10]

Another successful example of a natural product as a source for medicine is the penicillin antibiotic agent, which was serendipitously discovered by FLEMING in 1929 from the filamentous fungus *Penicillium notatum*. The broad therapeutic use of penicillins in the 1940's marked the beginning of the so-called "Golden Age" of antibiotics and led to the intensive investigation on nature as a source of novel bioactive compounds.[1, 5]

Apart from plants, marine organisms serve as a versatile source for naturally active compounds. They do not possess a history as traditionally used medicine; however, there are some indications for their usage as dies and soil fertilizers by the Phoenicians.[1] The outstanding, prolific source of biodiversity in the sea has yet to be explored more intensively. Oceans cover around 70% of the Earth's surface. Here, life originated about 3.5 billion years ago and developed a huge biodiversity which accounts for more than 95% of the whole biosphere.[15-16] Approximately 80% of the ocean's area is accounted to the so-called deep sea, which starts around 200 m below the surface and extends down to 1 000 m and beyond. Its unique and extreme environment is characterized by high pressure, extreme temperatures, lack of light, extreme pH-values, toxic chemicals such as H_2S, variable salinities, and oxygen concentrations.[17] These environmental conditions differ considerably from the terrestrial world, but microbes are capable of occupying almost every conceivable habitat for life. Under these extreme circumstances, the production of novel bioactive compounds is fostered.[15] Additionally, the struggle for space and survival is another driving force for the development of new and bioactive substances used in the defense of habitat.[18] The mentioned extreme conditions lead to superior natural products compared to the terrestrial-derived ones in terms of chemical novelty.[17] But only after the progression in deep-sea exploration, these novel natural products could be discovered. The emergent role of marine natural products is also manifested in the data of the year 2016 where 1277 new bioactive compounds from the sea were described in the literature.[19] It is undeniable that these compounds are attracting increasing attention as a consequence of their wide variety of biological activities such as antitumor,[20-22] antiviral,[23] anti-HIV,[24] antiangiogenesis,[25] antituberculosis activity,[26] among others. In addition to that, these products are highly potent as their marine environment causes rapid dilution.[27] Due to the technical advances such as sampling strategies and nanoscale NMR for structure determination, the discovery and isolation of marine natural product was more feasible and had considerable success in the last years.[17]

1.1.3 Natural products as lead sources for drug discovery

Natural products are not only interesting because of their structural diversity, but moreover, they provide highly selective and specific biological activities based on their specific mechanisms of action. The HMG-CoA reductase inhibition exhibited by lovastatin and the tubulin-assembly promotion induced by paclitaxel are two prime examples. Therefore, naturally occurring compounds play a significant role in the identification of lead structures for the development of novel drugs.[4, 11] It is estimated that in the early 1900s around 80% of the medicines were derived from roots, barks, and leaves.[28] The rise of natural product-based drug candidates during the 20th century began with the elucidation of the active compounds in natural sources. In this regard, some well-known drugs[1] were developed from traditional medicine:

- the antihypertensive agent reserpine (Raudixin®) derived from *Rauwolfia serpentina*, (used in Ayurvedic medicine against snakebites)
- the synthetical basis for anti-asthma agents salbutamol (Ventolin®) and salmeterol (Serevent®) obtained from ephedrine (known in the traditional Chinese medicine)
- the muscle relaxant tubocurarine chloride (Tubarine®) (basis of arrow poison curare of indigenous groups in the Amazon)

Interestingly, less than 10% of the world's estimated biodiversity has been tested in biological screenings.[29] Only 5–15% of the approximately 300 000 species of higher plants have been systematically, chemically, and pharmacologically investigated.[2] The marine environment as a source for novel drugs remains comparatively unexplored as outlined in the previous chapter. Its extensive study began in the mid-1970's with the technological progress in deep-sea exploration. In 1969, cytarabine (Cytosar-U®) was introduced as the first drug derived from a marine natural product to the medical anticancer market. This was followed by the antiviral drug vidarabine (Vira-A®) in 1976 and the analgesic agent ziconotide (Prialt®) in 2004.[5] Nevertheless, many interesting biologically active compounds suffer from poor pharmacological profiles; hence, synthetic modifications with respect to stability and bioavailability are sought. It is stated that 80% of the commercial drugs based on natural products require synthetic efforts to improve physiochemical properties in terms of pharmacokinetics/pharmacodynamics.[30]

The relevant contribution of natural products as sources of new drugs has been demonstrated in a review from NEWMAN and CRAGG dealing with the development of approved drugs from 1981–2014 (Figure 3). They revealed that 67% of the 1211 new chemical entities (NCEs, a drug that contains no already approved active moiety by the FDA) formally are derived from a synthetic origin. Within these 67%, 18% correspond to synthetic molecules containing pharmacophores derived from natural products (S* and S*/NM) and 14% mimic or model a natural product inhibitor of the molecular target of interest (NM). Hence, only 35% are of purely synthetic origin (S). Their analysis also showed that 83% of new approved anticancer drugs and 78% of anti-infectives were either *per se* or were based on natural products. The data points out the dominant role of the biologically active natural substances for these two categories. On the other side, it displays the drop of natural products as new drugs in comparison to the time range 1981–2007.[4, 29]

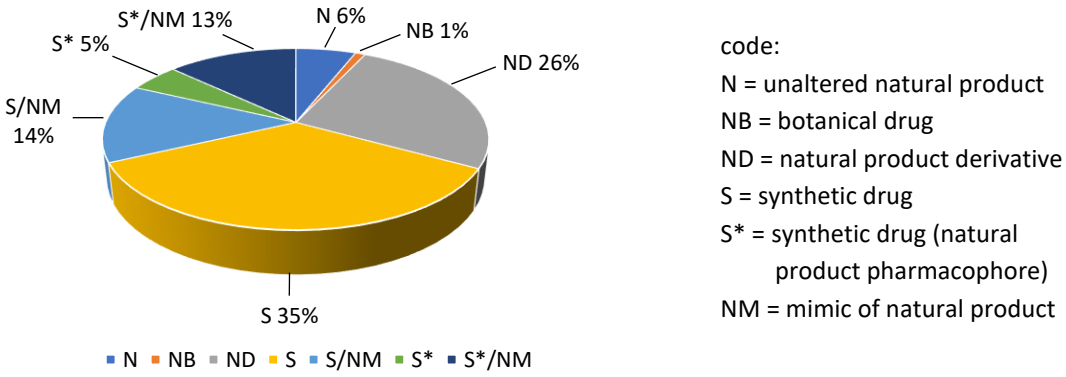
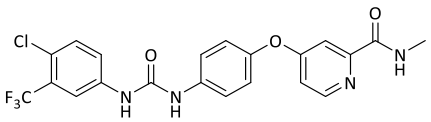


Figure 3: Approved small-molecule drugs from 1981–2014; n = 1211.[4]

The reason for the decline can be traced back to the circumstance that the industry embraced the era of combinatorial chemistry and high-throughput screening (HTS) in the last two decades.[31] It was assumed that the chemical assembly of as many substances as possible by synthesis robots and trawling through vast libraries of small molecules with rather simple structures by automated procedures will identify new lead compounds against biological targets; however, this approach showed little success.[32-33] In this period, only one *de novo* combinatorial chemistry-synthesized drug, sorafenib (Nexavar®), which treats renal cell and hepatocellular carcinoma, has been approved (Figure 4).[4]



sorafenib

Figure 4: The structure of only *de novo* synthesized drug sorafenib.

Despite the great success of natural products in drug discovery, they are substantially underrepresented in current small molecule-based compound libraries. For a successful design of drug discovery program based on natural products, four main elements are thought to be crucial: acquisition of biomass, effective screening, bioactivity-driven fractionation, rapid and effective structure elucidation.[2] These procedures still remain challenging. Next to this time-demanding task, a limited supply of the natural sources, low isolation yield, and structurally complex molecules for modifications and/or synthesis are the main factors. Although the development of new technologies was embraced,[34] the HTS hit-rate lies only around 0.1% and in most cases, the identified hit is not suitable to become a lead structure for drug development due to the lack of activity and selectivity.[10] Moreover, the quality and outcome of HTS strongly depend on the chemical and structural diversity of the screened compound library. In this regard, the compound libraries based on combinatorial chemistry only cover a limited chemical space in comparison to already approved drugs and natural products.

It was shown that the greater number of sp^3-centers and higher structural complexity that are typical in natural products leads to higher success rates in drug discovery campaigns. Prominent examples of this hypothesis are Taxol® and Rapamycin® whose impact in biology and therapy could never be predicted *a priori*.[35] The main differences between natural products and approved drugs in comparison to components from combinatorial chemistry libraries are that the former are usually less hydrophobic and include less aromatic moieties; they have a higher number of chiral centers; more O- and less N-, S-, and halogen atoms; as well as higher levels of three-dimensionality and structural rigidity (Figure 5).[10, 14] It is stated that about 40% of the molecular scaffolds found in natural products are missing in today's medicinal chemistry contingent.[34] Overall, these failures of the last decades reflect that we are far from the vision to produce a drug candidate by rational design on a computer or by virtual screening of chemical space. [36] Natural products provide in general a greater structural

diversity than the standard combinatorial chemistry libraries can create or modulate and hence possess major opportunities to bind to a range of assay targets.[29]

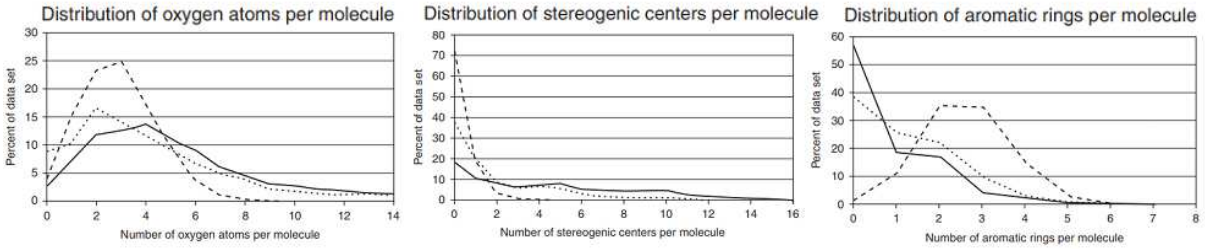


Figure 5: Property diagrams of natural products (—), drugs (·····), and synthetic (from combinatorial chemistry) compounds (-----).[10]

An alternative approach that the pharmaceutical industry is currently pursuing is the combinatorial chemistry- and diversity-oriented synthesis. Herein the goal is to preselect a range of structurally diverse molecules starting from a common core that is elaborated following the principle of combinatorial chemistry and therefore provide a large and diverse compound library. However, these libraries possess a small hit rate compared to natural products and additionally potential side effects arise due to the less specific binding of these still rather simple molecules.[37-38] Natural products are only represented in 1% of all existing libraries due to the incompatibility of HTS with their solubility and self-fluorescence.[35, 39] New technological advances and development of new methods such as combinatorial biosynthesis or improved natural product sourcing are expected to overcome these drawbacks in the future.[40] Despite pharmaceutical companies have abandoned the research on natural products, they still provide a major source of new drugs candidates and consequently will secure their future on account of their unbeatable potencies.[41-42] In an essay on "Advancing the Drug Discovery and Development Process", NICOLAOU made an interesting statement concerning the role of natural products in the future.[43]

> *"The three-dimensional structures of natural products and their wealth of chiral centers should serve as an inspiration and motivation for drug designers. The dimensionality and chirality of biological receptors and the fact that natural products have evolved along and against such biomolecules explains their divers, potent, and often selective biological properties. Employing them and molecules like them as leads and introducing some of their structural features in drug designs makes good sense and should be a complementary approach to the currently employed drug design"*

Referring to NICOLAOU's statement, another perspective on natural products is given in a review of CRANE and GADEMANN. Here, they evaluate an approach based on natural product derived fragments which display a reduced molecular weight, structural complexity, and reduced number of synthetic steps while retaining or even improving the key biological parameters (e.g., bioactivity, pharmacokinetics, solubility, etc.).[30] An interesting example for this structural simplification concept is the development of bryostatin analogs. The marine natural product possesses a large range of biological activities and either has been or is currently being evaluated in 37 clinical trials for the treatment of various cancer types.[30] Studying the mode of action led to the assumption that the bigger part of the structure acts as a framework for three distinct oxygen atoms, two alcohols, and a lactone unit. The simplification of the so-called scaffold region (upper part of the molecule) led to analog A (picolog) which was found to be more potent than the parent compound and practically suitable for large-scale synthesis (Figure 6).[37]

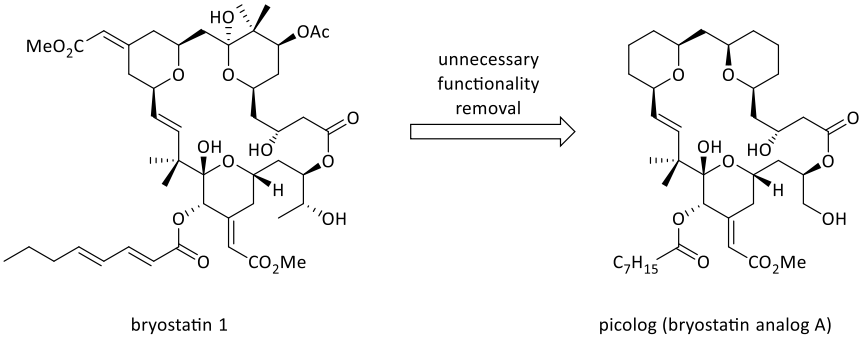


Figure 6: Structural simplification of bryostatin 1 to analog A.[37]

The described conceptional approach is similar to the one reported by WALDMANN, the biology-oriented synthesis. This method is based on the compatibility analysis of structures of ligand-sensing cores embedded in protein domain folds with scaffold structures of natural products. Therefore, it is aimed for the preparation of scaffold-based compound libraries by reduction of the structural complexity while the bioactivity should be retained.[44] Several examples demonstrated the potential of this approach in bridging the gap between computational methods and compound library synthesis.[45] In spite of the trend in pharmaceutical companies, one should not neglect the fact that nature carried out its own version of combinatorial chemistry and HTS to reach an optimum of biologically active compounds for over three billion years.[37] Moreover, the opinions in the chemical society are suggesting a renaissance of natural products due to the failure of alternative drug discovery methods to

provide new lead compounds for therapeutic key areas: immunosuppression, anti-infections, and metabolic diseases.[30, 37, 41, 46]

1.1.4 The role of total and semisynthesis in drug development

As mentioned in the previous chapter, a major drawback in the use of natural products as sources for drug development is the low isolation yield and limited supply from its natural resource. Especially, in the case of marine natural products, the isolation process itself is quite extensive. However, despite small isolable quantities, they possess attractive biological activities and chemical structures which make them an interesting target for organic synthesis.

In the drug discovery process, lead structures are identified by testing substances against specific biological targets which have been identified to be involved in diseases or malfunctions. After identification of such leads, there is a need to generate larger amounts of the material for further modification, biological testings, and evaluation of its structure-activity relationship (SAR). The large-scale supply of the desired compound can be generally pursued by microbial fermentation, biotechnology, or total synthetic approaches (Figure 7).[17]

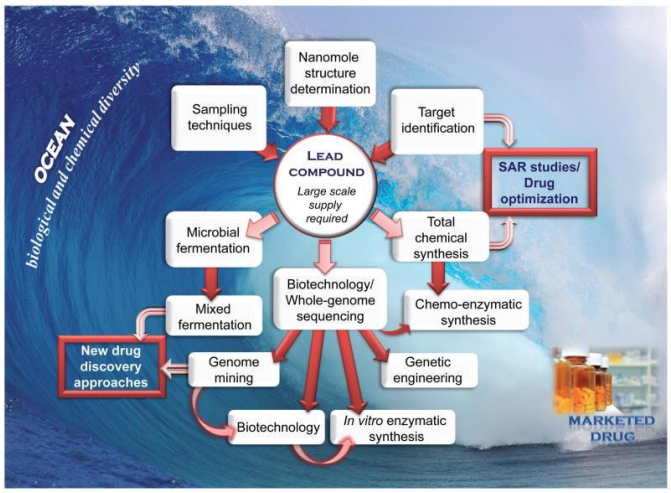
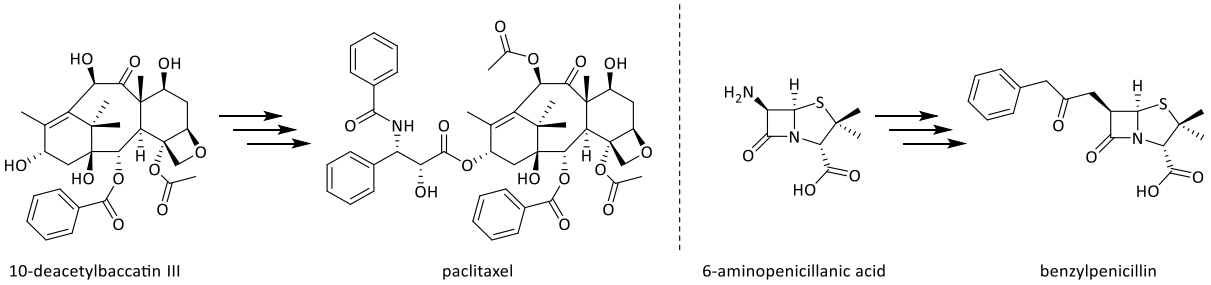


Figure 7: The discovery of a lead compound from marine sources. Reprinted with permission of Luesch et al. Copyright 2011 Future Science.[17]

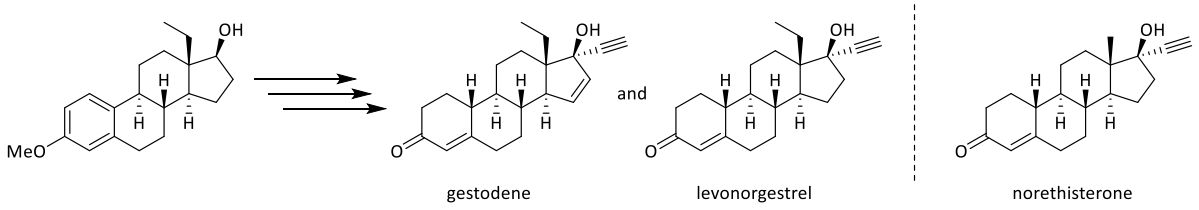
A total synthesis is thereby an important tool for large-scale supply and lead optimization. The desired product is chemically synthesized starting from readily accessible building blocks. Besides the total synthesis, a semisynthetic approach—using chemical and molecular biological methods—can also deliver a large amount of the target compound. Herein an advanced intermediate is biosynthetically produced and further manipulated in a chemoselective, regioselective, and stereoselective fashion to give the desired molecule. This

approach is usually used when the precursor molecule is highly structurally complex, expensive, or not readily accessible by a total synthetic route. The chemotherapy drug paclitaxel (Taxol®) and the antibiotic derivatives of penicillin are examples of products successfully obtained through semisynthesis (Scheme 1).[47] 10-deacetylbaccatin III, which was isolated from a yew tree, is the starting point for the synthesis of paclitaxel. On the other side, the fermentation brew of the *Penicillium* mold gives 6-aminopenicillanic acid as a key building block for the synthesis of various penicillins.



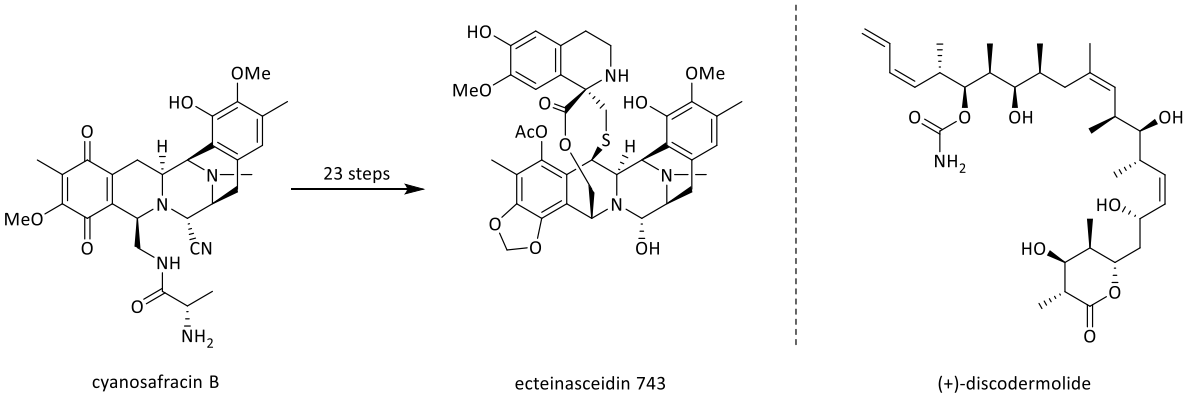
Scheme 1: Paclitaxel (Taxol®) and benzylpenicillin (Penicillin G®) and their biosynthetic precursors.[47]

In most cases, the lead natural compound is not selective enough against the desired target and therefore has to be further derivatized.[47] Semisynthetic approaches tend to be economically advantageous because of their shorter preparation. On the other hand, late-stage modifications are challenging due to the structural complexity of the semisynthetic precursors. A total synthetic approach can be more flexible as it allows access to a wider range of diversity during synthesis. As an example, the first oral contraceptive, norethisterone (Aygestin®), was initially accessed semisynthetically from estrone. SAR studies led to the discovery of the more active levonorgestrel (Plan B®) and gestodene (Femodene®). The presence of the unnatural 13-ethyl group prevented their synthesis from the natural steroid skeletons, thus, imposing the use of a total synthetic approach (Scheme 2).[47]



Scheme 2: Norethisterone, levonorgestrel, and gestodene with one possible precursor.[47]

There are also examples where the total synthesis of a molecule led to the discovery of a semisynthetic approach, as reported with the antitumor agent ecteinascidin 743 (Yonelis®), a highly potent antitumor drug for chemotherapy. The target molecule could be obtained in 23 steps starting from the fermentatively accessible cyanosafracin B, a fragment inspired by COREY's synthesis (Scheme 3). Another outstanding example is (+)-discodermolide (Scheme 3). Novartis has installed a hybrid synthesis combining strategies of existing total synthetic approaches. They produced this highly potent microtubule-stabilizing agent in 39 steps in total (26 LLS) in a 60 g scale. Unfortunately, the compound was halted in Phase II of the clinical trials.[47]



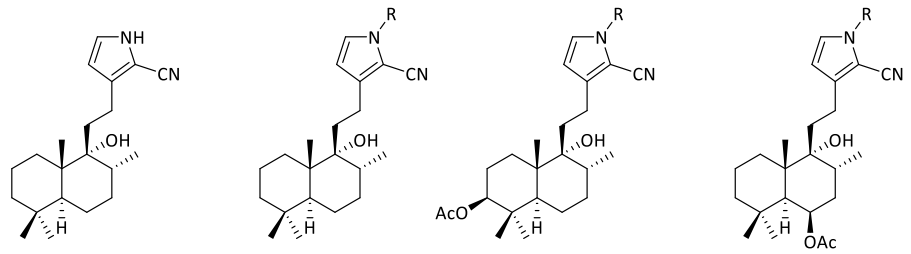
Scheme 3: Semisynthesis of esteinasceidin 743 (Yonelis®) from its precursor cyanosafracin B and (+)-discodermolide.[47]

These examples show that despite the negative attributes associated with total syntheses, such as cost-inefficient strategies, lengthy synthetic routes with long development time, low overall yield, and impracticality of scale-up, the total and semisynthetic methods are an integral part of modern industrial research and drug development.[47] Above that, in cases where no suitable natural occurring precursors are accessible and the supply of the lead substance cannot be guaranteed by natural sources, total synthesis represents the only alternative. Moreover, the totally synthetic approach allows proving the preliminary structural assignment or the resolution of unspecified stereocenters. There were several cases in which the initial structural proposal had to be revised.[48-52] Overall, total synthesis is a great academic tool to extend the basic chemistry knowledge, and in addition, it is a starting point for the discovery of novel reactions and development of efficient chiral and catalytic reactions.[1]

1.2 The natural products (+)-vitepyrroloid A and B

A synthetic approach to natural products aims for a deeper understanding of the chemical and physical features of the targeted molecule, as it was outlined in the previous chapters. In this context, the natural products (+)-vitepyrroloids A and B attracted our attention in virtue of their unprecedented structures and interesting biological activity.

The widespread shrub *Vitex trifolia* L. of the family of Verbenaceae is known in the southern provinces of mainland China for its antioxidant, tracheospamolytic, cytotoxic, and trypanocidal activity.[53] Its fruits have already been used in the traditional treatment of colds, migraine, headache, and rheumatism.[54] In 2017, Xu and co-workers reported the isolation of four diterpenoid alkaloids from the dried leaves of this shrub, namely vitepyrroloids A–D. The congeners contain an unprecedented 2-cyanopyrrole labdane core but differentiate in the substitution at the pyrrole nitrogen and/or in the oxidation pattern of the decalin system (Figure 8, **1a**–**1d**). The absolute configuration was determined by spectroscopic and X-ray crystallographic analysis.[55] In particular, (+)-vitepyrroloid A exhibits a cytotoxic activity against a human nasopharyngeal carcinoma cell line (CNE1) with an IC_{50} of 8.7 μM. Nasopharyngeal carcinoma is a rare disease worldwide but is more common in certain geographic areas such as Southern Asia and North Africa. An effective chemotherapy against this tumor is urgently required since the healing prognosis of this carcinoma at advanced stage remains poor and early diagnosis is rare.[56-57] However, the low isolation yield (30 kg of air-dried leaves gave 8.5 mg of the natural product) makes this biological material barely available. Therefore, a synthetic approach to these natural products would access satisfying amounts of substrates to perform extensive biological tests.

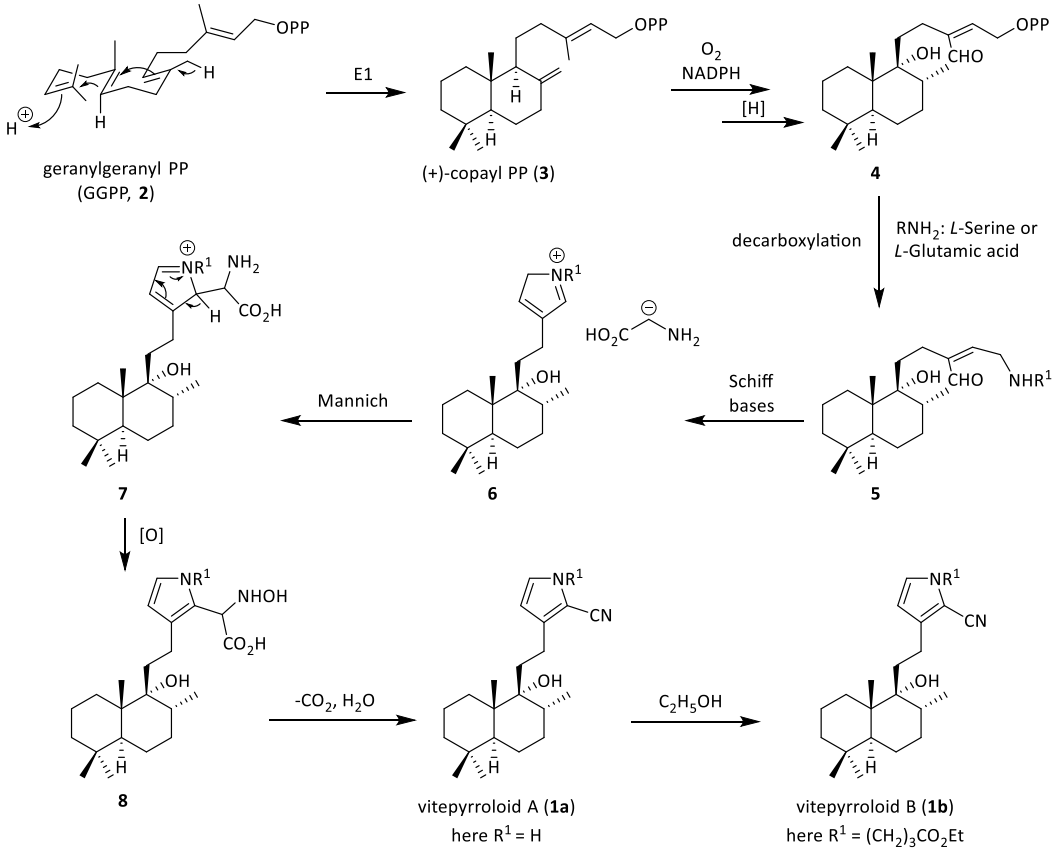


vitepyrroloid A (**1a**) | vitepyrroloid B (**1b**) R = $(CH_2)_3CO_2Et$ | vitepyrroloid C (**1c**) R = $(CH_2)_3CO_2H$ | vitepyrroloid D (**1d**) R = $(CH_2)_2OH$

Figure 8: Structure of vitepyrroloids A–D (**1a**–**1d**).

Until now, no synthesis has been published for vitepyrroloids A and B despite their interesting structure and biological features. The biosynthesis of these compounds was described along

with their isolation in a report by XU and co-workers (Scheme 4).[55] They assumed that the vitepyrroloids might be derived from geranylgeranyl pyrophosphate (GGPP, **2**) which after acid-catalyzed cyclization, leads to (+)-copayl PP (**3**). This process would be followed by sequential oxidation and reduction. Afterward, reaction with ammonia, *L*-glutamic, or *L*-serine followed by decarboxylation would give the intermediate **5**. Conversion of amine **5** to **7** could be achieved *via* SCHIFF base formation and MANNICH reaction. Final oxidation followed by loss of CO_2 and H_2O leads to vitepyrroloid A and after esterification with ethanol to vitepyrroloid B. Oxidation and acetylation of the intermediate **1a** would give the remaining vitepyrroloids.



Scheme 4: Biosynthesis of vitepyrroloid A (**1a**) and B (**1b**).[55]

1.3 The natural product actinoranone

Streptomyces is a genus of the order of actinomycetes derived from the phylum of Actinobacteria, which can be of marine or terrestrial habitat.[58] As part of an expedition program devoted to studying the marine actinomycetes, by now a largely unexplored compound class, the group of FENICAL isolated the natural product actinoranone from the strain CNQ-027 in 2013. This strain shares 97.6% 16S rRNA gene sequence identity with the known species *Streptomyces marinus*, thus, might represent a new species adapted to life in the sea.[59] The novel meroterpenoid exhibits a significant *in vitro* cytotoxicity against HCT-116 human colon carcinoma cells with an LD_{50} of 2.0 μg/mL. Colon cancer is the fourth most common cause for cancer death beyond lung, liver, and stomach tumors.[60] More than 1.2 million people receive the diagnosis and around 600 000 die from this disease every year.[61]

Actinoranone possesses an unprecedented dihydronaphthalene polyketide skeleton and belongs to the meroterpenoids that are defined as compounds of mixed polyketide-terpenoid origin. This term was introduced in 1968 by CORNFORTH and differentiated polyketide–terpenoids from non-polyketide–terpenoids.[62] The structure of the natural product was elucidated by mass spectrometry and NMR spectroscopy. By applying a modified MOSHER's ester method and ROESY NMR analyses, the relative configuration of the bicyclic terpenoid unit (C5, C9, and C10) was determined and the absolute configurations at C15 was initially predicted as *R.* The absolute configuration at configuration at C8' (*syn* relative to C15) was deduced by interpretation of the ROESY NMR analysis of the protons attached to C15 and C8´.[63] Recently, YE and co-workers accomplished the first synthesis of actinoranone and three diastereomers, thereby, giving proof of the relative configuration at the decalin skeleton and revising the stereochemistry at C15 and C8' (*anti*-relationship). In the end, the configuration was assigned as 5*S*, 9*S*, 10*S*, 15 *R*, 8'*S* (Figure 9, **9**).[64]

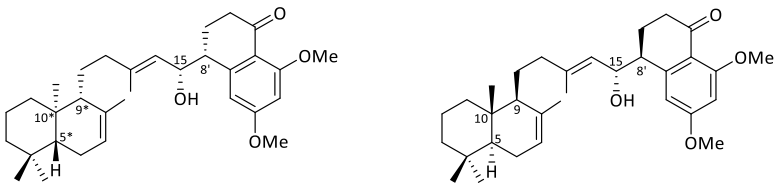
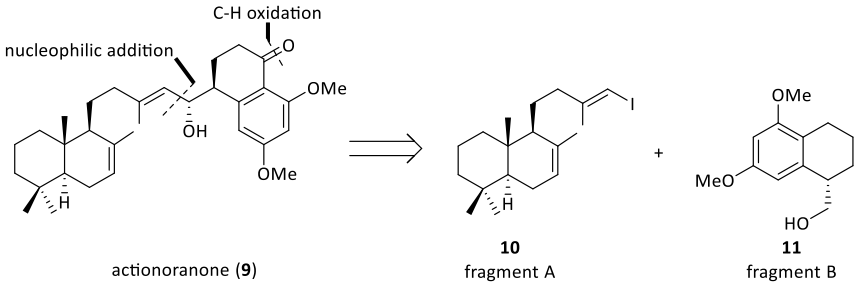


Figure 9: Originally proposed and revised structure of actinoranone (**9**).

In actinoranone, as well as in (+)-vitepyrroloid A and B (chapter 1.2), the labdane-type diterpenoid unit is present. In general, labdane-related diterpenoids comprise over 5 000 known natural products having in common the substituted decalin structural motif.[65] This structural motif is often found in natural products possessing important pharmaceutical activities: (–)-15-oxopuupehenol with antimalarial activity, widendiol A inhibits the cholesteryl ester transfer protein, acuminode cytotoxicity against melanoma, rhinocerotinoic acid with anti-inflammatory activity, (+)-zonarol a fungitoxic hydroquinone, (+)-zerumin B with antitumor activity against human tumor cell lines, and more.[66]

1.3.1 State of the art

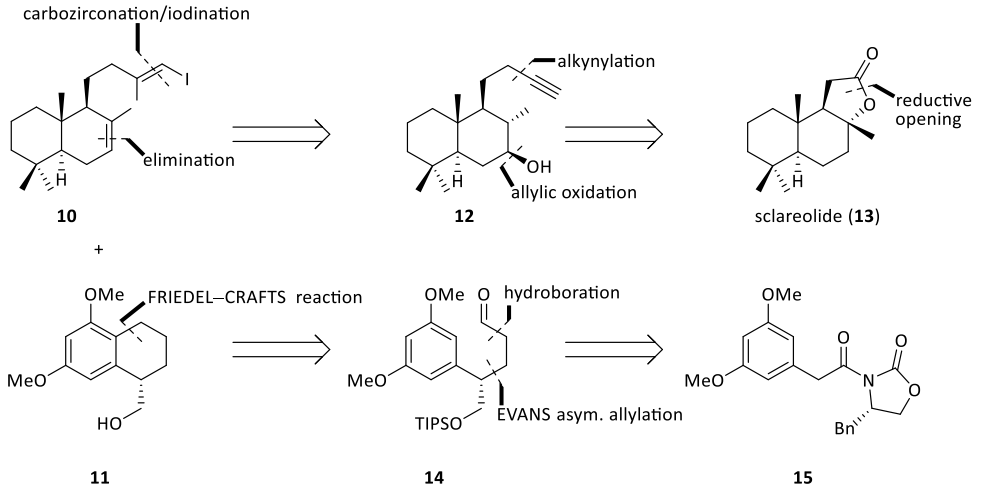
Regarding actinoranone, two syntheses were independently reported in 2017 by the groups of PASTRE[67] and YE.[64] In terms of retrosynthetic analysis, both synthetic studies evaluated the same disconnection of the allylic C–C bond within the vinyl alcohol unit, thus, leading to the corresponding vinyl iodide **10** and bicyclic alcohol **11** as main leading fragments (Scheme 5). The final coupling would employ the nucleophilic addition of the vinyl metal species derived from fragment A to the aldehyde derived from fragment B. At the end, C–H benzylic oxidation would give the natural product.



Scheme 5: General retrosynthetic disconnection strategy employed by the YE and PASTRE groups.[64, 67]

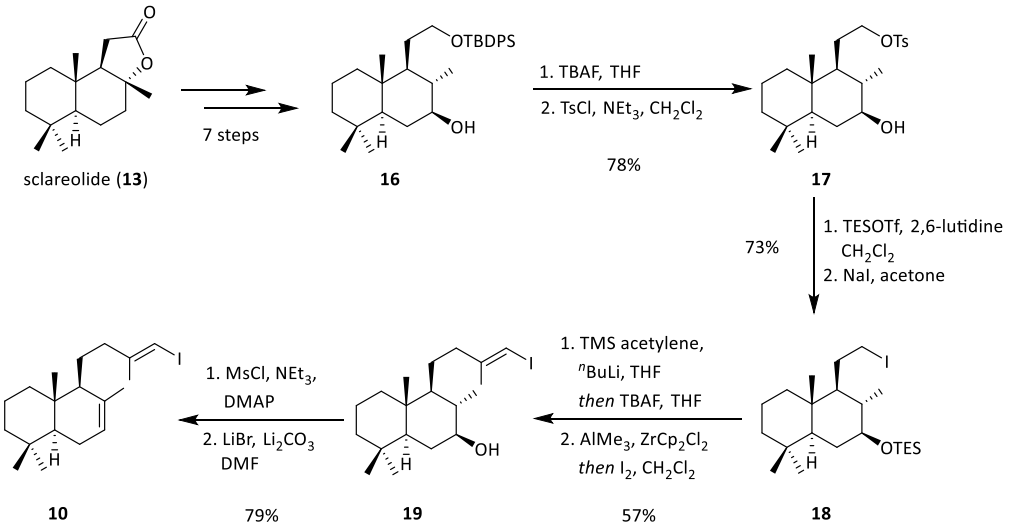
The first synthesis of actinoranone, carried out by YE and co-workers, proposed (+)-sclareolide as starting point for the synthesis of fragment A.[64] They assumed that the vinyl iodide **10** might be accessible from alkyne **12** by a NEGISHI's carbonzirconation/iodination sequence which in turn could be derived from (+)-sclareolide (**13**) through several transformations and oxidation steps (Scheme 6). Fragment B was traced back to a 3,5-dimethoxyphenylacetic acid functionalized with a chiral auxiliary unit (**15**); thus, stereochemical information could be

introduced *via* an EVAN's asymmetric allylation. Further transformations and a FRIEDEL–CRAFTS type cyclization would lead to the target fragment B (Scheme 6).



Scheme 6: Retrosynthetic analysis of the YE group.[64]

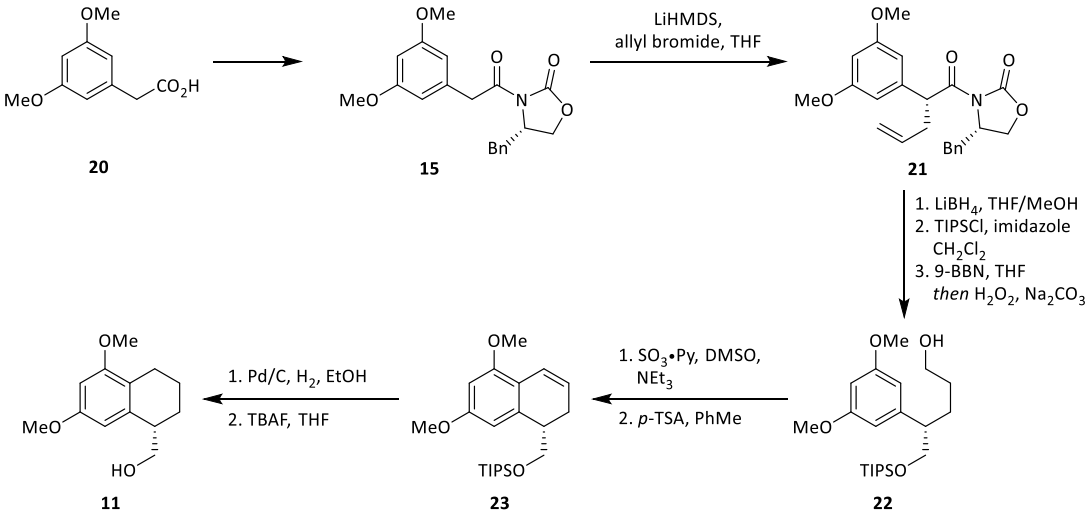
YE's route started from commercially available (+)-sclareolide (**13**) which was converted into alcohol **16** in seven steps following a known literature procedure.[68] Afterwards, the protected alcohol was transformed to the iodide **18** by a deprotection/FINKELSTEIN-like reaction sequence using sodium iodide as nucleophile. Protection of the secondary alcohol as TES-ether allowed alkynylation employing TMS acetylene. Subsequent removal of the of the silyl groups with TBAF yielded the terminal alkyne moiety and the secondary alcohol **12**.



Scheme 7: Synthesis of fragment A (**10**) by YE's group.[64]

In the following step, a *cis*-carbozirconation/iodination protocol from NEGISHI was applied to convert the alkyne into the desired vinyl iodide unit **19**. The secondary alcohol was finally eliminated affording fragment A in 15 steps with 11% overall yield (Scheme 7).

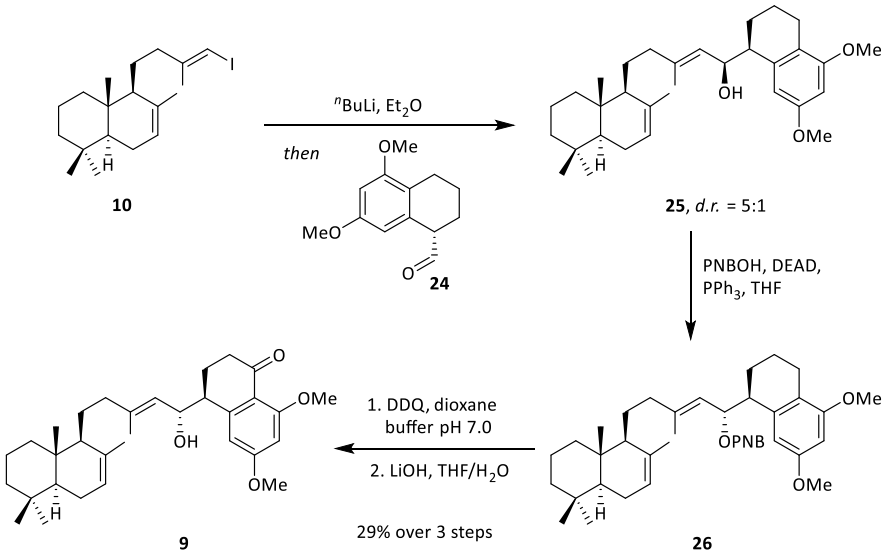
The preparation of fragment B commenced with the transformation of commercially available 3,5-dimethoxyphenylacetic acid (**20**) into (*S*)-oxazolidinone imide **15** in two steps. By applying an EVAN's asymmetric alkylation, the allyl unit was enantioselectively introduced. The auxiliary was cleaved and after protection of the resulting alcohol, the terminal double bond was selectively hydroborated with the sterically demanding 9-BBN. Oxidative work-up led to primary alcohol **22** which was further oxidized using PARIKH–DOERING conditions. Next, FRIEDEL–CRAFTS reaction forged the second ring (**23**). Finally, hydrogenation and deprotection with TBAF led to the bicyclic fragment B in a total of nine steps with 15% overall yield (Scheme 8).



Scheme 8: Synthesis of fragment B (**11**).*

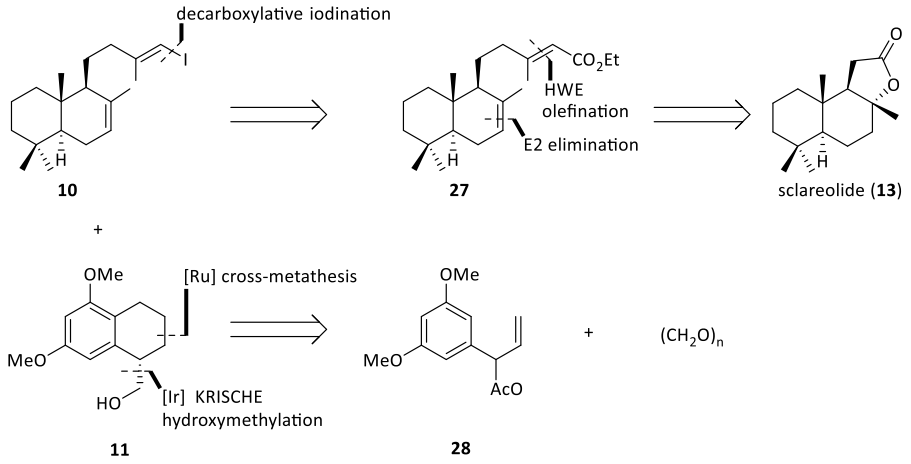
To connect the two fragments, the vinyl iodide **10** was treated with ^{n}BuLi leading to a halogen-metal exchange. Thus, the freshly prepared aldehyde **24** from **11** using DESS–MARTIN periodinane as oxidation agent was directly added to the *in situ* prepared vinyllithium species leading to the formation of allyl alcohol **25** with a diastereomeric ratio of 5:1. MITSUNOBU reaction inverted the configuration at the secondary alcohol. Finally, benzylic oxidation with DDQ and ester cleavage led to the natural product actinoranone (**9**, Scheme 9).

* There are no yields and *dr* given in the publication of the YE group as their original reported synthesis route led to the wrong diastereomer of actinoranone. 15% overall yield and *dr* = 10:1 belong to their published route.



Scheme 9: Endgame of the synthesis of actinoranone (**9**).[64]

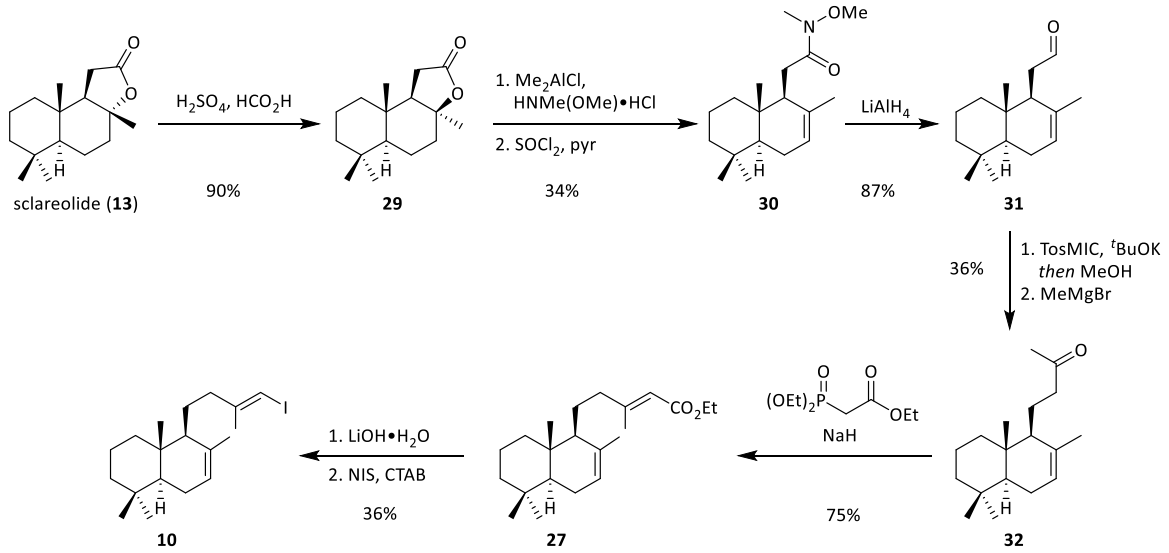
PASTRE et al. published an alternative formal synthesis[67, 69] of actinoranone in 2017 which was based on the same retrosynthetic disconnection leading to the same fragments A and B as proposed by YE. They envisioned to access the vinyl iodide by a decarboxylative iodination of the ester which was derived from the commercially available (+)-sclareolide by HORNER–WADSWORTH–EMMONS olefination and E2 elimination. Fragment B should be obtained by applying Ru-catalyzed cross-metathesis and Ir-catalyzed KRISCHE hydroxymethylation to the allylic acetate **28** (Scheme 10).



Scheme 10: Retrosynthetic analysis of the NOVAES and PASTRE.[67, 69]

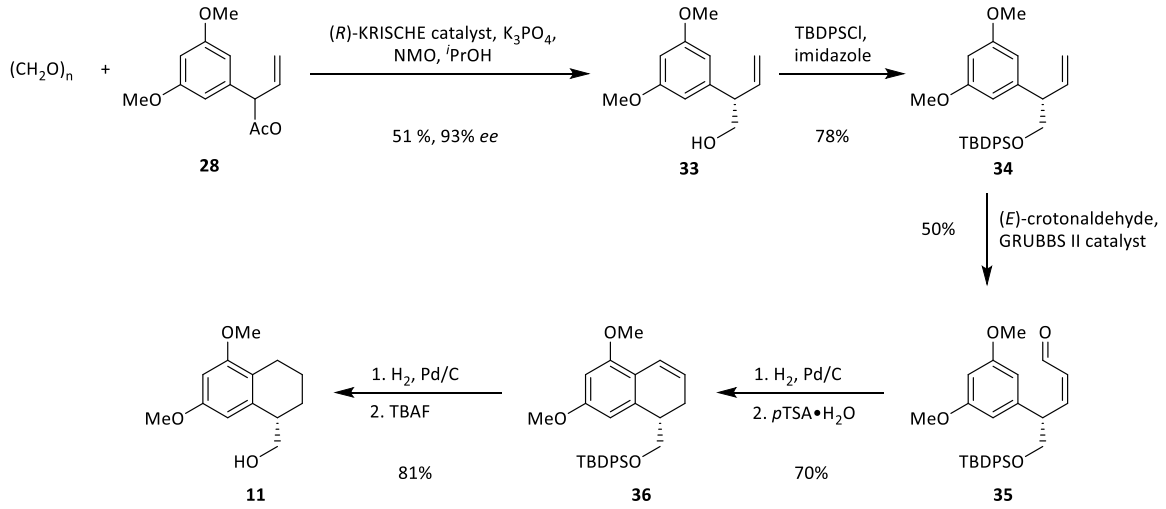
The formal synthesis commenced with the transformation of (+)-sclareolide (**13**) into its epimer with the aid of sulfuric acid. Then, WEINREB amide **30** was obtained after treatment of lactone **29** with Me_2AlCl followed by E2 elimination which produced the desired trisubstituted

endo-olefin. The WEINREB amide **30** was reduced to aldehyde **31** which was further transformed into the corresponding nitrile by application of VAN LEUSEN reaction. In the next step, GRIGNARD addition to the nitrile moiety gave the ketone **32** which was then subjected to a HORNER–WADSWORTH–EMMONS olefination. The route to fragment A for the polyketide unit was finished by hydrolysis of the ester **27** and final decarboxylative iodination. Fragment A was obtained in nine steps starting from (+)-sclareolide with 3.4% overall yield (Scheme 11).



Scheme 11: Synthesis route of fragment A (**10**).[67, 69]

The approach to the tetralin system started with the Ir-catalyzed enantioselective hydroxymethylation of the allylic acetate **28** which was previously prepared in two steps from 3,5-dimethoxybenzaldehyde. This was followed by alcohol protection and then cross-metathesis with crotonaldehyde using GRUBBS II catalyst to give the enal **35**. After hydrogenation of the double bond, the route of PASTRE was identical to the approach of the YE group. Briefly, FRIEDEL–CRAFTS reaction, hydrogenation, and deprotection with TBAF led to fragment B in 9 steps in total and 3.5 % overall yield (Scheme 12).



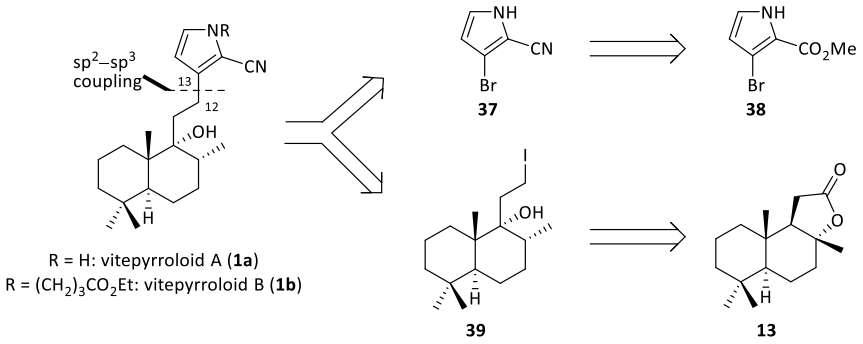
Scheme 12: Synthesis route of fragment B (**11**).[67, 69]

In summary, the synthesis of YE and co-workers consists of 29 steps in total and 19 steps longest linear sequence (LLS). They needed seven steps to install the desired trisubstituted *endo*-double bond in the synthesis of fragment A leading to a rather low overall yield of 11%. The required stereo information in fragment B was introduced by a stoichiometric auxiliary approach with modest diastereoselectivity. On the other hand, PASTRE and co-workers accomplished the formal synthesis in 20 steps (11 steps LLS). In this case, they epimerized the natural compound (+)-sclareolide and performed an E2 elimination to get to the *endo*-alkene in a rather low yield. Further transformations led to fragment A in low 3.4% overall yield. Ir-catalyzed enantioselective hydroxymethylation and cross-metathesis were used for the key steps in the synthesis of fragment B. Here, the route suffered from low yields in both steps which contributed to an overall yield of 3.5% over nine steps.

2) SCIENTIFIC GOALS

The class of labdane-type diterpenoids possesses an attractive structural motif displaying important pharmaceutical activities. Two new representatives, (+)-vitepyrroloids A (**1a**) and B (**1b**), have been isolated and their biological activity against a nasopharyngeal carcinoma was evaluated. However, more data and material are required to assess a complete biological screening, thus, strengthening the need to find synthetic strategies towards this class of natural products. The following work addresses the first synthetic approach towards these natural products by utilizing a terpene feedstock as a suitable building block, hence, minimizing C–C-bond forming reactions.

In this dissertation, a retrosynthetic cut between C12 and C13 of (+)-vitepyrroloid A and B was proposed (Scheme 13). This disconnection led to the bromo-pyrrole **37** and the iodide **39** as main fragments. With this cut, it was opted for a late-stage Csp^2–Csp^3 cross-electrophile coupling for the fusion of iodide **39** and bromide **37**. The bromo-pyrrole would be prepared in few manipulations from commercially available 3-bromopyrrole-2-carboxylic acid methyl ester (**38**). (+)-Sclareolide (**13**) was expected to be a convenient terpene feedstock as starting building block. Vitepyrroloid B should be accessible by manipulation of vitepyrroloid A or by using a suitable *N*-alkyl bromo-pyrrole fragment for the cross-electrophile coupling.

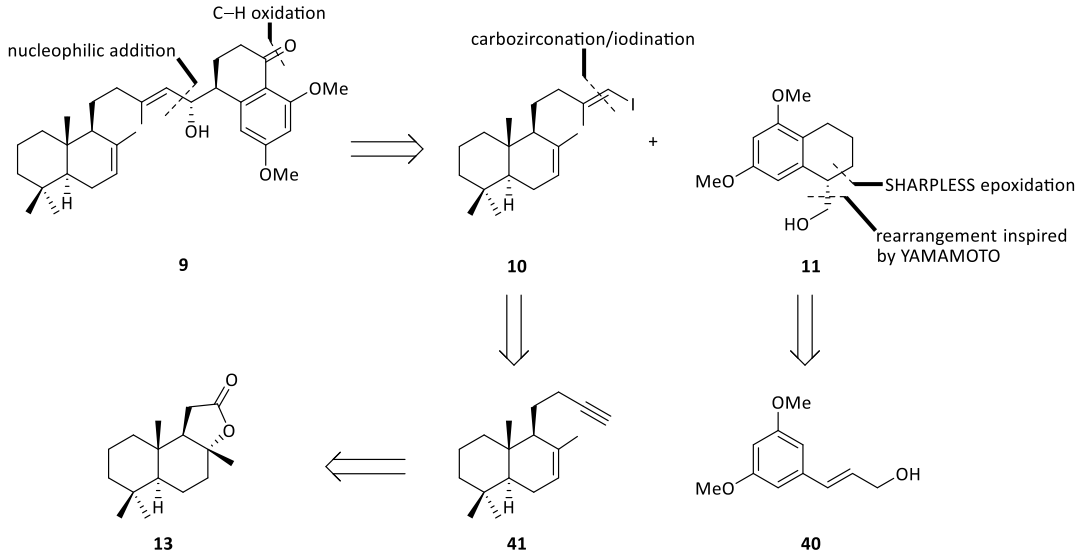


Scheme 13: Retrosynthetic analysis of (+)-vitepyrroloid A (**1a**) and B (**1b**).

The meroterpenoid actinoranone (**9**) also features a labdane-diterpenoid unit, which is connected to a tetralin system. In preliminary studies, an interesting biological activity against HCT-116 human colon carcinoma was found.[63] Colon cancer is the fourth most common cause of fatal cancer beyond lung, liver, and stomach; hence, the development of new active agents for treatment is still crucial.[70] In 2017, two independent syntheses, based on the same

retrosynthetic cut, towards actinoranone were published. YE and co-workers' approach consisted of 29 steps in total and 14 in the longest linear sequence.[64] PASTRE's route towards the skeleton of actinoranone comprised of 20 steps with 11 in the longest linear sequence.[67] In general, the polyketide motif was assembled in a concise manner; however, the diterpenoid unit was obtained after rather long-winded approach. Whilst some synthetic effort has been carried out, the published syntheses lack generality and efficiency. Identification of a shorter and more concise method became a key objective in the following thesis.

Retrosynthetically, actinoranone was planned to be disconnected accordingly to YE and PASTRE leading to the same vinyl iodide and bicyclic alcohol fragments (**10** and **11**, respectively). The alkene in fragment A was thought to be synthesized from the corresponding alkyne **41** by carbozirconation and subsequent iodination. Alkyne **41** should be prepared from commercially available (+)-sclareolide (**13**) with a few modifications. Relating to fragment B, it was envisioned to access the bicyclic alcohol **11** from 3,5-dimethoxybenzaldehyde. At the outset, it was expected to install the stereo information *via* an asymmetric SHARPLESS epoxidation, which might then be transferred to a β-siloxy aldehyde through a by YAMAMOTO[71] introduced organoaluminum-promoted rearrangement (Scheme 14).



Scheme 14: Retrosynthetic analysis of a new approach to actinoranone (**9**).

3) PUBLICATIONS AND MANUSCRIPTS

In the following section the published article and the submitted manuscript are listed, and the contributions of the author are detailed.

3.1 Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)–C(sp3) Cross-Electrophile Coupling

M. Menger, D. Lentz, M. Christmann, *J. Org. Chem.* **2018**, *83*, 6793–6797.

The article is electronically available (https://doi.org/10.1021/acs.joc.8b00882).

Abstract:

A concise and scalable five-step synthesis of (+)-vitepyrroloid A and a six-step synthesis of (+)-vitepyrroloid B are reported. Both natural products are interesting labdane diterpenoid alkaloids from *Vitex trifolia* L. The presented approach features a Ni-catalyzed Csp^2–Csp^3 cross-electrophile coupling between a (+)-sclareolide-derived alkyl iodide and 3-bromo-2-cyanopyrrole.

Author's contribution:

I developed the synthetic strategy towards (+)-vitepyrroloid A and (+)-vitepyrroloid B and afterwards executed all reactions. All analytical data such as NMR, IR, and ESI-MS were evaluated by me. The crystal for X-ray crystallographic analysis were provided by me. I developed and wrote the general outline of the manuscript with assistance of the corresponding author.

3.2 Formal Synthesis of Actinoranone Using a Racemization-Free One-Pot Semipinacol Rearrangement/Wittig Reaction

M. Menger, M. Christmann, *manuscript in preparation.*

Abstract:

The syntheses of the tetralone type polyketide and bicyclic diterpenoid fragments of the natural product actinoranone are reported. Key feature of this route is the exceptional rigorous chirality transfer by applying a organoaluminum-promoted rearrangement introduced by YAMAMOTO—a siloxy-epoxide rearrangement reaction—followed by subsequent WITTIG homologation in the synthesis of the polyketide fragment. This straightforward approach enables access to the skeleton of the marine natural product in 16 steps (11 steps for LLS).

Authors' contribution:

I developed the general synthetic route towards the natural product actinoranone and executed all synthetic steps. Analytical data such as NMR, IR, and ESI-MS were evaluated by me. The manuscript was written by me with assistance of the corresponding author.

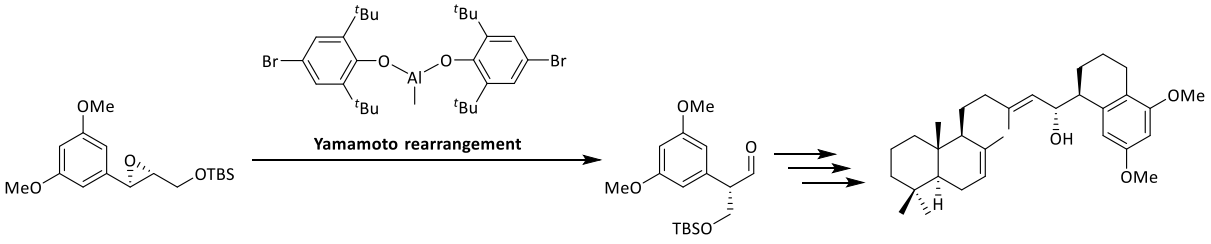
Formal Synthesis of Actinoranone Using a Racemization-Free One-Pot Semipinacol Rearrangement/Wittig Reaction

*M. Menger and M. Christmann**

Freie Universität Berlin, Institute for Chemistry and Biochemistry, Takustr. 3, 14195 Berlin, Germany

*corresponding author

ABSTRACT



The syntheses of the tetralone type polyketide and bicyclic diterpenoid fragments of actinoranone are reported. Key feature of this route is the exceptional rigorous chirality transfer by applying a organoaluminum-promoted rearrangement introduced by Yamamoto—a siloxy-epoxide rearrangement reaction—in the synthesis of the polyketide fragment. This straightforward approach is giving access to the skeleton of the marine natural product in 16 steps (11 steps for LLS).

1. Introduction

The marine environment is becoming the number one source for the discovery of new potentially bioactive molecules and drug leads.[1] The diversity of life in the terrestrial habitat is extraordinary, but the greatest biodiversity and chemical novelty occurs in the oceans.[2-4] Marine actinomycetes are a prolific source of secondary metabolites. In general, this Actinobacteria subclass is comprising half of the discovered secondary metabolites, in particular, antibiotics,[5] antitumor agents,[6] immunosuppressive agents,[7] and enzymes.[8] A large number of terrestrial actinomycetes have been screened and isolated but the distribution of this compound class in the sea is largely unexplored. The vast majority of the marine actinomycetes are derived from the single genus *Streptomyces*. This is the largest genus of Actinobacteria and is widely spread in marine and terrestrial ecosystems.[9] Interestingly, the genus *Streptomyces* alone accounts for the majority the antibiotics used today.[10-11]

In recent years, expanding studies of marine actinomycetes have yielded quite a number of bioactive molecules with diverse chemical structures.[12] As part of this program, Fenical and

co-workers isolated actinoranone from the marine actinomycetes strain CNQ-027 in 2013.[13] This strain shares only 97.6% 16S rRNA gene sequence identity with the genus *Streptomyces marinus*, hence might represent new species adapted to live in the sea.[14] The isolated cytotoxic meroterpenoid is constituted by a tetralone type polyketide and a bicyclic diterpenoid fragment connected by a single C-C bond between C15 and C8´and displayed an LD_{50} value of 2.0 µg/mL against HCT-116 human colon carcinoma.[13] The first total synthesis of actinoranone by Yu[15] in 2017 revised the initial proposal for **1** based on ROESY and Mosher´s ester analyses and revealed a *anti* relative configuration for C15 and C8´ (Figure 1). A second formal synthesis of the natural product was performed by the group of Pastre in the same year.[16] With regards to the retrosynthetic analysis, disconnection between C14 and C15 recognized vinyl iodide **2** and the bicyclic alcohol **3** as key fragments in the synthesis of this unusual marine natural product (Scheme 1). Fragment **2** could be clearly obtained from the sesquiterpene lactone sclareolide[17-25] while synthesis of alcohol **3** proved to be ambiguous.

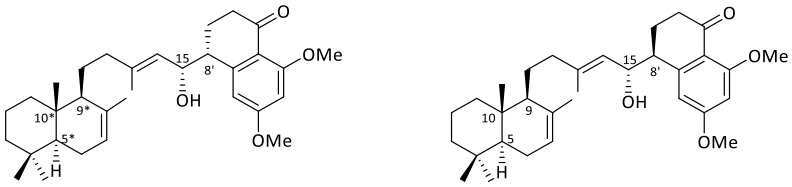
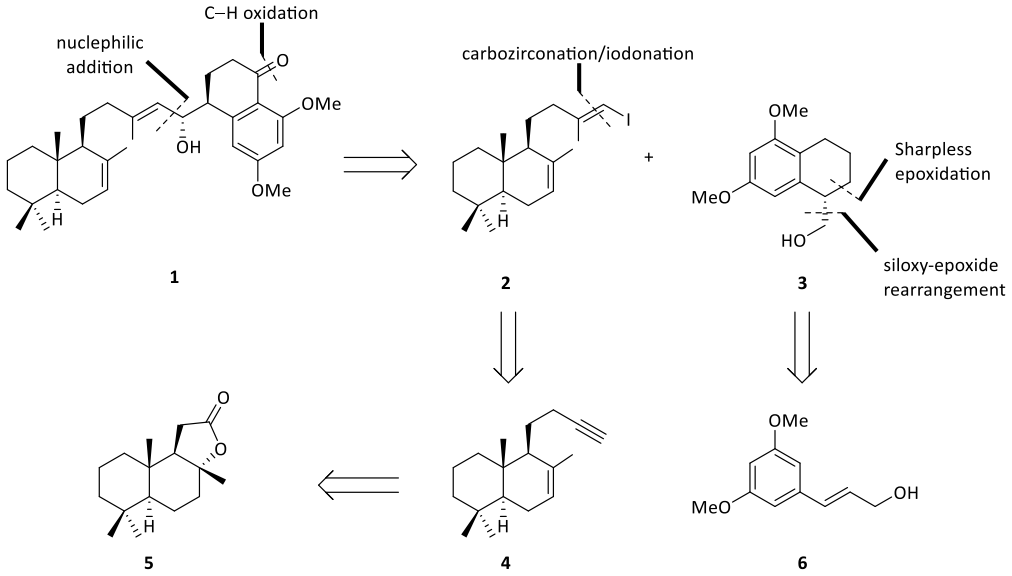


Figure 10: Originally proposed and revised structure of actinoranone 1.

The synthesis of Ye and co-workers consisted of 29 steps in total and 19 in the longest linear sequence. They introduced the stereocenter in the bicyclic fragment by an auxiliary-route with modest diastereoselectivity. In addition to that, the Pastre group accomplished a formal synthesis in 20 steps (11 steps LLS). They applied a different strategy to install the trisubstituted double bond by first epimerizing (+)-sclareolide and then performing a stereoselective elimination. For the tetralone system **3**, they applied an Ir-catalyzed enantioselective hydroxymethylation and cross-metathesis. In general, both routes show a concise approach to the polyketide motif while applying different strategies for the introduction of the stereocenter, but rather run through a long approach for fragment **2**. We envisioned a robust synthetic approach for both fragments to pave the way for a more efficient preparation of the meroterpenoid.

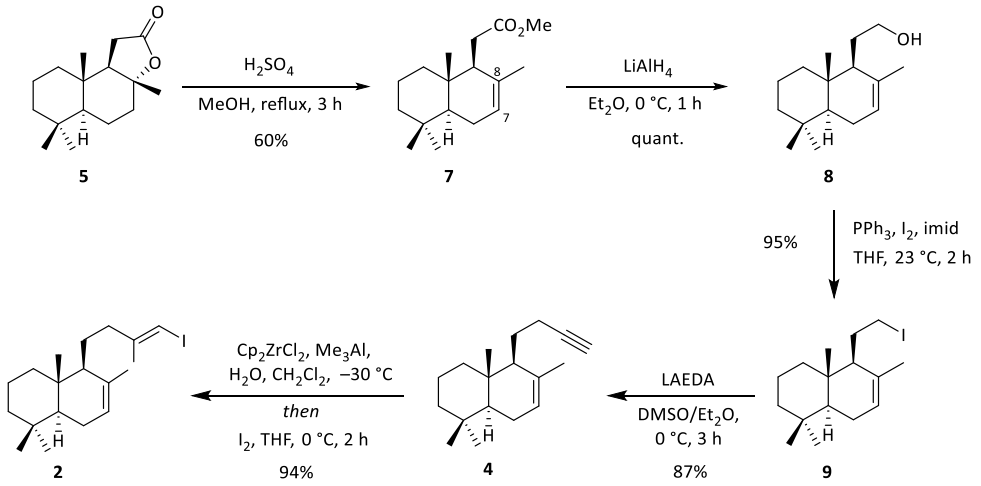
We planned the synthesis of iodide **2** employing a carbozirconation and subsequent iodination as the last step from alkyne **4**. Polyketide **3** could be prepared starting from **6** *via* enantioselective Sharpless epoxidation followed by a stereoselective siloxy-epoxide rearrangement introduced by Yamamoto(Scheme 1).



Scheme 1: Retrosynthetic analysis of actinoranone 1.

2. Results and Discussion

The synthesis of fragment **2** started with the preparation of trisubstituted $\Delta^{7,8}$-alkene **7** from commercially available (+)-sclareolide (**5**) (Scheme 2). Treatment of **5** with sulfuric acid in methanol caused a one-pot methanolysis of the lactone followed by elimination of the obtained tertiary alcohol at C8.[26] The ratio of $\Delta^{8,9}$-alkene, $\Delta^{7,8}$-alkene **7**, and *exo*-alkene was optimized by screening different reaction temperatures and times. After three days at 23 °C, a mixture of alkene-isomers ($\Delta^{7,8}$, $\Delta^{8,9}$, $\Delta^{8,19}$ = 1.0:0.2:0.7) with $\Delta^{7,8}$-alkene **7** as the major product was obtained. Refluxing the solution for 24 h favored formation of the thermodynamically more stable $\Delta^{8,9}$-alkene resulting in a 1:1 ratio of alkene isomers ($\Delta^{7,8}$, $\Delta^{8,9}$).

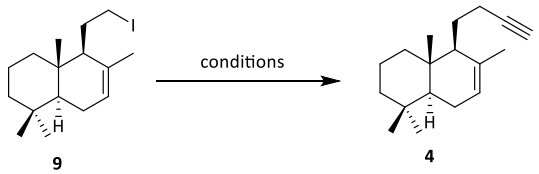


Scheme 2: Synthesis of fragment **2**.

Reduction of the reaction time to 3 h gave the best result for the desired $\Delta^{7,8}$-alkene **7** (60% yield, 1.0:0.67). Other acids such as HCl, AcOH, or H_3PO_4 gave a similar ratio or no product at all, respectively. Nonetheless, the rate of the $\Delta^{7,8}$-, $\Delta^{8,9}$-, $\Delta^{8,19}$-alkene could be enhanced in comparison to the 1:2:0 ratio stated in literature.[26]

Next, the $\Delta^{7,8}$-alkene **7** was transformed to perform a two-carbon homologation. The ester **7** was reduced to the primary alcohol **8** which was converted into iodide **9** using Appel conditions in excellent yield (Scheme 2). The desired two-carbon homologation reaction to alkyne **4** needed some effort in terms of optimization. The usage of lithium acetylide ethylenediamine complex (LAEDA) in DMSO[27-28] at ambient temperature gave the desired product **4** in a moderate yield of 42% (Table 1, entry 1). Changing the solvent to DMF (entry 2) slightly enhanced the yield of **4**, whereas usage of HMPA[29] decreased the yield to 7% (entry 3). Other methods such as the reaction with *in situ* generated lithium trimethylsilylacetylide[30] or Sonogashira coupling[31] with trimethylsilylacetylide did not show any conversion (not displayed). Treatment of **9** with sodium acetylide[32] in DMF improved the reaction yield to 58% (entry 4). Further improvement led to the reaction conditions[33] displayed in Scheme 2. Treatment of the iodide **9** with LAEDA in a 1:1 mixture of DMSO/Et_2O gave alkyne **4** in 87% (entry 5).

Table 1: Two-carbon homologation of 9.



9 **4**

Entry	Conditions	Solvent	t (h)	Yield[a] (%)
1	LAEDA (2.0 equiv) at 23 °C	DMSO	72	42
2	LAEDA (3.0 equiv) at 50 °C	DMF	16	45
3	LAEDA (2.0 equiv) at 23 °C	HMPA	18	7
4	Na–≡ (2.0 equiv) at 0 °C	DMF	2	58
5	LAEDA (3.0 equiv) at 23 °C	DMSO/Et_2O[b]	3	87

[a] Isolated yield. [b] 1:1 v/v was used.

With alkyne **4** in hand, we turned our focus to Negishi's[34-35] zirconium-catalyzed carboalumination-iodination sequence. This protocol is a common and useful tool in organic chemistry for the synthesis of trisubstituted alkenes.[36-37] Application of Wipf's protocol[38] led to *E* vinyl iodide **2** in 94% yield. The control of reaction temperature and slow addition of

reactants were crucial to avoid protonation (by quenching the iodide), as reported by Ye and co-workers.[15]

Taken together, the key intermediate **2** was obtained from (+)-sclareolide in five steps with 47% overall yield. Our synthetic sequence combined the approaches of the Ye and Pastre group in the respect that the carbonzirconation/iodination sequence and the selective elimination to get $\Delta^{7,8}$-alkene **7** were applied, respectively. Thereby, we established a significant improvement of the synthesis of fragment **2** (Figure 2) in comparison to the previously reported approaches of Ye (11%, 15 steps)[15] and Pastre (3.4%, 9 steps).[16]

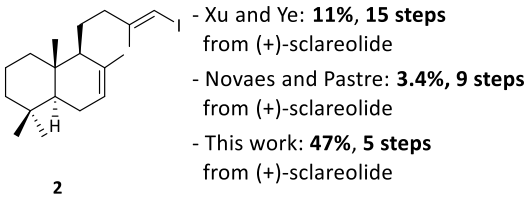
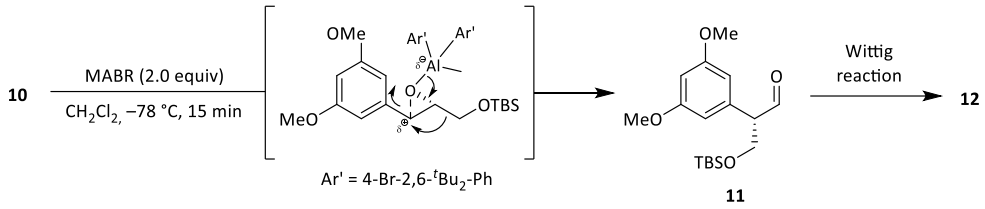


Figure 2: Comparison of the synthetic approaches to fragment 2.

Our approach to the tetralone fragment envisioned the installation of the benzylic stereocenter of the alcohol 3 by using a epoxide rearrangement introduced by Yamamoto under rigorous chirality transfer (see Scheme 1). Therefore, the required epoxide was prepared starting from the readily available allylic alcohol 6 (Scheme 3).[39] A catalytic Sharpless epoxidation[40] followed by treatment with TBSOTf permitted stereoselective preparation of the epoxy silyl ether required for the rearrangement in good yield and excellent enantiomeric excess (10, Scheme 3). At this point, we investigated the antiperiplanar migration of the vicinal C–C bond to benzylic position using a Yamamoto inspired rearrangement.[40-43] Therefore, we applied the original reaction conditions using stoichiometrically amounts of the in situ formed aluminum-based Lewis acid MABR (methylaluminum bis-(4-bromo-2,6-di-tert-butylphenoxide)).[44-48] The originally described work-up with $NaF{\cdot}H_2O$ gave aldehyde 11 in 33% yield and a decreased enantiomeric excess (ee) of 60% (Table 1, entry 1). Therefore, we decided to screen various work-up methods to avoid undesired racemization (entries 2–6). Pouring the crude into diluted aqueous HCl enhanced the yield to 65%, while strongly reduced ee (33%) was observed (entry 2). Addition of saturated aqueous NH_4Cl or H_2O did not give better results in terms of yield and enantioselectivity (entries 3 and 4). Removal of the reaction solvent yielded 36% of 11 (57% ee, entry 5). The newly formed β-siloxy aldehyde proved to be sensitive to the applied work-up conditions. Hence, we decided to directly submit the reaction mixture to Wittig olefination. Direct addition of the freshly prepared Wittig reagent gave poor yield of 11 (entry 6). Thus, the reaction mixture was concentrated and re-dissolved in THF prior ylide addition. To our delight, unsaturated ester 12 was obtained in 44% yield suppressing the undesired racemization (entry 7). After extensive screening, we found out that addition of THF followed by careful removal of CH_2Cl_2 gave the best result. Unsaturated ester was finally obtained in 71% yield and 96% ee (entry 8).

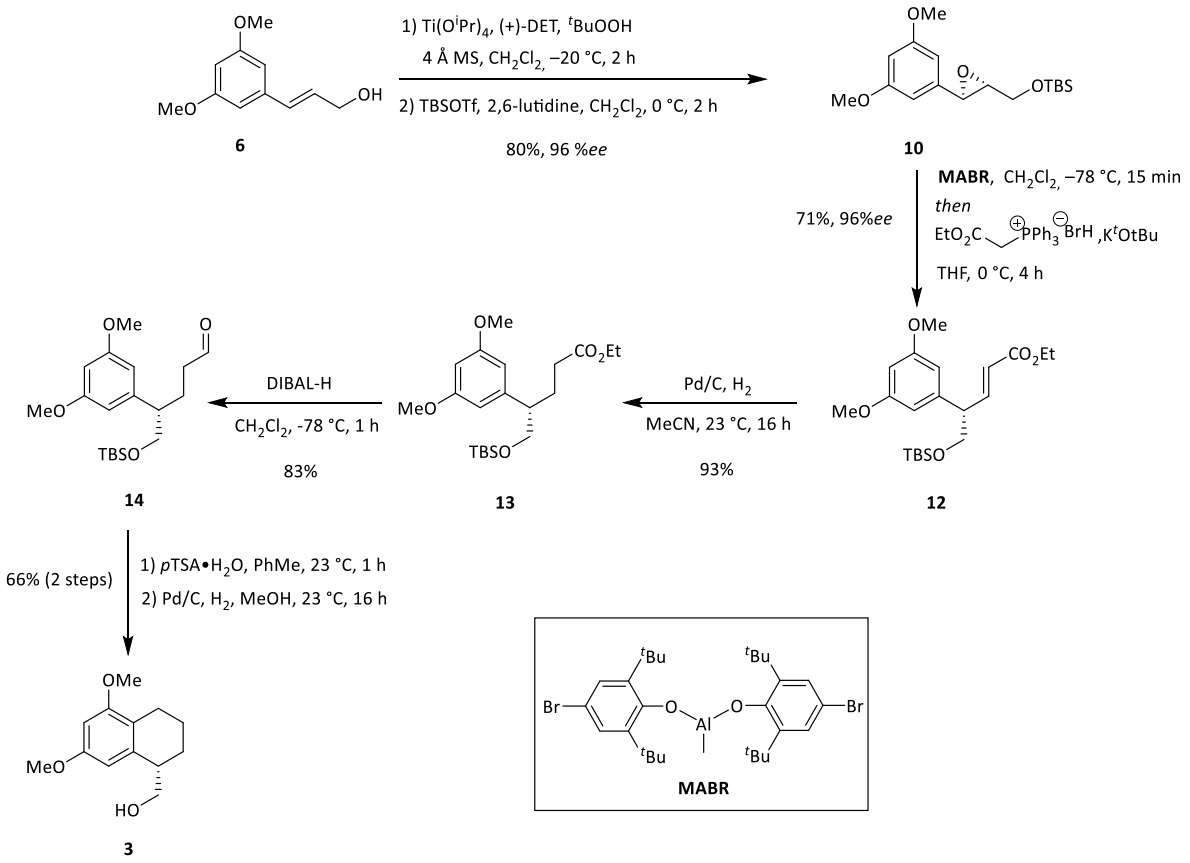
Table 2: Optimization of the siloxy-epoxide rearrangement.



Entry	Conditions Work-up[a]	Product	Yield[b] (%)	*ee* (%)
1	NaF (6.0 equiv), H_2O (8.0 equiv) addition, stirring at 23 °C for 30 min, filtration over Celite®	**11**	33	60
2	Poured into diluted HCl solution, extraction with CH_2Cl_2	**11**	65	33
3	Addition of saturated NH_4Cl solution, extraction with CH_2Cl_2	**11**	38	7
4	Addition of H_2O (excess), extraction with CH_2Cl_2	**11**	61	14
5	Removal of CH_2Cl_2 under HV	**11**	36	57
6[c]	Addition to Wittig reagent	**11**	3	–
7	Removal of CH_2Cl_2 under HV, redissolved in THF and addition to Wittig reagent	**12**	44	96
8	Addition of THF, removal of CH_2Cl_2 under HV, addition to Wittig reagent	**12**	71	96

[a] After the described work-up, flash column chromatography (10:1 = pentane: Et_2O) was performed. [b]Isolated yield. [c]*ee* was not measured.

The route to fragment **3** continued with the hydrogenation of the double bond of **12** using Pd/C (10 w%) under H_2-atmosphere. The use of MeOH as solvent led to alkene reduction accompanied by undesired cleavage of the silyl group.[49] Changing the solvent to MeCN gave ester **13** in 93% yield. At this point, synthesis towards the bicyclic alcohol **3** was completed using an approach similar to Pastre´s route.[16] Thus, ester **13** was transformed into aldehyde **14** *via* DIBAL-H reduction in 83% yield. Acid catalyzed cyclization using *p*TSA followed by hydrogenation employing Pd/C in MeOH (10 w%, slightly acidic) led to bicyclic alcohol **3** in 66% yield.



Scheme 15: Synthesis of fragment 3.

Overall, the key fragment **3** was obtained in a sequence of nine steps starting from 3,5-dimethoxybenzaldehyde. Our route does not differ in the step count in comparison to Ye's and Pastre's but displays another synthetic approach to this bicyclic system. We improved Pastre's approach by changing the way to install the stereogenic center. They used a hydroxymethylation route which gave good result in terms of enantioselectivity but low reaction yield of 51%. We used on the other side the Sharpless epoxidation and organoaluminum-promoted rearrangement procedure to install the stereocenter in good yield and enantioselectivity. Ye relied on an auxiliary approach where an oxazolidinone unit has to be firstly introduced and later cleaved of again. Thereby, we improved the overall yield to 17% (Figure 3) compared to the Ye (15%) and Pastre group (3.5%).

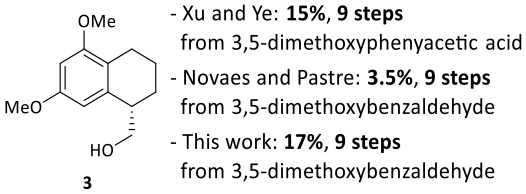


Figure 11: Comparison of the synthetic approaches to fragment 3.

Finally, the coupling of both fragments was performed following Ye's[15] and Pastre's[16] procedure. Oxidation of **3** employing DMP gave aldehyde **15**, which was readily added to a

solution of *in situ* lithiated vinyl iodide **2**. The allylic alcohol **16** was obtained in 70% yield completing the formal synthesis of actinoranone (Figure 4).

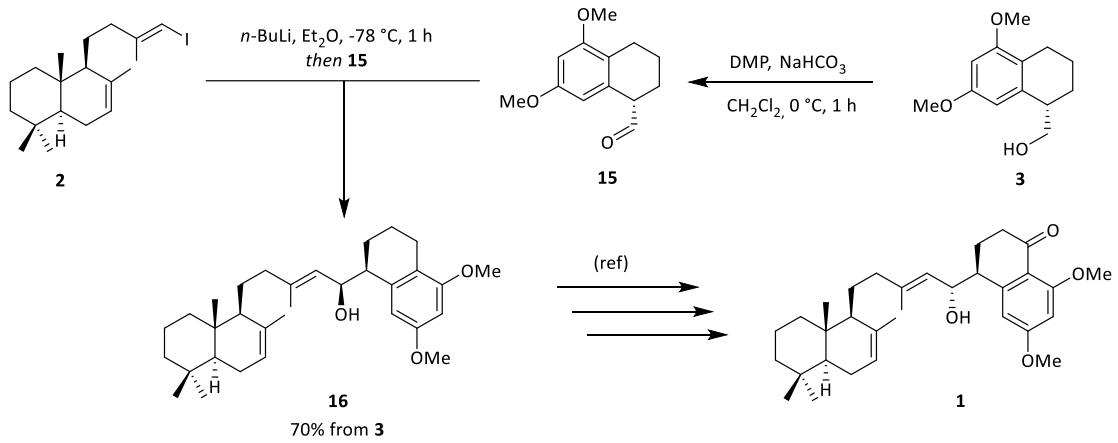


Figure 12: Completion of the formal synthesis of actinoranone 1.[15]

According to Xu's and Ye's work,[15] actinoranone **1** can be obtained in three additional steps inverting the configuration at C-15 under Mitsunobu conditions, performing a benzylic C–H oxidation using DDQ, and basic hydrolysis of the ester.

3. Conclusion

In summary, we reported a convergent formal synthesis of actinoranone **1** starting from commercially available (+)-sclareolide **5** and allylic alcohol **6**. The synthesis of the terpenoid fragment was completed in five steps and 47% yield using a two-carbon homologation and a subsequent zirconium-catalyzed carboalumination led to bicyclic terpenoid **2**. The polyketide fragment was obtained in nine steps with 17% overall yield. Hereby, we displayed another route to install the stereocenter at the benzylic position by using a catalytic Sharpless epoxidation which is followed by a organoaluminum-promoted epoxide rearrangement introduced by Yamamoto with rigorous chirality transfer. Assembling of actinoranone´s carbon framework could be achieved in 16 steps (11 steps LLS, 12% overall yield) offering a more efficient alternative to the previous works of Ye's (26 steps, 19 steps LLS) and Pastre's (20 steps, 11 steps LLS).

Acknowledgments

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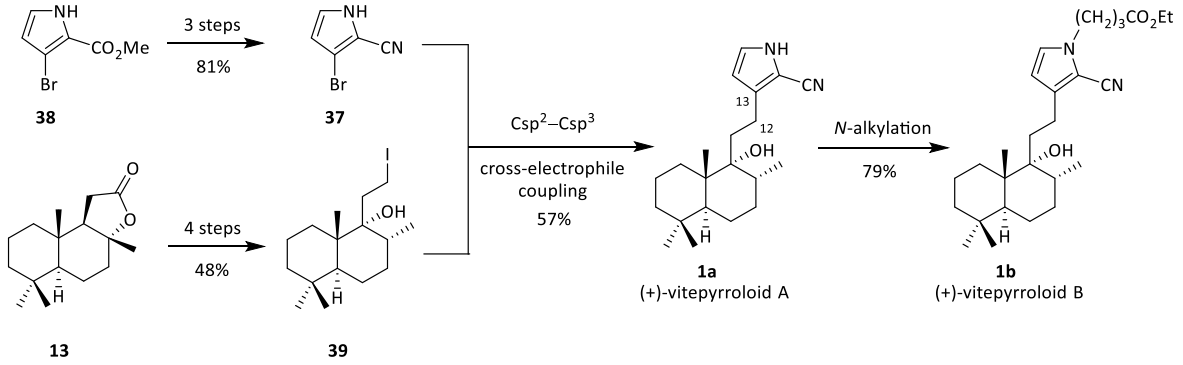
4) CONCLUSION AND OUTLOOK

In summary, the syntheses of three natural products, (+)-vitepyrroloid A (**1a**), (+)-vitepyrroloid B (**1b**), and actinoranone framework (**25**), were successfully achieved in the course of this thesis. This work has demonstrated the potential of the diterpenoid (+)-sclareolide as a suitable building block for the synthesis of suchlike compounds. In each case, a strategic disconnection of the molecule of interest led to suitable fragments that were targeted by succinct and straightforward synthetic routes. (+)-Sclareolide, a sesquiterpene lactone and natural product derived from various plant sources such as *Salvia sclarea*, *Salvia yosgadensis*, and cigar tobacco, was identified as a readily available useful basis.[72-73] Therefore, a minimal amount of C–C bond formations and stereocenter introduction was necessary to obtain the desired compounds by employing readily available diterpene starting material.

In more detail, the syntheses of (+)-vitepyrroloids A (**1a**) and B (**1b**) were accomplished in five and six steps in the longest linear sequence, respectively. 3-Bromopyrrole-2-carboxylic acid methyl ester (**38**) served as starting point for the three-step preparation of the aryl bromide fragment **37**. The sequence included amide formation and final dehydration (81% yield in three steps, Scheme 15). The alkyl iodide fragment **39** was obtained from (+)-sclareolide (**13**) in a four-step route (48% yield, Scheme 15) featuring methanolysis and double bond formation, stereoselective epoxidation followed by reductive opening, and conclusive APPEL-like iodination. The key step consisted of the Csp^2–Csp^3 cross-electrophile coupling to connect the two fragments. This type of coupling reaction received increasing attention and showed a rapid development in the last two decades. The direct coupling of two electrophiles under reductive conditions could be achieved avoiding Umpolung reactions and preformed nucleophiles that would, for instance, demand protecting group manipulations.[74-76] Despite these advantages, potential side reactions due to selectivity issues, reductive homocoupling, hydride functionalization, or catalyst deactivation are constituting the main drawbacks of this methodology. In addition, the rather restricted active systems are enhancing the challenge for a broad substrate scope and its application in natural product synthesis. However, we overcame this major challenge by screening a variety of catalytic systems and found that a reported procedure[77] using NiI_2/bpy and Zn worked best for our desired coupling step with an initial yield of 12% for the natural product **1a**. Taking inspiration from other successful coupling methods reported in the literature, we optimized the reaction conditions employing

increased temperatures and using NaI as an additive to provide an improved yield of 40%.[75] In the end, two equivalents of alkyl iodide **39** were required in order to achieve a successful coupling of the fragments with an improved yield of 57%. Proceeding from this natural product, (+)-vitepyrroloid B (**1b**) was obtained after *N*-alkylation in 79% yield (Scheme 15).

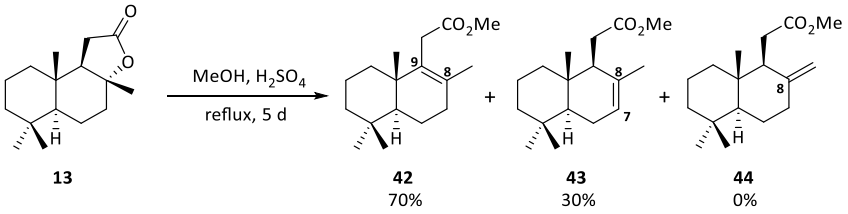


Scheme 15: Syntheses of the natural products (+)-vitepyrroloid A (**1a**) and B (**1b**).

These findings indicate that some competing reactions are taking place leading to a decreased product formation rate, which could be partially overcome by investigating the positive effect of the additive and an increased amount of alkyl iodide **39**. Mechanistic studies carried out by the WEIX group[78] revealed that an initial oxidative addition of the aryl halide to Ni(0)-catalyst is taking place. The alkyl halide serves as a radical precursor, which then reacts in a one-electron oxidative addition with the preformed aryl-Ni(I) complex. Based on these assumptions, the high amount of alkyl iodide **39** implies that the primary radical formation might be slow or hampered. This hypothesis is in alliance with the observation that NaI enhanced the reaction in the beginning. The additive favors suppression of homocoupling between aryl halides and thereby ensures productive cross-coupling. However, the exclusive addition of NaI is not enough to gain higher conversion to the desired product. Further studies such as identification of all by-products and NMR- or MS-assisted reaction tracking would be required to elucidate the rate-determining step and side reactions. Thereafter, the yield might be increased and in the best case, the amount of alkyl iodide needed could be reduced. Higher reaction temperature and reduced reaction time might also lead to further improvement. The literature examples also showed that the use of alkyl bromides generally led to higher product yields in the coupling reaction.[78] Studying the effect of different halide species is, therefore, another approach to increase the reaction yield. In general, a strategic investigation of the cross-electrophile coupling of these fragments should be envisioned. Nevertheless, the

application of this method led to a concise and protecting-group-free synthesis of (+)-vitepyrroloid A (**1a**) and B (**1b**) and thus demonstrated the usefulness of this strategy in natural product synthesis. Although the idea of cross-electrophile coupling has been already realized, this thesis demonstrated one of the rare examples where this method has been applied in a semisynthesis along with a synthetic approach of the HODGSON group.[79] Beyond that, another strategy for the coupling was presented in this work: the electrochemical sp^2–sp^3 cross-electrophile coupling.[80] In the first attempts, this method showed promising results with 21% product yield and should be further investigated to access the natural products in higher quantity; thus, a broader study of the biological activity should be fulfilled. So far, (+)-vitepyrroloid A (**1a**) and B (**1b**) have only been tested against human nasopharyngeal carcinoma cells after their initial isolation.[55]

The installation of a $\Delta^{8,9}$-alkene in (+)-sclareolide was another key step in the synthetic route towards the labdane diterpenoids. To obtain the alkene, (+)-sclareolide (**13**) was treated with sulfuric acid in methanol resulting in the methanolysis of the lactone and subsequent tertiary alcohol elimination. The ratio of $\Delta^{8,9}$-, $\Delta^{7,8}$-, and *exo*-alkene (**42**, **43**, and **44**) was optimized by increasing the reaction temperature and time, which shifted the equilibrium to the thermodynamic product **42** (70% yield, Scheme 16). The application of harsh conditions such as the reaction execution in a pressure tube at 95 °C did not result in a further shift of the equilibrium toward the thermodynamic product.



Scheme 16: Methanolysis and elimination of the resulting tertiary alcohol starting from (+)-sclareolide (**13**).

The use of other acids such as HCl, AcOH, or H_3PO_4 did not improve the product ratio any further. In a first attempt, the pure $\Delta^{7,8}$-alkene **43** was again exposed to the general reaction conditions resulting in a mixture of the isomers after three hours ($\Delta^{8,9}$: $\Delta^{7,8}$: $\Delta^{8,19}$ = 1:2.2:0.1). This finding might suggest a reaction protocol with a few iterations. Herein the reaction should be quenched after a certain time to isolate the $\Delta^{8,9}$-alkene **42** and then the remaining to $\Delta^{7,8}$-alkene could be exposed again to the reaction set-up. The procedure should, hence, increase the overall yield by "harvesting" the desired $\Delta^{8,9}$-alkene **42**. Another scenario is imaginable in

which the undesired alkenes **43** and **44**, are isomerized, for instance, by Pd catalysis to **42**. Nevertheless, the improved yield of the thermodynamic product in comparison to the reported results (1:2 ratio of $\Delta^{8,9}$-:$\Delta^{7,8}$-alkene)[81] displays a great accomplishment. The results also demonstrate the possibility to control the formation of a specific alkene by varying the reaction conditions.

The same conceptional strategy, consisting of methanolysis and subsequent tertiary alcohol elimination of (+)-sclareolide, was applied in the formal synthesis of actinoranone (**9**). However, in this case, the $\Delta^{7,8}$-alkene **43** was required for the formation of the desired decalin fragment. The best results were obtained after refluxing the reaction mixture for three hours giving 60% of the trisubstituted *endo*-alkene **43** (Scheme 16). This reaction time indicates the point before the equilibrium is shifted to the thermodynamic product **42** and after the kinetic *exo*-alkene product **44** is isomerized. In addition, we were able to manage the separation of the isomeric products, which has previously been described as particularly challenging.[81] Follow-up transformations gave terminal alkyne **41**, which was converted to vinyl iodide **10** *via* NEGISHI's zirconium-catalyzed carboalumination/iodination sequence. Although this method was widely applied in organic synthesis,[82-83] the YE group encountered problems such as hydride functionalization using this strategy in their total synthesis of actinoranone.[64] We overcame these obstacles by strictly controlling the time of reagent addition and reaction temperature. After optimization of these key steps, we obtained the decalin fragment using a concise and protecting-group-free synthesis (47%, five steps, Figure 10). The results constitute a major improvement in the product yield with fewer steps in comparison to the synthetic route of YE (11%, 15 steps)[64] and PASTRE (3.4%, 9 steps).[67]

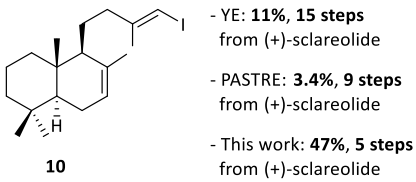


Figure 13: Comparison of the synthetic approaches to fragment **10**.

The tetralone fragment was synthesized in nine steps in a similar manner to the already published routes. Starting from 3,5-dimethoxybenzaldehyde, the epoxy silyl ether **45** was obtained after enantioselective SHARPLESS epoxidation of the previously formed allylic alcohol **40**. The following organoaluminum-promoted rearrangement inspired by YAMAMOTO

rigorously transferred the preinstalled stereo information. This aluminum-based LEWIS acid promoted rearrangement is a common method[60, 84-85] used to obtain β-siloxy aldehydes; however, we encountered many problems in isolating the β-siloxy aldehyde. Major loss of material and erosion of enantiomeric excess were detected after application of several work-up conditions. Since the aldehyde was unstable, it was directly converted in the following WITTIG reaction. In this case, no loss of stereo information was observed, and the unsaturated ester **46** was obtained in 71% yield (96% *ee*). To further improve this step, the removal of solvent and the addition rate to the WITTIG reagent should be rigorously controlled. The next steps included hydrogenation, reduction using DIBAL-H, FRIEDEL–CRAFTS cyclization, and final hydrogenation to obtain bicyclic alcohol **11**. The last two steps were in accordance with PASTRE's route. Using our approach, an increased overall yield was achieved for the polyketide fragment **11** as in the decalin route (17% overall yield, Figure 11).

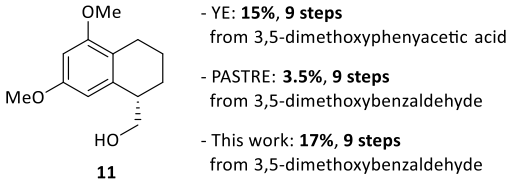
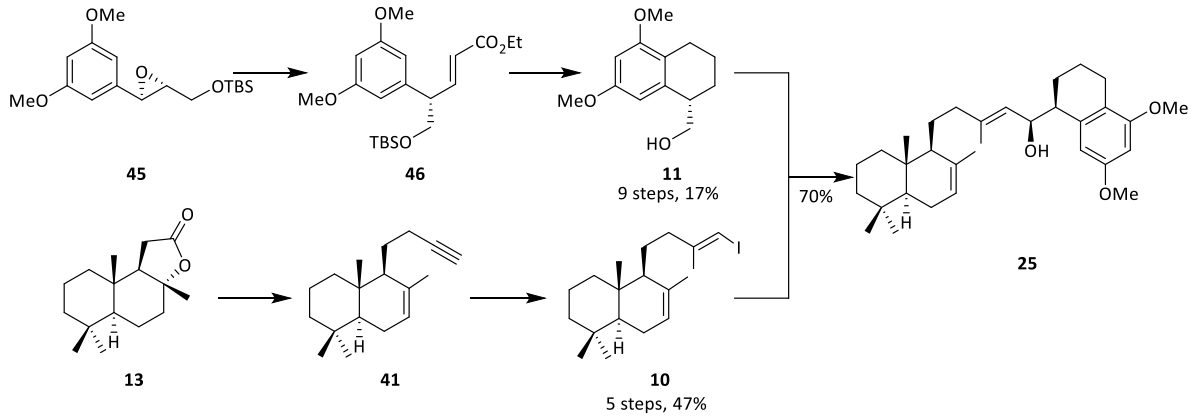


Figure 14: Comparison of the different approaches to fragment **11**.

The two fragments were finally coupled according to YE's[64] and PASTRE's[67] procedure to complete the skeleton of the natural product actinoranone (**9**) and thus its formal synthesis with 70% yield (Scheme 17).



Scheme 17: Sketch of the actinoranone backbone synthesis.

Unfortunately, we were not able to reproduce the three final steps towards the natural product following YE´s procedure.[64] This should be the aim of future work. Furthermore, a more succinct route towards the bicyclic alcohol fragment **11** should be envisioned. The synthesis of the ester **46** is straightforward but the cyclization and follow-up reaction towards fragment **11** is rather tedious. A direct cyclization approach at the ester stage might shorten the synthesis and would increase the overall yield. Nevertheless, we reported herein a new synthetic sequence to access the natural product actinoranone, which disclosed a more concise strategy compared to the YE's lengthy and PASTRE's low-yielding approaches of the terpenoid fragment (five steps, 47%). Our synthetic plan combined their routes regarding selective elimination and vinyl iodide formation. On the other side, the polyketide fragment **10** was obtained in the same step-count but with a higher overall yield (17% compared to 15% and 3.5%) in comparison to the two published routes. We hereby applied another approach to installing the stereocenter at the benzylic position by optimizing a known organoaluminum-promoted epoxide rearrangement introduced by YAMAMOTO. The assembly of actinoranone's framework was achieved in 16 steps (11 steps LLS, 12% overall yield) offering a more efficient alternative to the previously reported works.

Overall, the presented synthetic routes of vitepyrroloids A (**1a**) and B (**1b**) and actinoranone skeleton **25** demonstrated the potential of (+)-sclareolide as a suitable and powerful building block. By varying reaction conditions, we could control the formation of the desired alkene after methanolysis and alcohol elimination from the sesquiterpene lactone, thus, providing a tool towards the synthesis of the carbon framework of different natural products starting from the chiral pool.

Part B

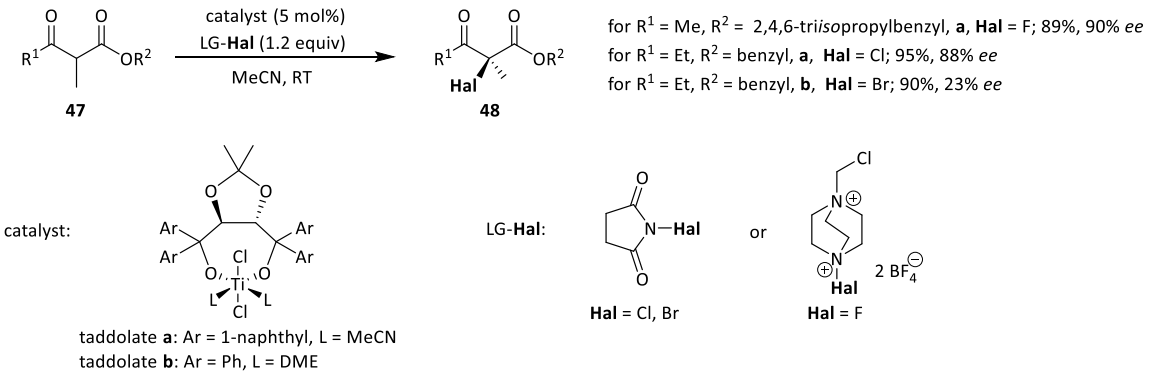
Mechanistic studies on the α-chlorination of aldehydes

1) INTRODUCTION

1.1 Asymmetric α-halogenation of carbonyl compounds

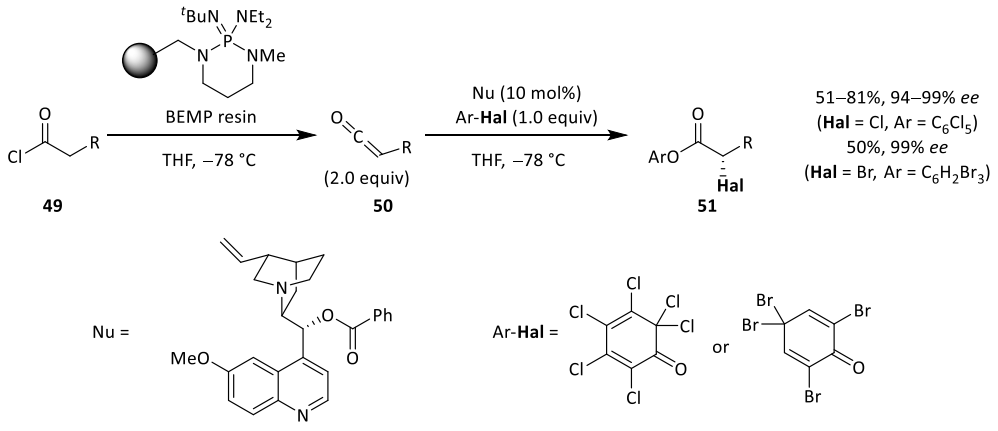
One of the major challenges in organic chemistry is the stereoselective carbon–halogen bond formation. Their importance arises from the beneficing of the obtained products as versatile synthetic intermediates due to the good leaving ability of the halogen atom. In particular, alkyl halides are key precursors for the formation of carbon–carbon bonds, ethers, amines, sulfides, or epoxides.[86] These properties are also useful in case of natural product synthesis where readily available, optically enriched, and multifunctional building blocks are beneficial. Additionally, halides are often introduced into pharmaceutically active compounds in medicinal chemistry to decrease the rate of metabolic degradation without affecting the existing positive pharmacological effects and therefore enhancing the therapeutic efficiency in comparison to their parent compounds.[87]

For a profitable stereoselective synthesis campaign, α-haloaldehydes signify extraordinary starting materials due to their bifunctional nature, availability from feedstock chemicals, and inherent chirality.[88] The first α-haloaldehyde synthesis was already reported by SCHRÖDER in 1871 who treated valeraldehyde with chlorine gas, which led to a racemic mixture of products.[86, 89] The preparation of optically pure α-haloaldehydes took almost a century, they were reported for the first time in the process of preparing 2-deoxy-2-fluorosugars in the 1960s.[90] Herein the stereogenic information was transferred from the carbohydrate chiral pool. Introduction of chiral information by means of carbon–halogen bond formation proved to be an arduous challenge to overcome in the latter half of the 20th century. It is striking that a wide range of catalytic asymmetric carbon–carbon, carbon–heteroatom, and carbon–hydrogen bond formations[91] are discussed in the literature; however, methods for the stereoselective formation of carbon–halogen bonds are much less reported. This could be ascribed to the common use of highly reactive molecular halides as halogen source. The incompatibility of these reagents with catalysis increased the demand for milder and more sophisticated halogenation reagents that offer greater tolerance in catalytic systems.[92] A milestone facing this challenge was the work of HINTERMANN and TOGNI in 2000 in which they reported the first catalytic asymmetric α-halogenation of carbonyl compounds using chiral LEWIS acid catalysis. With the use of titanium-based LEWIS acids, they successfully achieved α-fluorination and α-chlorination of 1,3-dicarbonyl compounds **47** (Scheme 18).[93-95]



Scheme 18: Asymmetric α-halogenation of β-ketoesters by HINTERMANN and TOGNI catalyzed by Ti(TADDOL)-based LEWIS acid.[93-95]

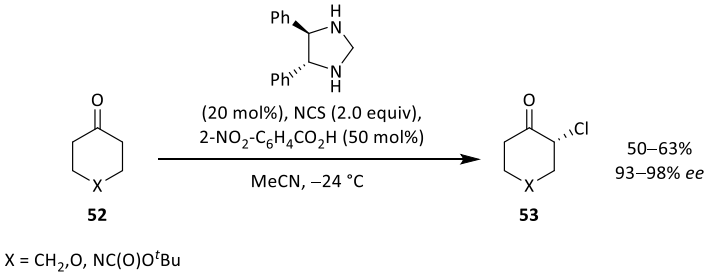
A variety of enantioselective halogenation of β-ketoesters based on LEWIS acid catalysis followed after this milestone work.[96-98] JØRGENSEN's method, comprising a selective α-bromination/α-chlorination by a chiral copper complex, attracted huge attention among these.[99] However, the formation of optically active α-halocarbonyl compounds was solely restricted to 1,3-dicarbonyls to this point. LECTKA et al. then introduced the enantioselective α-chlorination and α-bromination of acid chlorides **49** by chiral nucleophiles derived from cinchona alkaloids as phase-transfer catalysts and polyhalogenated quinones as halogen sources after resin-supported formation of ketenes **50** (Scheme 19).[92, 100-102]



Scheme 19: LECTKA's enantioselective α-chlorination/bromination of acid chlorides.[92, 100-102]

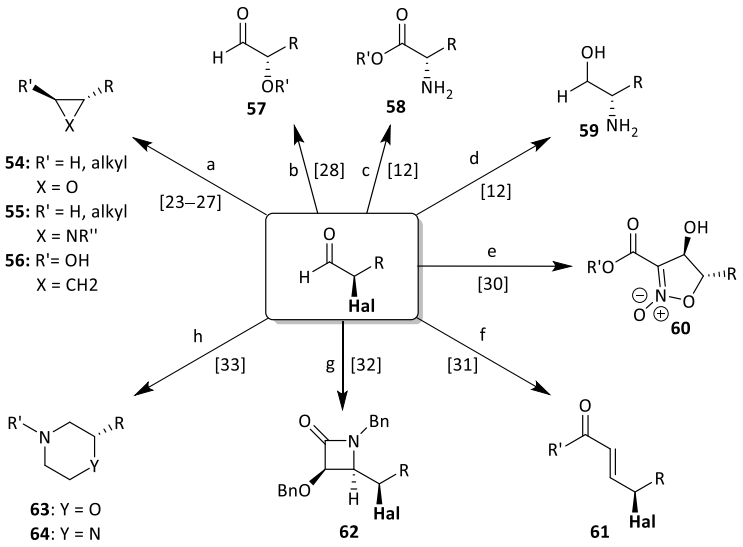
After the developed methods using LEWIS acids and cinchona alkaloid nucleophile, the introduction of new types of organocatalysts such as chiral secondary amines was the next important landmark in the development of asymmetric catalytic α-halogenation of carbonyl compounds. In 2004, not only the group of MACMILLAN[103] but also JØRGENSEN and co-workers,[104] as well as, BARBAS and co-workers[105] independently presented the first

organocatalytic α-chlorination and α-fluorination of aldehydes. The α-halogenation of ketones **52** by JØRGENSEN was also established using C_2-symmetric diamine and *N*-chlorosuccinimide (NCS) in the same year (Scheme 20).[106-107]



Scheme 20: JØRGENSEN's organocatalytic α-chlorination of alkyl and cyclic ketones using NCS.[107]

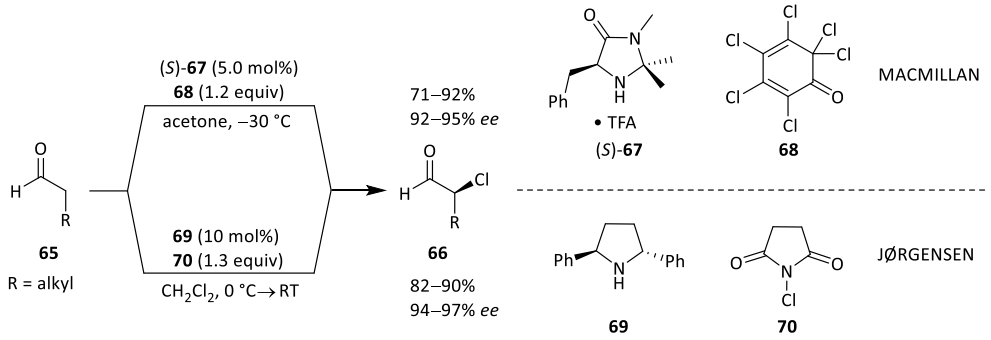
The development of the aforementioned organocatalytic approaches allowed for the scalable preparation of enantioenriched α-haloaldehydes, which can be employed as intermediates in organic and natural product synthesis since they are described as a highly versatile building.[88, 108-113] In this regard, the BRITTON group highlighted the broad utility of enantiomerically enriched α-chloroaldehydes to access, for example, chiral alkaloids,[114] hydroxytetrahydrofurans,[115] spiroketals,[116] carbohydrates,[117] hydroxypyrrolidines,[118] and iminosugars.[119] A general overview of possible follow-up transformations starting from α-haloaldehydes is depicted in Scheme 21. These products can be derived either by a stepwise procedure or in a one-flask approach in a stereoselective fashion. For instance, diastereoselective addition of organometallic reagents to α-chloroaldehydes were already predicted to proceed as *anti* by CORNFORTH's model in 1959.[120] These additions are enabling access to epoxides,[121] aziridines,[122] and cyclopropanes[123] (Scheme 21, a, **54**–**56**) in a stereoselective manner. Hydride reduction of the carbonyl group or reductive amination can lead to terminal epoxides[124-125] or aziridines (a, **54**/**55**).[126] Nucleophilic substitutions of the halide by an oxygen atom (b, **57**)[127] or an azide group[128] can give access to α-hydroxy or aminoesters (c, **58**).[104] The halohydrin obtained from hydride reduction of α-haloaldehydes can also be converted into hydroxyamines (d, **59**) by azide substitution and hydrogenolysis.[104] Moreover, HENRY reaction gives access to isoxazolines (e, **60**),[129-131] HORNER–WADSWORTH–EMMONS reaction yields allyl halides (f, **61**),[132] STAUDINGER cycloaddition with the corresponding imines affords β-lactams (g, **62**),[133-134] or a three-step sequence can provide morpholines (h, **63**) or piperazines (h, **64**).[135]



Scheme 21: Stereoselective transformations of α-haloaldehydes.

1.1.1. Organocatalytic α-chlorination of aldehydes

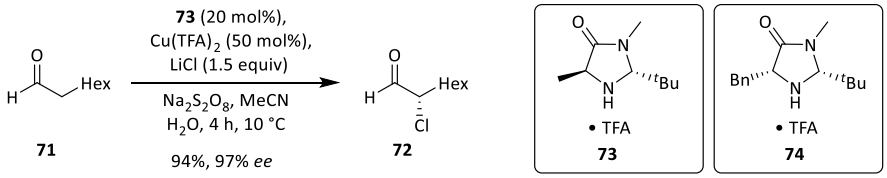
As mentioned in the previous chapter, the landmark works of MACMILLAN[103] and JØRGENSEN[104] disclosed the catalytic asymmetric α-halogenation of aldehydes, thus, affording new valuable and versatile intermediates for organic synthesis. Especially, the utility of α-chloroaldehydes was elegantly demonstrated by the BRITTON group where they applied both practical procedures.[88, 111, 113, 117-119] MACMILLAN et al. used a chiral imidazolidinone catalyst **67** and hexachloro-cyclohexadiene (**68**) as Cl-source, whereas JØRGENSEN et al. succeeded by using L-prolinamide or C_2-symmetric catalyst **69** and NCS (**70**) as Cl-source (Scheme 22).



Scheme 22: Organocatalytic α-chlorination of aldehydes by chiral secondary amines.[103-104]

Both approaches paved the way to α-chloroaldehydes **66** with excellent enantiomeric excess (*ee*) and good yields, albeit expensive materials such as catalyst **69** and Cl-source **68** were required, and a limited reaction scope was noticed. Shortly after these two methods, the

MACMILLAN group established a robust enantioselective α-chlorination of aldehydes by organo-SOMO (single occupied molecular orbital) catalysis aiming to introduce both, a less expensive catalyst and Cl-source. The transformation was performed at room temperature or at 10 °C to achieve more enantiocontrol using LiCl as an inexpensive Cl-source and the simple imidazolidinone catalyst **73** (Scheme 23, exemplarily with octanal **71**).[125]

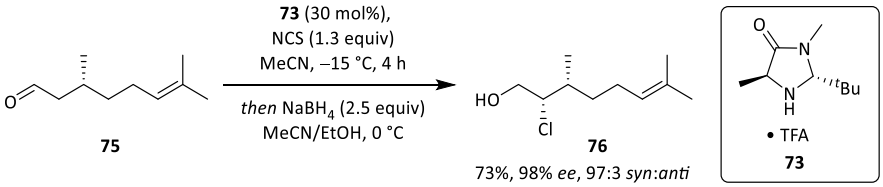


Scheme 23: Organo-SOMO catalysis by the MACMILLAN group with octanal.[125]

Interestingly, the presence of a methyl group at the imidazolidinone skeleton in the catalyst was essential to avoid rapid decay of enantiointegrity during the course of the reaction. This modification suppressed the iminium-enamine equilibration after Cl-addition, which was observed when benzyl derivative (*S*)-**74** was used as catalyst. These results might indicate that the α-chlorination is catalyst-controlled. In the MACMILLAN procedure, a so-called "linchpin" catalysis, the enantioenriched aldehyde was reduced afterward and directly subjected to base-promoted intramolecular substitution in a one-flask system to give terminal epoxides.[125] This concept implies that the enantioinducing step could be telescoped by conversion of the chiral intermediate into valuable follow-up building blocks.[136] In this particular case, achiral aldehydes were transformed into enantioenriched α-formyl chlorides, which were converted into epoxides, aziridines, or α-amino acids (see Scheme 21).[125]

One of our group's long-term interest comprehends the use of terpene feedstock as suitable building blocks in natural product synthesis.[137-139] By this, functionalization of the terpenes' carbon backbone is an essential key challenge. We reported a total synthetic route to ripostatin B where we converted a terpene-derived aldehyde into its corresponding epoxide using the aforementioned organo-SOMO methodology in this context.[139] Within this study, problems such as diminished reaction rate and decomposition of starting material were arising when extended to a wider set of aldehydes. The seminal methods of MACMILLAN and JØRGENSEN (see Scheme 22) were also discarded due to relatively costly catalyst **69** or Cl-source **68** on an early step considering a scale-up process. Therefore, we sought a practical asymmetric α-chlorination protocol with easily available reagents and reaction set-up. Our procedure

combined the works of MACMILLAN[125] on SOMO catalysis and JØRGENSEN´S[104] electrophilic chlorination, employing catalyst **73** and the inexpensive Cl-source NCS (**70**). The best result for the chlorohydrin **76** obtained after $NaBH_4$ reduction of chlorinated test substrate (*R*)-citronellal (**75**) is shown in Scheme 24.[108, 124]

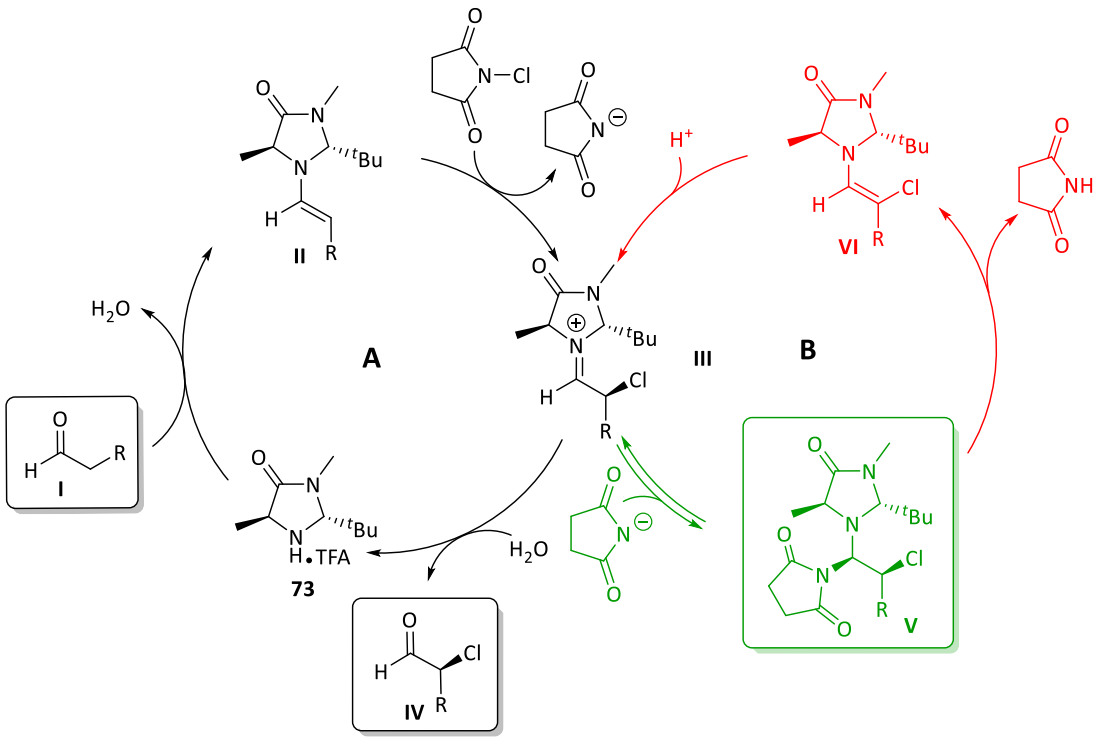


Scheme 24: Organocatalytic α-chlorination of our group.[124]

In the context of this study, we observed that a rather substoichiometric amount of catalyst is needed (30 mol%). We observed the same effect when we applied this method to another synthesis campaign with heptandial as substrate. In this case, we could explain the high amount of catalyst due to the formation of an aminal resulting from the attack of the succinimide anion to the transient α-chloroiminium intermediate. This has stimulated further examination and investigation on reaction mechanism and catalyst deactivation pathway.

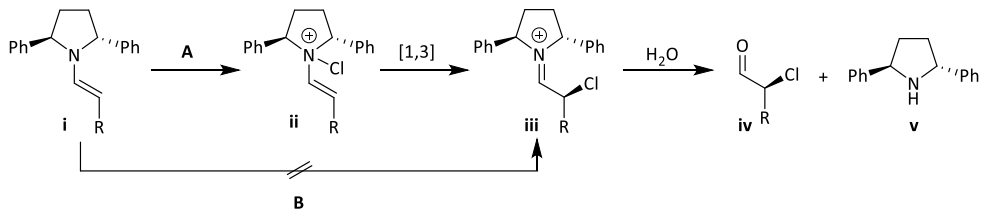
1.1.2 Current status of organocatalytic α-chlorination mechanism

In general, the oganocatalytic α-chlorination of aldehydes has been extensively discussed in literature.[140-141] The standard steric shielding model, outlined in cycle A (Scheme 25), is the generally assumed reaction mechanism applicable to MACMILLAN´S[125] and our system.[124] This pathway was suggested by MACMILLAN for organocatalyzed α-chlorination reactions with imidazolidinone catalyst systems (cycle A depicts this route with NCS as standard Cl-source according to the method established in our group, Scheme 25). After enamine **II** formation from aldehyde **I** and *N*-heterocyclic catalyst **73**, the addition of the electrophilic chlorine occurs on the opposite face to the proximal bulky substituent of the catalyst forming the α-chloroiminium ion **III**. Final hydrolysis releases the catalyst and the α-chloroaldehyde **IV**. Our findings of the needed high amount of catalyst in connection with the occurrence of an aminal as intermediate allows an extension of the standard mechanistic cycle. We hypothesized an off-cycle species (green, Scheme 25).



Scheme 25: Extended catalytic cycle **A** with aminal **V** (green) following the standard steric shielding mechanism (black) with aminal **V** and downstream cycle **B** proposed by BLACKMOND et al. (red).[140, 142-143]

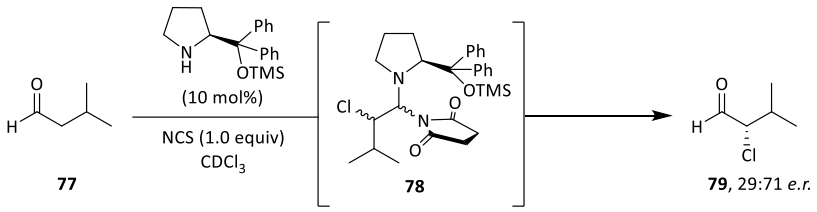
The standard model of steric shielding based on the catalyst has been questioned by the JØRGENSEN group. For their chlorination system using 2,5-diphenylpyrrolidine **69** as catalyst and NCS (**70**) as Cl-source, they proposed that enamine intermediate **i** does not show any appreciable shielding of the reacting α-carbon center (Scheme 26). The investigation on the mechanism using density functional theory (DFT) revealed a reaction of the electrophilic chlorine source with the more nucleophilic enamine nitrogen atom leading to *N*-chloroiminium ion intermediate **ii** (path **A** in Scheme 26).



Scheme 26: Mechanism for the organocatalytic α-chlorination proposed by JØRGENSEN.[141]

This proposal excluded the direct addition of Cl^+ to the enamine carbon center (**iii**, path **B** in Scheme 26) and rather envisioned a 1,3-sigmatropic chlorine shift forming thermodynamically favored **iii** *via* intermediate **ii** when a pyrrolidine catalyst is used.[141]

The group of JØRGENSEN has investigated the reaction mechanism for the α-chlorination using ^{1}H NMR studies to further elucidate product-limiting steps. They found that an aminal structure resulting from the succinimide anion addition to the formed α-chloroiminium ion **iii** under anhydrous conditions might have led to catalyst deactivation.[141] As indicated in the previous chapter, our group also detected these kind of intermediates under standard reaction conditions (see compound **V** in Scheme 25 as exemplary aminal). In the same context, BLACKMOND and co-workers investigated the accuracy of their proposed concept of "CURTIN–HAMMOND paradigm" on the organocatalytic α-chlorination of isovaleraldehyde (**77**) with NCS (**70**) and the JØRGENSEN–HAYASHI catalyst. Just as the JØRGENSEN group, they were able to detect aminal **78** (Scheme 27) in ^{1}H NMR-studies but did not succeed in its isolation.[140, 142-143]



Scheme 27: Mechanistic investigation by the BLACKMOND group with isovaleraldehyde (**77**) and NCS (**70**).[140]

Based on these findings, they proposed a secondary stereodetermining catalytic cycle with aminal **V** participating (exemplary depicted with imidazolidinone catalyst **73** and NCS (**70**), Scheme 25, red pathway) rather than being an off-cycle intermediate. In their opinion, *Z*-chloroenamine **VI** is formed after E2 elimination of succinimide from aminal **V**. The cycle would be completed by diastereoselective protonation to α-chloroiminium ion **III** which would then be hydrolyzed signifying the downstream to the primary cycle (Scheme 25). It is important to note that in accordance with the observed stereoinduction, the protonation in this scenario has to occur from the opposite face of the enamine compared to the aforementioned addition of the electrophilic chlorine. Nevertheless, the BLACKMOND group was not able to prove this diastereoselective protonation mechanism.[140] The effect of aminal **V** on the organocatalyzed reaction is not yet clarified. The isolation of this crucial adduct would be essential for an exhaustive investigation of the organocatalytic α-chlorination of aldehydes and allow the elucidation of its role in the catalytic cycle.

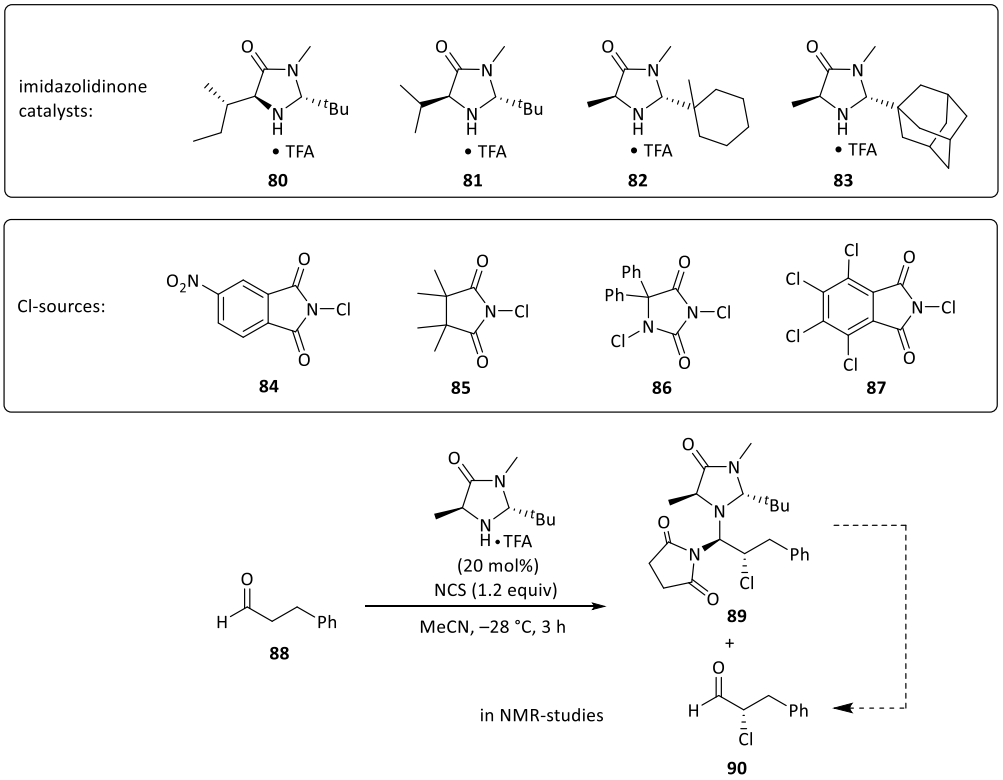
2) SCIENTIFIC GOALS

Despite a broad substrate scope and excellent enantio- and diastereoselectivity, the organocatalytic α-chlorination method established in our group showed some weaknesses with respect to catalyst loading (30 mol%). The observation of an aminal as by-product might explain the high amount of organocatalyst needed. These preliminary findings raised the question of the role of this aminal. Is it inevitably formed in a secondary catalytic cycle and thereby responsible for the enantioinduction of the reaction as suggested by the BLACKMOND group (cycle B, Scheme 25)? Or is it an off-cycle intermediate which lies in equilibrium with the α-chloroiminium ion and as a consequence suppresses the turnover of the catalyst from cycle A? These compelling questions should be answered by extensive ^{1}H NMR- and kinetic isotope effect studies of the envisioned isolable aminal compounds.

Furthermore, our early observations also prompted the question if the formation of the aminal could be avoided. This would then cause a higher catalyst turnover with probably beneficial effects on product yield and catalyst loading. At the outset, we chose hydrocinnamaldehyde (**88**) for its reliable UV-profile as a test substrate to investigate the organocatalytic α-chlorination. For this purpose, different imidazolidinone catalysts with varied substituent patterns (**80**–**83**), a large number of established and novel Cl-sources (**84**–**87**), the solvent influence, and the impact of additives such as BRØNSTED acids and LEWIS acids/bases was planned to be examined (Scheme 28).

Therefore, the objective of this work was the optimization of the reaction conditions for the organocatalytic α-chlorination of aldehydes with a broad substrate scope and excellent yields and enantiomeric excess. In this context, we sought to combine GC-MS measurements and NMR-studies for a deeper understanding of the reaction profile. These findings should give us the opportunity to adjust the reaction conditions and thus to enhance the aminal accumulation or even suppress its formation. Moreover, we were aiming for the isolation of the observed aminal with hydrocinnamaldehyde (**89**) to further study its stability and decay in terms of stereoselectivity (Scheme 28). Addition of H_2O and/or acids might provide information about the reactivity of the aminal. The reaction of this intermediate under deuterium conditions of the reaction set-up should give further indications of its decomposition and hence might elucidate the aminal role as either an off-cycle intermediate

or as part of a secondary stereodetermining catalytic cycle. With this study, we were seeking to rationalize the reaction mechanism in detail and thereby prevent accumulation or suppress the aminal formation to eventually optimize the organocatalytic α-chlorination of aldehydes.



Scheme 28: Some possible imidazolidinone catalysts and Cl-sources stated for the optimization of the organocatalytic α-chlorination and formation of the aminal and its possible decay.

3) PUBLICATION

In the following section the published article is depicted, and the contributions of the author are specified.

3.1 Mechanistic Studies on the Organocatalytic α-Chlorination of Aldehydes: The Role and Nature of Off-Cycle Intermediates

S. Ponath, **M. Menger**, L. Grothues, M. Weber, D. Lentz, C. Strohmann, and M. Christmann, *Angew. Chem. Int. Ed.* **2018**, *57*, 11683–11687.

The journal article is electronically available (https://doi.org/10.1002/anie.201806261).

Abstract:

In this mechanistic study, the isolation and characterization of aminal intermediates in the organocatalytic α-chlorination of aldehydes is reported. These species are stable, covalently linked ternary adducts of the substrate, the catalyst, and the chlorinating agent. NMR-assisted kinetic studies and isotopic labeling experiments with the isolated intermediates did not support its involvement in downstream stereoselective processes as proposed by BLACKMOND et al. By tuning the reactivity of the chlorinating reagent, we were able to suppress the accumulation of rate-limiting off-cycle intermediates. As a result, an efficient and highly enantioselective catalytic system with a broad functional group tolerance was developed.

Authors' contribution:

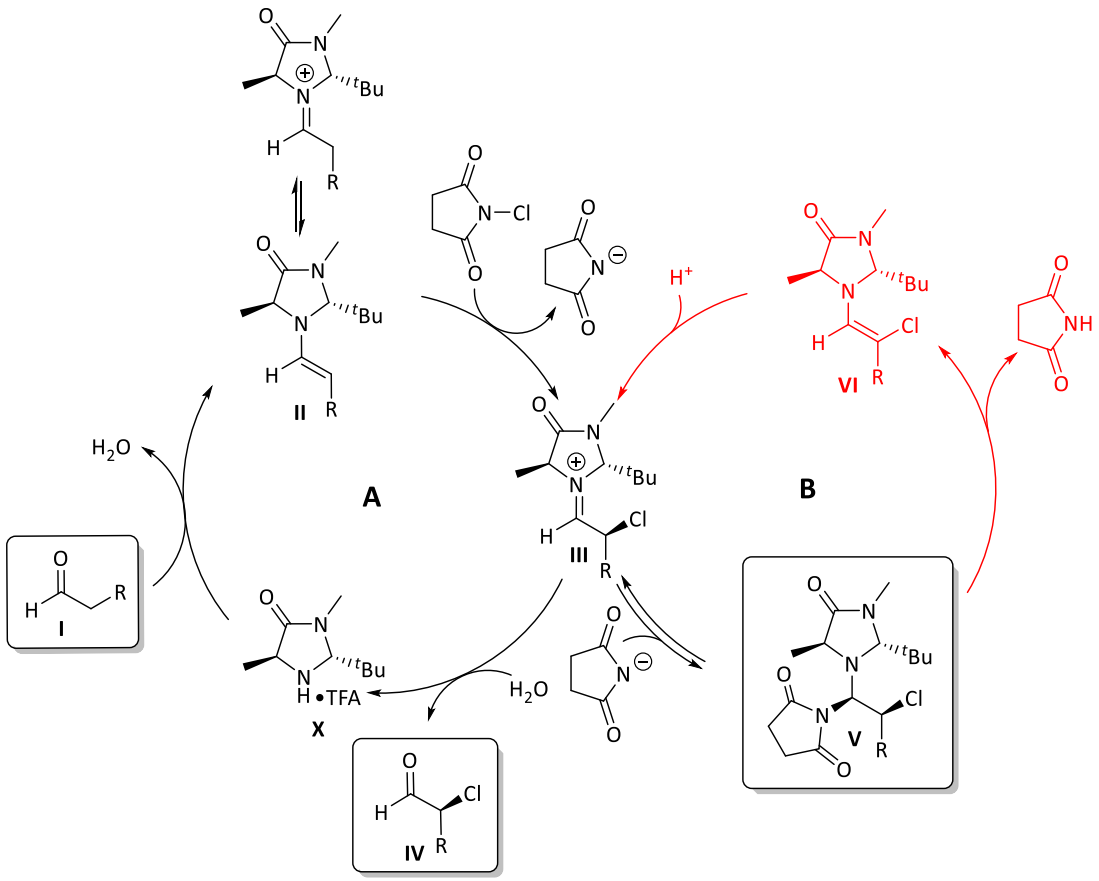
I developed the general concept to analyze the intermediate formation and started the project by elaborating the model reaction with hydrocinnamaldehyde, NCS, and MACMILLAN's imidazolidinone catalyst. In this context, I was able to isolate single crystals of the intermediate derived from octanal, pentanal, and hydrocinnamaldehyde. I explored the impact of several additives such as LEWIS-acids, BRØNSTED-acids, etc. and different solvents on the reaction outcome and aminal formation and suppression. Therefore, I developed a

feasible GC-MS method which was further used in the studies of the first author. In addition to that, preliminary NMR-studies following the reaction progress and the decomposition of aminal intermediate were conducted by me. Moreover, I was varying the alkyl-group at the C5 position of the imidazolidinone catalyst and screened several chlorine sources, mostly based on the structure of hydantoin, to enhance the α-chlorination of hydrocinnamaldehyde. Based on this exploratory work, the first author further pursued the study and investigated the impact of electron-deficient chlorine sources and imidazolidinone catalysts with variation at the C2 position. I assisted in the preparation of the manuscript, which was written by the first and corresponding author.

4) CONCLUSION AND OUTLOOK

The previous article showed our mechanistic study on the organocatalytic α-chlorination of aldehydes. During this investigation, we were able to isolate and fully characterize aminal intermediates consisting of the substrate, the organocatalyst, and the chlorinating agent. The α-chlorination of hydrocinnamaldehyde (**88**) using NCS (**70**) and imidazolidinone catalyst **73** served as a model reaction for a deeper investigation on the role of this ternary species. Based on ^{1}H NMR-assisted kinetic studies and isotopic labelling experiments the mechanism was finally elucidated.

The starting point of the study was the recognition of the high catalyst loading needed to pursue the organocatalytic α-chlorination of aldehydes in our previously developed method.[124] By analyzing the reaction outcome, we identified an aminal intermediate consuming the catalyst. Similar intermediates formed during the α-chlorination were already reported by others.[140-141] BLACKMOND et al. investigated the α-chlorination of aldehydes using JØRGENSEN-HAJASHI-catalyst and identified aminal intermediates in low-temperature ^{1}H NMR experiments. However, they were not able to isolate such species and concluded that the intermediates were part of a secondary catalytic cycle. In their so-called CURTIN-HAMMET paradigm they claimed that the observed enantioselectivity arose from the relative stability/reactivity of the intermediates downstream to the primary cycle (Scheme 29, red pathway). In addition, BLACKMOND suggested that this mechanistic concept may present a general phenomenon observed for amine catalysts lacking acidic/directing protons.[140, 142-143] With the isolation of the aminal intermediate of hydrocinnamaldehyde **89**, we were in the position to elucidate its role in the mechanistic cycle. We found that the choice of chlorine source had a major impact on reaction rate and intermediate accumulation. Electron-rich counterions caused a higher amount of aminal formation whereas electron-deficient counterions increased the reactivity towards the product. A ^{1}H NMR study of the model system using imidazolidinone catalyst **73**, hydrocinnamaldehyde (**88**), and tetramethylsuccinimide (**85**) or *N*-chloronitrophthalimide (**84**) as chlorine sources revealed rapid decomposition of the aminal when **84** was employed. The weakened N–C bond in aminals of type **V** facilitates the decay of the intermediate. The result marks the good leaving group ability of the nitrophthalimide anion. The relative amount of the ternary intermediate can thus be controlled by modulating the reactivity of the chlorine source.



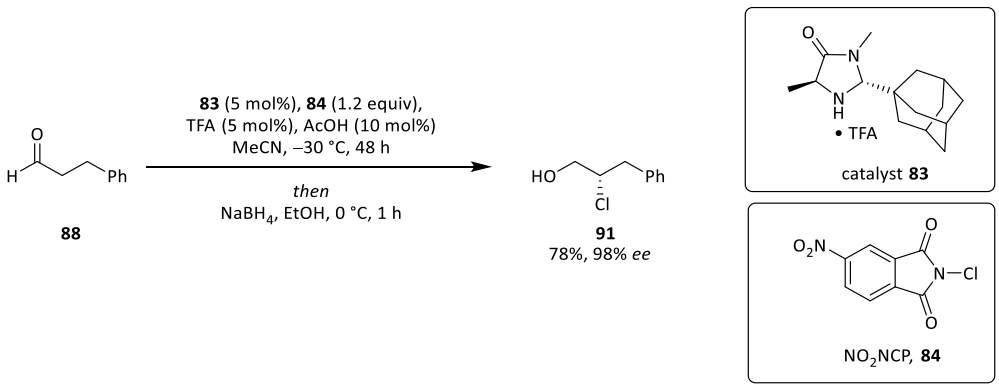
Scheme 29: Extended catalytic cycle **A** following the standard steric shielding mechanism (black) and downstream cycle **B** proposed by BLACKMOND (red).[140, 142-143]

The kinetic profile also showed that the rate of product formation was not depending on the decomposition of **V** in a secondary catalytic cycle as suggested by BLACKMOND.[140, 142-143]

Additionally, the decay of the aminal **89** was investigated by subjecting the intermediate to the general reaction conditions in the presence of deuterated solvent and acid additives. Product formation was slow but after one hour no deuterium was incorporated in the α-position of the aldehyde. This finding is in contrast to the proposed mechanism of the BLACKMOND group. They assumed that after chlorine addition, E2 elimination is taking place leading to the *Z*-chloroenamine **VI** (red pathway, Scheme 29). Diastereoselective protonation would then lead to the α-chloroiminium ion **III** of the primary cycle.[140, 142-143] Under these circumstances, deuterium incorporation should be detected after decomposition of the intermediate. After 19 h most of the intermediate had been decayed and ^{1}H NMR of the product mixture displayed partial deuterium incorporation probably due to racemization of the product as underlined by the drop of enantiomeric excess. After 66 h, the α-chlorohydrocinnamaldehyde (**90**) was nearly racemic.

All these observations support a classical mechanistic proposal where the enamine chlorination is the stereo-determining step. Moreover, we pointed out that the off-cycle aminal intermediate **V** can become rate-limiting by deactivating the catalyst, this could be overcome by the choice of chlorinating agent. The general application of this mechanistic concept remains to be surveyed. In this regard, our model system should be applied to other organocatalysts such as the JØRGENSEN–HAJASHI-catalyst, which has been already used by the BLACKMOND group. Thus, we could directly compare both reactions and intermediate formation to give a final proof for an off-cycle intermediate. Moreover, the formation of additional adducts should be investigated in more detail. It was found, for instance, that additives can affect the reaction. Optimal results were obtained when a 1:1:2 ratio of catalyst:TFA:AcOH was used. This observation indicates that acetic acid might play an additional role beyond being a proton source. Short-lived adducts with iminium intermediates could be one possible explanation. It would be interesting to investigate the exact role of these additives and their impact on the stability of the aminal intermediate. Therefore, an intensive mass spectrometry study could be conducted to identify additional adducts. In addition, ^{1}H NMR-assisted kinetic studies at low-temperature, e.g., at reaction temperature itself (–30 °C) or even lower (–78 °C) could be performed to gain further insight into the additive impact and finally establish a fully corrected mechanistic catalytic cycle.

With a deeper understanding of the α-chlorination of aldehydes, we were able to improve the previous reaction conditions.[124] Intensive screening of imidazolidinone catalysts with altered alkyl rests at C2 and C5 position, chlorine sources, solvents, and different acids led to the optimal conditions shown in Scheme 30.



Scheme 30: Newly developed organocatalytic α-chlorination of hydrocinnamaldehyde (**88**).

We thereby reduced the catalyst loading from 30 to 5 mol%. In general, the utility of the catalytic system was explored for the α-chlorination of a broad and diverse set of aldehydes. The reaction showed good functional group tolerance (e.g., for Boc-protected primary amine, aryl, alkenyl, and alkynyl side chains) and excellent enantio- and diastereoselectivity (96–99% *ee*). In the case of (*S*)-citronellal, an allylic chlorination was taking place causing a major drop in the product yield. A slow addition of chlorinating agent **84** was crucial to suppress the undesired side reaction with the electron-rich double bond. Nevertheless, this finding could be of interest for a future methodical application.

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6) APPENDIX

6.1 Supporting Information

6.1.1 Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)–C(sp3) Cross-Electrophile Coupling

The supporting information is left as it is in the published version.

6.1.2 Formal Synthesis of Actinoranone Using a Racemization-Free One-Pot Semipinacol Rearrangement/Wittig Reaction

The support information consists of the mechanistic procedures, spectra and HPLC analysis of the outlined substances in the manuscript.

Supporting Information

Formal Synthesis of Actinoranone Using a Racemization-Free One-Pot Semipinacol Rearrangement/Wittig Reaction

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Experimental section

General procedures

All reactions sensitive to moisture and/or air were performed under an argon atmosphere using Schlenk techniques. Reagents and solvents were obtained from commercial sources and used as received unless otherwise noted. Anhydrous solvents (THF, CH_2Cl_2, Et_2O, PhMe) were purified using the solvent purification system MB-SPS-800 (Braun). The solvents (EtOAc, Et_2O, *n*-pentane) used for column chromatography and work up were purified from commercially available technical grade solvents by distillation under reduced pressure. Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded at the following frequencies: ^{1}H NMR at 400, 500, and 700 MHz, ^{13}C NMR at 100, 125, and 175 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet), coupling constant (Hz), and integration. High resolution mass spectra were measured with a TOF mass spectrometer. TLC visualization was accomplished using UV light and/or staining in a Cer(IV)-sulfate solution (5.0 g phosphomolybdic acid, 16 mL conc. H_2SO_4, 200 mL H_2O, 4.0 g cerium(IV) sulfate) or acidic *p*-anisaldehyde solution (450 mL EtOH, 25 mL anisaldehyde, 25 mL conc. H_2SO_4, 8 mL AcOH) and subsequent charring. Yields refer to isolated yields after flash column chromatography.

*Synthesis of Methyl 2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**7**)*[1-2]

(3a*R*)-(+)-Sclareolide **5** (1.00 g, 4.00 mmol) was dissolved in MeOH (19 mL) and then treated with conc. H_2SO_4 (0.7 mL). After refluxing for 3 h, MeOH was distilled off and the residue dissolved in Et_2O (100 mL), washed with H_2O (2 x 50 mL), saturated aqueous $NaHCO_3$ solution (2 x 50 mL) and brine (20 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude alkenes were separated by column chromatography (*n*-pentane/Et_2O = 120:1 to 80:1) giving $\Delta^{7,8}$-**7** (636 mg, 2.4 mmol, 60%) and $\Delta^{8,9}$-**7** (424 mg, 1.60 mmol, 40%) alkenes as colorless oils.

7: R_f = 0.46 (*n*-pentane/Et_2O = 40:1); ^{1}H (500 MHz, $CDCl_3$): δ = 5.47 – 5.39 (m, 1H), 3.68 (s, 3H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.17 (dd, *J* = 16.5, 9.7 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.84 (dddt, *J* = 17.5, 12.0, 4.5, 2.4 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.56 – 1.53 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 (dd, *J* = 12.2, 4.7 Hz, 1H), 1.18 (td, *J* = 13.1, 3.6 Hz, 1H), 1.09 (td, *J* = 13.0, 3.9 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 175.5, 133.8, 122.9, 51.9, 50.7, 49.9, 42.2, 39.2, 36.1 33.3, 33.1, 23.8, 22.0, 21.5, 18.9, 14.1 (2C) ppm.

*Synthesis of 2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6, 7,8,8a-octahydronaphthalen-1-yl)ethan-1-ol (**8**)*

To a suspension of $LiAlH_4$ (0.230 g, 6.05 mmol, 1.5 equiv) in anhydrous Et_2O (20 mL), a solution of ester **7** (1.07 g, 4.04 mmol, 1.0 equiv) in anhydrous Et_2O (40 mL) was added slowly at 0 °C. The mixture was stirred for 1 h before it was quenched by the addition of aqueous HCl (1 M; 50 mL). Afterwards, the mixture was extracted with Et_2O (4 x 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/EtOAc = 5:1), alcohol **8** (0.954 g, 4.04 mmol, quant.) was obtained as colorless oil.

8: R_f = 0.39 (*n*-pentane/EtOAc = 5:1); ^{1}H (400 MHz, $CDCl_3$): δ = 5.41 (brs, 1H), 3.78 (dt, *J* = 9.5, 5.2 Hz, 1H), 3.66–3.47 (m, 1H), 2.04–1.91 (m, 1H), 1.92–1.78 (m, 1H), 1.72 (dd, *J* = 14.2, 7.2 Hz, 2H), 1.66 (s, 3H), 1.66–1.64 (m, 1H), 1.57–1.45 (m, 4H), 1.40 (d, *J* = 13.9 Hz, 1H), 1.18 (dd, *J* = 11.9, 5.1 Hz, 1H), 1.13 (dd, *J* = 13.1, 3.9 Hz, 1H), 0.95 (dt, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 134.7, 122.8, 64.5, 50.8, 50.2, 42.4, 39.3, 36.6, 32.3, 33.1, 30.6, 23.9, 22.2, 22.0, 18.9, 13.7 ppm.

*Synthesis of (4aS,5S,8aS)-5-(2-iodoethyl)-1,1,4a,6-tetrame- thyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**9**)*

To a solution of alcohol **8** (500 mg, 2.12 mmol, 1.0 equiv) in anhydrous THF (35 mL), PPh_3 (666 mg, 2.54 mmol, 1.2 equiv), imidazole (288 mg, 4.23 mmol, 2.0 equiv) and I_2 (644 mg, 2.54 mmol, 1.2 equiv) were subsequently added and the mixture was stirred for 2 h at 23 °C. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) giving alkyl iodide **9** (693 mg, 2.00 mmol, 95%) as colorless oil.

9: R_f = 0.98 (*n*-pentane); ^{1}H (400 MHz, $CDCl_3$): δ = 5.42 (brs, 1H), 3.38 (ddd, *J* = 10.3, 9.4, 4.7 Hz, 1H), 3.14 (td, *J* = 9.4, 7.5 Hz, 1H), 2.05 (dddd, *J* = 14.7, 10.3, 7.5, 1.8 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.89 – 1.72 (m, 3H), 1.67 (s, 3H), 1.65 – 1.60 (m, 1H), 1.56 – 1.51 (m, 1H), 1.47 (tq, *J* = 10.2, 3.4 Hz, 1H), 1.41 (dtd, *J* = 13.1, 3.2, 1.7 Hz, 1H), 1.19 (dd, *J* = 12.0, 4.9 Hz, 1H), 1.15 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.04 (td, *J* = 13.1, 4.1 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.74 (s, 3H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 133.7, 123.4, 56.6, 50.1, 42.3, 39.3, 36.8, 33.3, 33.1, 32.7, 23.9, 22.2, 22.0, 18.8, 13.9, 8.5 ppm.

*Synthesis of (4aS,5S,8aS)-5-(but-3-yn-1-yl)-1,1,4a,6-tetrame-thyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**4**)*

To a suspension of LAEDA (40.0 mg, 0.434 mmol, 1.5 equiv) in anhydrous DMSO/Et_2O (1:1 v/v; 0.6 mL), was added a solution of iodide **9** (100 mg, 0.289 mmol, 1.0 equiv) in anhydrous Et_2O (0.3 mL) at 0 °C. The reaction was stirred for 1 h and then another portion of LAEDA (40.0 mg, 0.434 mmol, 1.5 equiv) was added. After 3 h the reaction was quenched by the addition of H_2O (2.0 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phases were washed with H_2O (2 x 10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) giving the alkyne **4** (61.7 mmol, 0.252 mmol, 87%) as colorless oil.

4: R_f = 0.76 (*n*-pentane); ^{1}H (500 MHz, $CDCl_3$): δ = 5.41 (brs, 1H), 2.37 (dddd, *J* = 16.7, 9.1, 5.0, 2.6 Hz, 1H), 2.18 (dtd, *J* = 16.7, 8.3, 2.6 Hz, 1H), 2.02 – 1.97 (m, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.89 – 1.83 (m, 2H), 1.76 – 1.70 (m, 2H), 1.68 (s, 3H), 1.59 – 1.48 (m, 1H), 1.48 – 1.37 (m, 3H), 1.22 – 1.17 (m, 1H), 1.15 (dd, *J* = 13.1, 3.8 Hz, 1H), 1.01 (td, *J* = 13.1, 3.8 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 134.7, 122.9, 100.1, 85.0, 68.4, 53.8, 50.2, 42.4, 39.2, 36.7, 33.3, 26.4, 23.9, 22.3, 22.0, 20.5, 18.9, 13.8 ppm.

*Synthesis of (4aS,5S,8aS)-5-((E)-4-iodo-3-methylbut-3-en-1-yl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**2**)*[3]

To a solution of Cp_2ZrCl_2 (24.0 mg, 0.0820 mmol, 0.5 equiv) in anhydrous CH_2Cl_2 (6.0 mL), Me_3Al (2 M in PhMe; 0.24 mL, 0.489 mmol, 3.0 equiv) was added slowly at –30 °C. The pale-yellow mixture was stirred for 30 min at 23 °C and cooled to –30 °C again. At this point, H_2O (4.40 µL, 0.245 mmol, 1.5 equiv) was added and the mixture stirred for additional 30 min, and then a solution of alkyne **4** (40.0 mg, 0.163 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.30 mL) was added. After 1 h, I_2 (54.0 mg, 2.12 mmol, 1.3 equiv) dissolved in anhydrous THF (0.60 mL) was added and the yellow solution was stirred for 4 h at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by extraction with *n*-pentane (3 x 30 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane) yielding vinyl iodide **2** (44.0 mg, 0.154 mmol, 94%) as colorless solid.

2: R_f = 0.94 (*n*-pentane); ^{1}H (500 MHz, $CDCl_3$): δ = 5.89 (q, *J* = 1.1 Hz, 1H), 5.40 (brs, 1H), 2.46 – 2.33 (m, 1H), 2.16 (dddd, *J* = 13.7, 10.3, 6.2, 0.8 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.89 – 1.86 (m, 1H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.83 – 1.78 (m, 1H), 1.68 (brs, 3H), 1.62 – 1.47 (m, 3H), 1.47 – 1.38 (m, 2H), 1.34 – 1.26 (m, 1H), 1.20 – 1.12 (m, 2H), 0.93 (td, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 148.7, 135.0, 122.8, 75.0, 54.4, 50.3, 42.4, 42.2, 39.3, 36.9, 33.3, 33.1, 25.7, 24.2, 24.0, 22.3, 22.0, 18.9, 13.7 ppm.

*Synthesis of (E)-3-(3´,5´-dimethoxyphenyl)prop-2-en-1-ol (**6**)[4-5]*

Triethyl phosphonoacetate (6.05 mL, 14.1 mmol, 1.8 equiv) was added to a suspension of NaH (60 w% mineral oil; 0.580 g, 24.0 mmol, 1.8 equiv) in anhydrous THF (71 mL) at 0 °C. The suspension cleared after stirring for 30 min, and then a solution of the 3,5-dimethoxybenzaldehyde (2.00 g, 12.0 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added. Stirring was continued for additional 16 h during gradual warming to 23 °C. The mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude ester was dissolved in anhydrous CH_2Cl_2 (50 mL) and DIBAL-H (1 M in CH_2Cl_2; 36.0 mL, 36.1 mmol, 3.0 equiv) was slowly added at 0 °C. The reaction mixture was stirred for 1 h and then quenched by careful addition of aqueous HCl (1 M; 30 mL). The mixture was stirred for 30 min and then extracted with Et_2O (4 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (Et_2O/*n*- pentane = 2:1) giving allylic alcohol **6** (2.01 g, 10.4 mmol, 86%) as colorless oil.

6: R_f = 0.66 (*n*-pentane/Et_2O = 1:3); ^1H (500 MHz, $CDCl_3$): δ = 6.56 – 6.55 (m, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 6.53 – 6.51 (m, 1H), 6.38 – 6.36 (m, 1H), 6.34 (dd, *J* = 15.9, 5.7 Hz, 1H), 4.63 (brs, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 6H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 161.0 (2C), 138.9, 131.1, 129.2, 104.7 (2C), 100.0, 63.7, 55.4 (2C) ppm.

*Synthesis of tert-butyl(((2R,3R)-3-(3´,5´-dimethoxyphenyl) oxiran-2-yl)methoxy)dimethylsilane (**10**)[6]*

To a suspension of (+)-DET (0.240 mL, 1.41 mmol, 0.18 equiv) and powdered (or grinded) 4 Å MS in anhydrous CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (0.350 mL, 1.17 mmol, 0.15 equiv) was added at –20 °C. The mixture was stirred for 30 min and then ^{t}BuOOH (5.5 M in decane; 2.85 mL, 15.7 mmol, 2.0 equiv,) was added. After stirring for additional 30 min at –20 °C, a solution of allylic alcohol **6** (1.52 g, 7.83 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (3.5 mL) was added. The reaction mixture was stirred for 2 h at –20 °C and then quenched by the addition of aqueous NaOH (10% w/w; 10 mL) and brine (10 mL). The mixture was filtered through a pad of Celite and the filtrate was then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude epoxide was dissolved in anhydrous CH_2Cl_2 (77 mL) and treated with 2,6-lutidine (1.09 mL, 9.40 mmol, 1.2 equiv) and TBSOTf (1.98 mL, 8.61 mmol, 1.1 equiv) at 0 °C. The solution was stirred for 2 h at this temperature before quenching with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/Et_2O = 11:1), TBS-protected epoxide **10** (2.03 g, 6.26 mmol, 80%, 96% *ee*) was obtained as colorless oil.

10: R_f = 0.74 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{25}$ = –28.7 ($CHCl_3$, c = 1.0); IR: $\tilde{\nu}$ = 833, 1152, 1252, 1347, 1461, 1470, 1597, 2360, 1856, 2929, 2953 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 6.44 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 3.96 (dd, *J* = 12.1, 3.0 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.78 (s, 6H), 3.76 (d, *J* = 2.1 Hz, 1H), 3.12 – 3.07 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 161.2 (2C), 140.0, 103.5 (2C), 100.5, 63.0, 62.7, 56.0, 55.5 (2C), 26.0 (3C), 18.6, –5.1 (2C) ppm; HRMS (ESI): $[M+Na]^+$ calculated for $C_{17}H_{28}O_4SiNa^+$: 347.1649, found: 347.1640; $[M+K]^+$ calculated for $C_{17}H_{28}O_4SiK^+$: 363.1389, found: 363.1391.

*Synthesis of ethyl (S,E)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pent-2-enoate (**12**)*[6]

4-Bromo-2,6-di-*tert*-butylphenol (703 mg, 2.46 mmol, 4.0 equiv) was dissolved in anhydrous CH_2Cl_2 (14 mL) and the yellow solution was degassed (freeze-pump-thaw; three cycles). Subsequent addition of Me_3Al (2 M in PhMe; 0.62 mL, 1.23 mmol, 2.0 equiv,) gave a colorless solution. Stirring was continued for 1 h till the gas development has ceased. After cooling to –78 °C, a solution of epoxide **10** (200 mg, 0.616 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added to give a bright yellow solution. After 15 min stirring, anhydrous THF (3.0 mL) was added to the mixture and CH_2Cl_2 was carefully removed HV during warming to 23 °C. The resulting solution was then added to a suspension of the Wittig reagent (845 mg, 1.85 mmol, 3.0 equiv) and KO^tBu (200 mg, 1.79 mmol, 2.9 equiv) in anhydrous THF (8.0 mL) which was previously reacted for 30 min at 0 °C. The reaction mixture was stirred for additional 4 h at 0 °C and quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with Et_2O (4 x 50 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O = 11:1) yielding ester **12** as pale-yellow oil (173 mg, 0.437 mmol, 71%, 96% *ee*).

12: R_f = 0.45 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{25}$ = +12.8 ($CHCl_3$, c = 1.4); IR: $\tilde{\nu}$ = 833, 1152, 1428, 1461, 1594, 1717, 2856, 2929, 2953 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.39 – 6.26 (m, 3H), 5.85 (dd, *J* = 15.8, 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.78 (s, 6H), 3.54 (q, *J* = 6.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 166.4, 160.8 (2C), 148.4, 142.0, 122.5, 106.4 (2C), 98.7, 66.2, 60.1, 55.2 (2C), 51.2, 25.7 (3C), 18.1, 14.1, –5.6 (2C) ppm; HRMS (ESI): $[M+H]^+$ calculated for $C_{21}H_{34}O_5SiH^+$: 395.2249, found: 395.2230; $[M+Na]^+$ calculated for $C_{21}H_{34}O_5SiNa^+$: 417.2068, found: 417.2082.

*Synthesis of ethyl (S)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pentanoate (**13**)*

A mixture of alkene **12** (173 mg, 0.437 mmol, 1.0 equiv) and Pd/C (17.5 mg, 40 mg/mmol, 10% w/w) in MeCN (2.0 mL) was stirred under H_2 atmosphere for 16 h at 23 °C. The mixture was filtered through a pad of Celite and the filter cake washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography (*n*-pentane/Et_2O = 9:1) giving ester **13** (161 mg, 0.406, 93%) as pale-yellow oil.

13: R_f = 0.44 (*n*-pentane/Et_2O = 8:1); $[\alpha]_D^{26}$ = +8.15 ($CHCl_3$, c = 0.75); IR: $\tilde{\nu}$ = 835, 1154, 1204, 1429, 1462, 1595, 1733, 2856, 2930, 2953 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.2 Hz, 2H), 6.32 (t, *J* = 2.6 Hz, 1H), 4.08 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.77 (s, 6H), 3.73 – 3.63 (m, 2H), 2.71 – 2.62 (m, 1H), 2.24 – 2.15 (m, 3H), 1.87 – 1.79 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), –0.01 (s, 3H), –0.03 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 173.8, 160.9 (2C), 144.8, 106.4 (2C), 98.5, 67.9, 60.3, 55.4 (2C), 48.5, 32.5, 27.3, 26.0 (3C), 18.4, 14.4, –5.3 (2C) ppm; HRMS (ESI): $[M+Na]^+$ calculated for $C_{21}H_{36}O_5SiNa^+$: 419.2224, found: 419.2218; $[M+K]^+$ calculated for $C_{21}H_{36}O_5SiK^+$: 435.1964, found: 435.1949.

*Synthesis of (S)-5-((tert-butyldimethylsilyl)oxy)-4-(3´,5´-dimethoxyphenyl)pentanal (**14**)*

To a solution of ester **13** (73.0 mg, 0.184 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1.8 mL), was added DIBAL-H (1.0 M in CH_2Cl_2; 0.20 mL, 0.202 mmol, 1.1 equiv) at –78 °C. After stirring for 1 h, the reaction was quenched by the addition of saturated aqueous potassium sodium tartrate (5.0 mL), stirred for 30 min and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification of the crude by column chromatography (*n*-pentane/Et_2O = 5:1), aldehyde **14** (53.8 mg, 0.153 mmol, 83%) was obtained as colorless oil.

14: R_f = 0.42 (*n*-pentane/Et_2O = 6:1); $[\alpha]_D^{25}$ = +11.0 ($CHCl_3$, c = 1.05); IR: $\tilde{\nu}$ = 835, 1110, 1152, 1204, 1252, 1428, 1461, 1594, 1724, 2856, 2929, 2952 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 9.70 (t, *J* = 1.6 Hz, 1H), 6.50 – 6.17 (m, 3H), 3.77 (s, 6H), 3.72 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.66 (dd, *J* = 10.0, 7.4 Hz, 1H), 2.66 (ddt, *J* = 10.2, 7.4, 5.1 Hz, 1H), 2.36 (td, *J* = 7.8, 1.4 Hz, 2H), 2.29 – 2.07 (m, 1H), 1.91 – 1.74 (m, 1H), 0.87 (s, 9H), –0.01 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 202.5, 161.0 (2C), 144.6, 106.4 (2C), 98.6, 67.9, 55.4 (2C), 48.4, 42.2, 26.0 (3C), 24.5, 18.4, –5.3 (2C) ppm; HRMS (ESI): $[M+H]^+$ calculated for $C_{19}H_{32}O_5SiH^+$: 353.2143, found: 353.2161.

*Synthesis of (S)-(5,7-dimethoxy-1,2,3,4-tetrahydronaphtha-len-1-yl)methanol (**3**)*

A solution of aldehyde **14** (53.8 mg, 0.153 mmol, 1.0 equiv) in anhydrous PhMe (5.2 mL) was treated with *p*TSA·H_2O (28.5 mg, 0.153 mmol, 1.0 equiv). The reaction was stirred for 1 h at 23 °C and quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The mixture was extracted with EtOAc (3 x 20 mL), the combined organic phases were washed with brine (30 mL), dried over

anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O = 8:1) giving the corresponding 3,4-alkene (45.1 mg, 0.135 mmol, 88%) as colorless oil.

R_f = 0.78 (*n*-pentane/Et_2O = 5:1); $[\alpha]_D^{25}$ = +1.77 ($CHCl_3$, c = 0.93); IR: $\tilde{\nu}$ = 833, 1092, 1148, 1207, 1319, 1425, 1463, 1576, 1603, 2856, 2928, 2952 cm^{-1}; ^1H (500 MHz, $CDCl_3$): δ = 6.71 (dd, *J* = 9.8, 2.9 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 5.73 (ddd, *J* = 9.5, 5.9, 2.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.65 – 3.44 (m, 2H), 2.89 – 2.82 (m, 1H), 2.51 (ddd, *J* = 17.4, 6.0, 2.6 Hz, 1H), 2.42 – 2.29 (m, 1H), 0.89 (s, 9H), 0.00 (s, 6H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 159.5, 156.0, 138.5, 122.7, 120.7, 116.2, 105.8, 97.0, 64.5, 55.7, 55.5, 41.0, 26.1 (3C), 24.3, 18.5, –5.2, –5.3 ppm.; HRMS (ESI): $[M+H]^+$ calculated for $C_{19}H_{30}O_3SiH^+$: 335.2037, found: 335.2054; $[M+Na]^+$ calculated for $C_{19}H_{30}O_3SiNa^+$: 357.1856, found: 357.1869.

A mixture of the intermediate alkene (45.1 mg, 0.135 mmol, 1.0 equiv) and Pd/C (5.40 mg, 40 mg/mmol, 10% w/w) in MeOH (1.0 mL) was stirred under H_2 atmosphere for 16 h at 23 °C. To the mixture EtOAc (80 mL) was added and the suspension filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography (*n*-pentane/EtOAc = 3:1) giving alcohol **3** (22.5 mg, 0.101 mmol, 75%) as colorless oil.

3: R_f = 0.28 (*n*-pentane/EtOAc = 3:1); $[\alpha]_D^{25}$ = –2.2 ($CHCl_3$, c = 1.0); ^1H (500 MHz, $CDCl_3$): δ = 6.39 (d, *J* = 2.2 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 3.81 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 6H), 2.92 (p, *J* = 5.4 Hz, 1H), 2.62 (dt, *J* = 16.9, 5.1 Hz, 1H), 2.53 – 2.42 (m, 1H), 1.95 – 1.86 (m, 1H), 1.81 (dd, *J* = 10.5, 3.6 Hz, 2H), 1.75 – 1.69 (m, 1H), 1.47 (brs, 1H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 158.3, 158.3, 138.4, 119.4, 104.2, 96.3, 67.0, 55.4, 55.3, 40.8, 24.9, 22.6, 19.1 ppm.

*Synthesis of (S,E)-1-((S)-5,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)-3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pent-2-en-1-ol (**16**)*

To a solution of alcohol **3** (23.0 mg, 0.103 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (1.0 mL), $NaHCO_3$ (13.0 mg, 0.152 mmol, 2.2 equiv) and DMP (44.0 mg, 0.104 mmol, 1.5 equiv) were added at 0 °C. The mixture was stirred for 1 h and then concentrated under reduced pressure. The obtained residue was purified by column chromatography (*n*-pentane/EtOAc = 3:1; R_f = 0.75 (*n*-pentane/EtOAc = 3:1)) to give aldehyde **15** which was immediately used in the following step.

^{n}BuLi (2.5 M in hexane; 60 µL, 0.138 mmol, 2.0 equiv) was added to a solution of vinyl iodide **2** (27.0 mg, 0.0690 mmol, 1.0 equiv) in anhydrous Et_2O (1.2 mL) at –78 °C. After 1 h, the freshly prepared aldehyde **15** in Et_2O (1.2 mL) was added and the reaction was stirred for 16 h at the same temperature. The mixture was quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with EtOAc (4 x 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. After purification by column

chromatography (*n*-pentane/EtOAc =10:1), vinyl alcohol **16** (34.7 mg, 0.0721 mmol, 70%) was obtained as colorless oil.

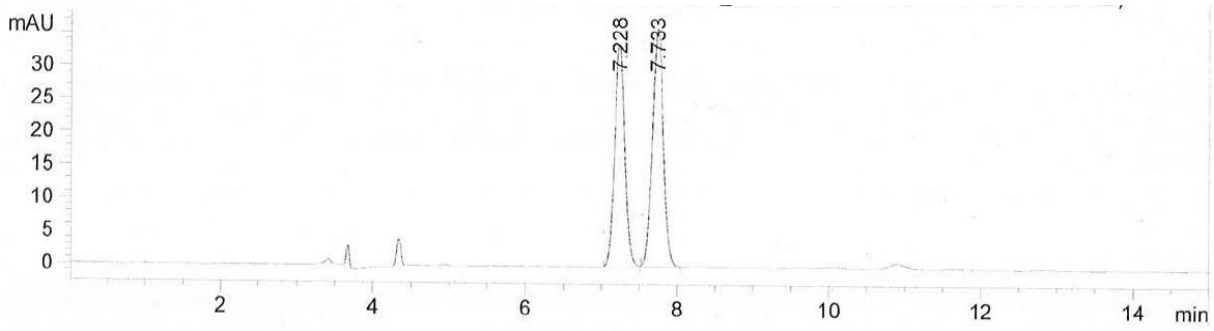
16: R_f = 0.24 (*n*-pentane/EtOAc = 9:1); $[\alpha]_D^{25}$ = +20.6 ($CHCl_3$, c = 1.60); ^1H (500 MHz, $CDCl_3$): δ = 6.48 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 2.1 Hz, 1H), 5.39 (brs, 1H), 5.30 (d, *J* = 8.0 Hz, 1H), 4.76 (ddd, *J* = 7.8, 4.7, 2.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.88 – 2.79 (m, 1H), 2.62 (dt, *J* = 16.7, 6.4 Hz, 1H), 2.51 (dt, *J* = 17.0, 6.3 Hz, 1H), 2.21 (td, *J* = 13.2, 12.6, 4.5 Hz, 1H), 2.02 – 1.74 (m, 8H), 1.69 (s, 3H), 1.66 – 1.60 (m, 2H), 1.58 (s, 3H), 1.49 – 1.30 (m, 4H), 1.29 – 1.12 (m, 3H), 0.97 – 0.92 (m, 1H), 0.88 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 158.5 (2C), 139.3, 138.9, 135.7, 126.2, 122.7, 120.7, 105.0, 96.4, 72.0, 55.7 (2C), 55.0, 50.6, 44.6, 42.7, 42.6, 39.6, 37.2, 33.6, 33.4, 26.1, 24.2, 23.8, 23.0, 22.6, 22.3, 20.6, 19.2, 17.2, 13.9 ppm.

References:

(1) Koltsa, MN; Mironov, GN; Vlad, PF, *Chem. Nat. Compd.* 1991; 27: 183.
(2) Carman, RW; Deeth, HC, *Aust. J. Chem.* 1971; 24: 1099.
(3) Davoust, M; Cantagrel, F; Metzner, P; Briere, J-F, *Org. Biomol. Chem.* 2008; 6: 1981.
(4) Sauerberg, P; Mogensen, JP; Jeppesen, L; Bury, PS; Fleckner, J; Olsen, GS; Jeppesen, CB; Wulff, EM; Pihera, P; Havranek, M; Polivka, Z; Pettersson, I, *Bioorg. Med. Chem. Lett.* 2007; 17: 3198.
(5) Bengtsson, C; Nelander, H; Almqvist, F, *Chem. Eur. J.* 2013; 19: 9916.
(6) Gao, S; Wang, Q; Chen, C, *J. Am. Chem. Soc.* 2009; 131: 1410.

HPLC-Analysis of **10** was performed using Chriralpeak IA, 2% EtOH/heptane, 20 °C, 0.8 mL/min

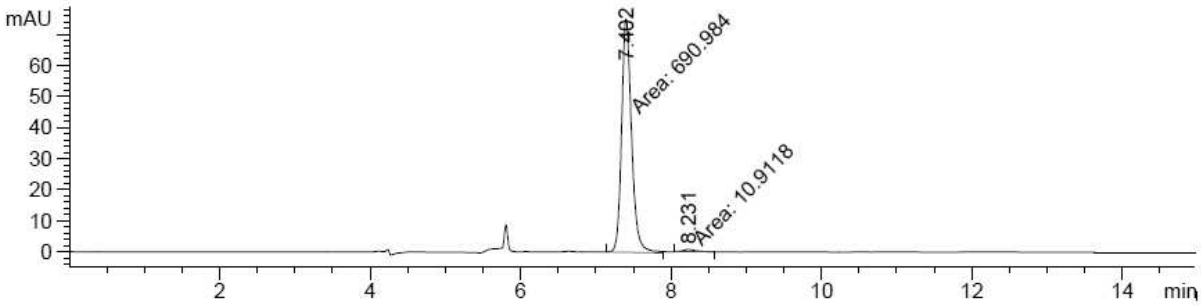
1) Racemic mixture



Signal 4: DAD1 E, Sig=270,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.059	BB	0.3403	129.15785	5.92515	53.4591
2	20.617	BB	0.4096	112.44359	4.10512	46.5409
Totals :				241.60144	10.03027	

2) **10** synthesized using (+)DET.

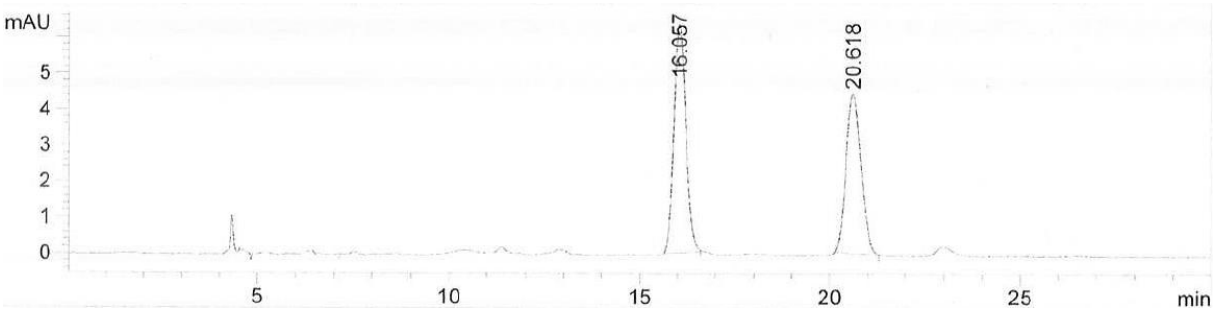


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.402	MM	0.1529	690.98389	75.30731	98.4454
2	8.231	MM	0.2230	10.91184	8.15380e-1	1.5546
Totals :				701.89572	76.12269	

HPLC-Analysis of **11** was performed using Chiralpeak IC, 1% isopropyl alcohol/hexane, 20 °C, 0.8 mL/min

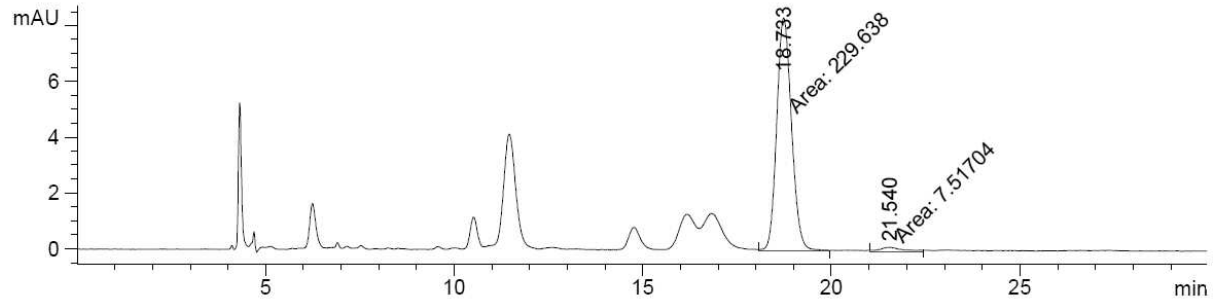
1) Racemic mixture



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

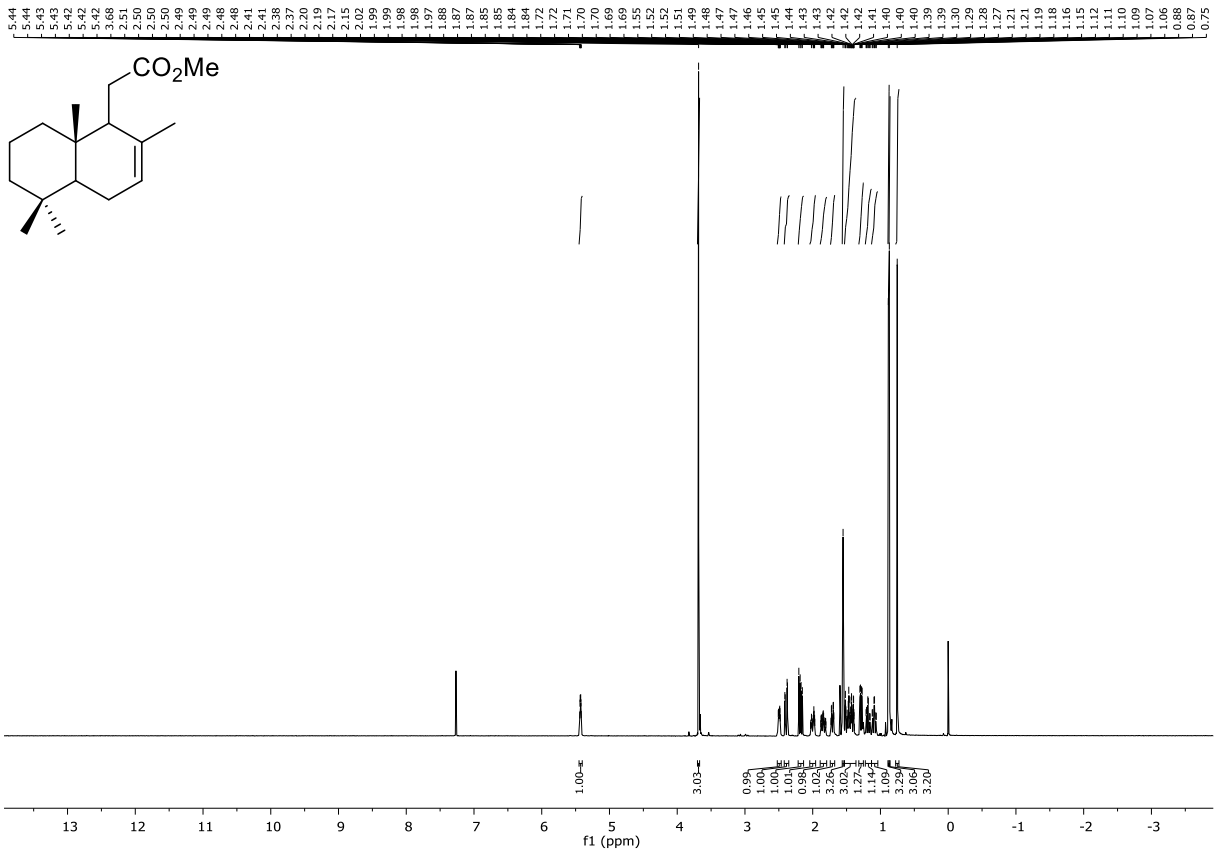
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.625	BB	0.1072	38.71054	5.56300	33.3180
2	8.363	BB	0.1516	77.47461	7.95887	66.6820
Totals :				116.18515	13.52186	

2) **11** synthesized by Yamamoto conditions.



Signal 2: DAD1 C, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.733	MM	0.4433	1.48440e4	558.10101	97.8033
2	22.782	MM	0.8827	333.40402	6.29488	2.1967
Totals :				1.51774e4	564.39589	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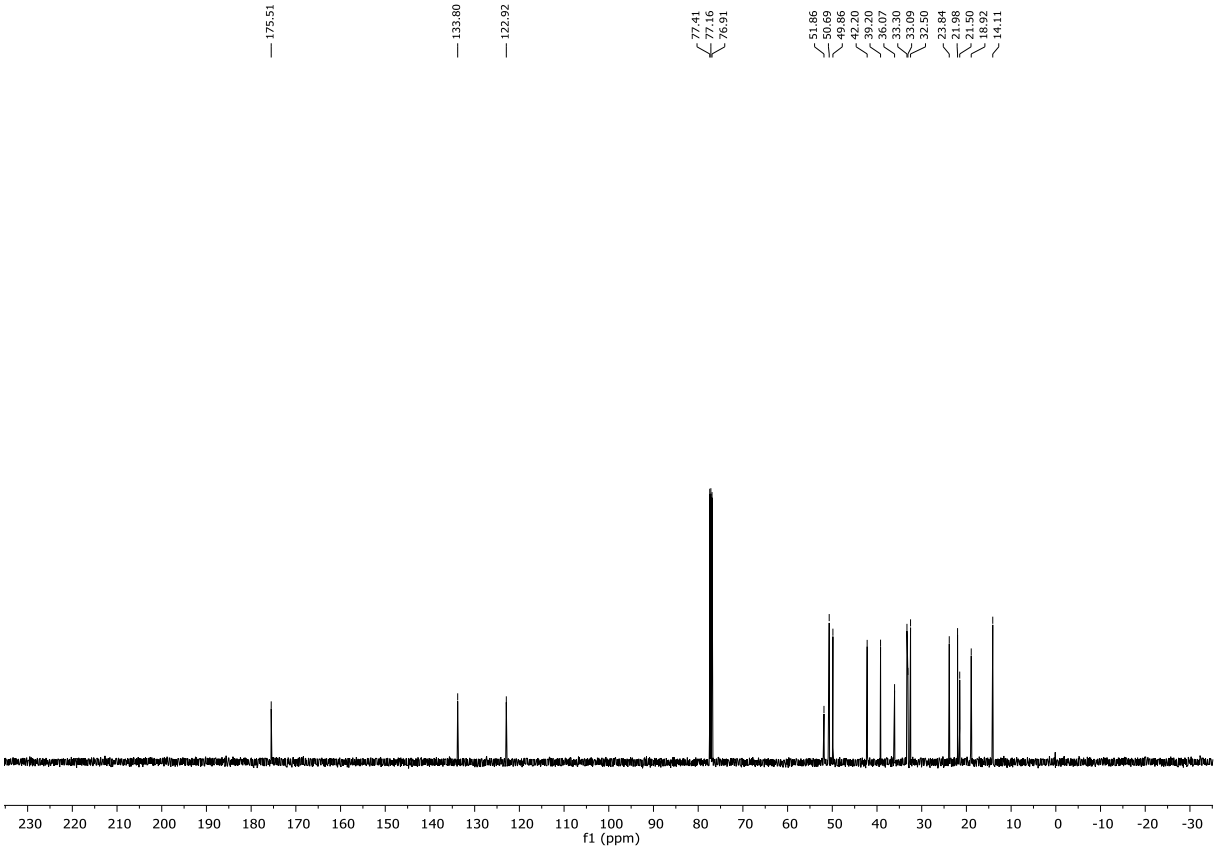
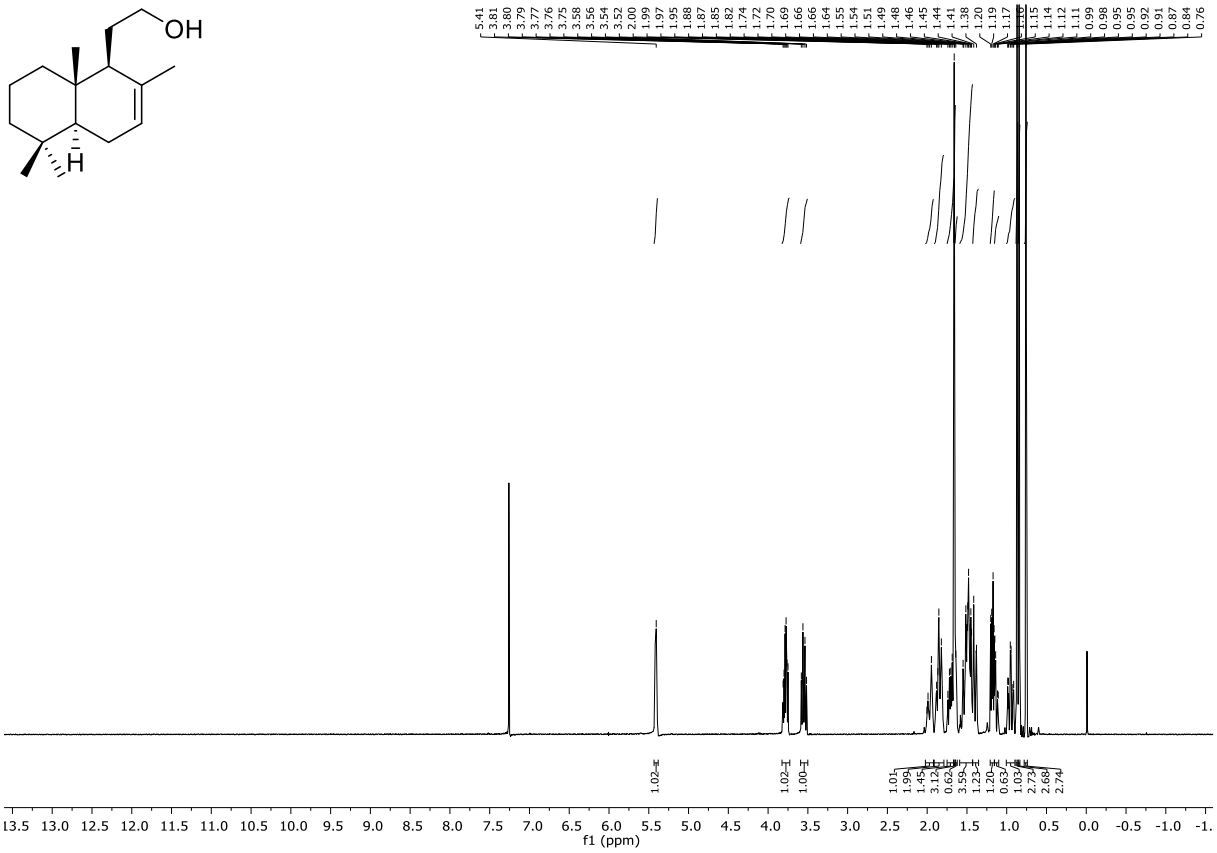
f1 (ppm)


f1 (ppm)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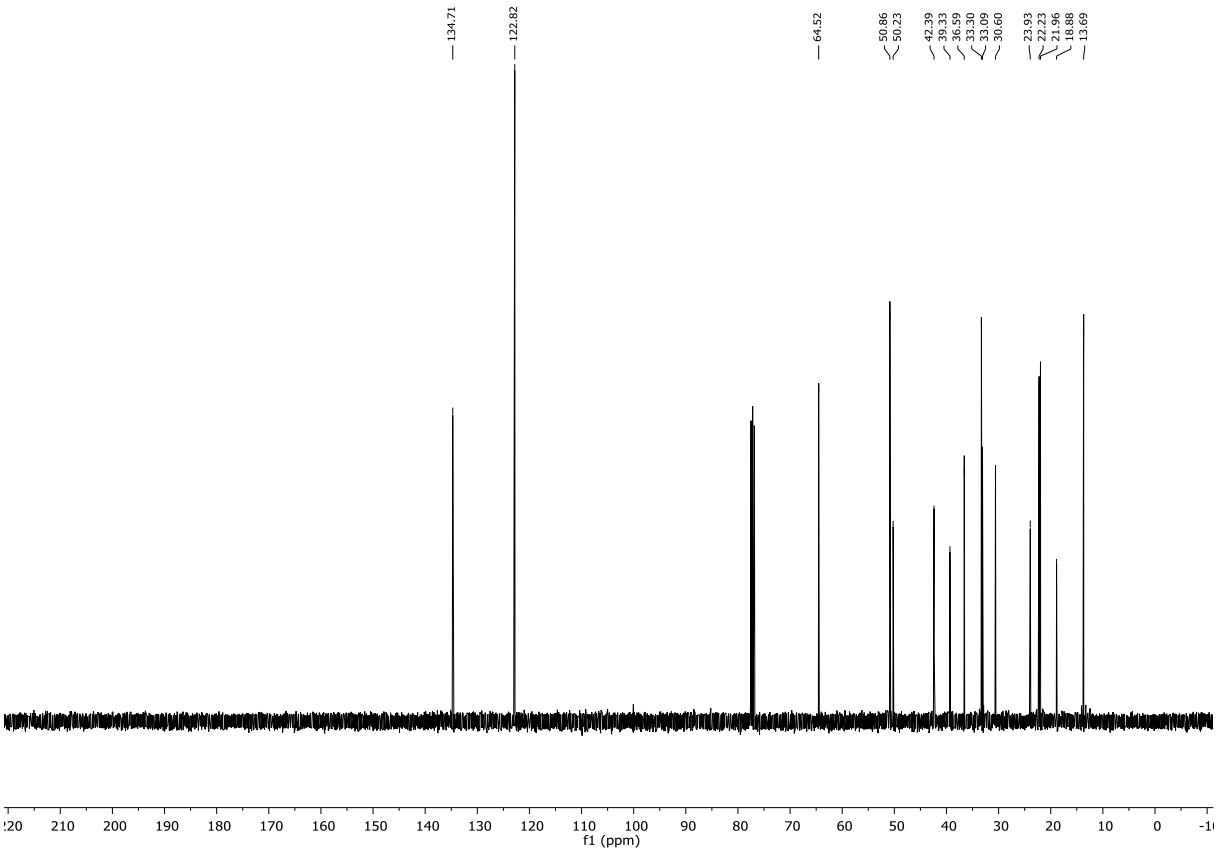
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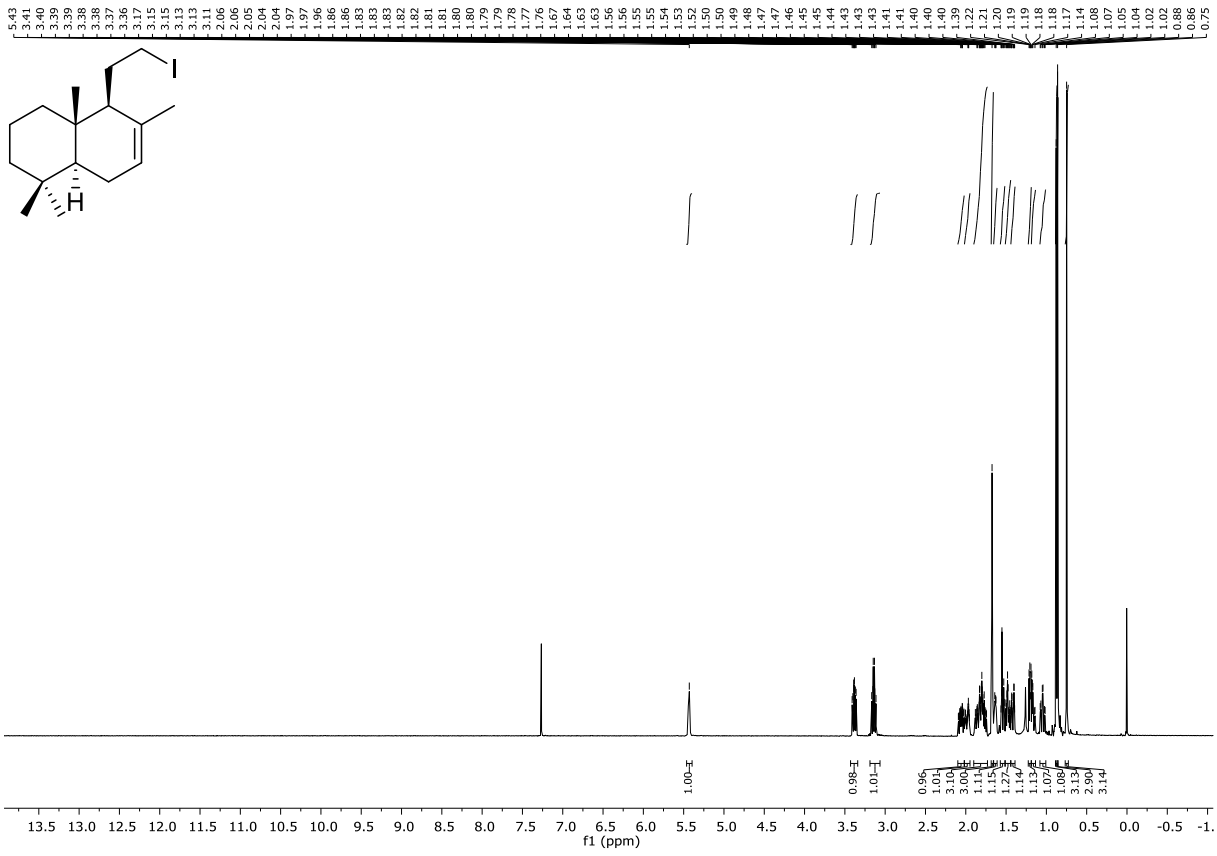
I
H
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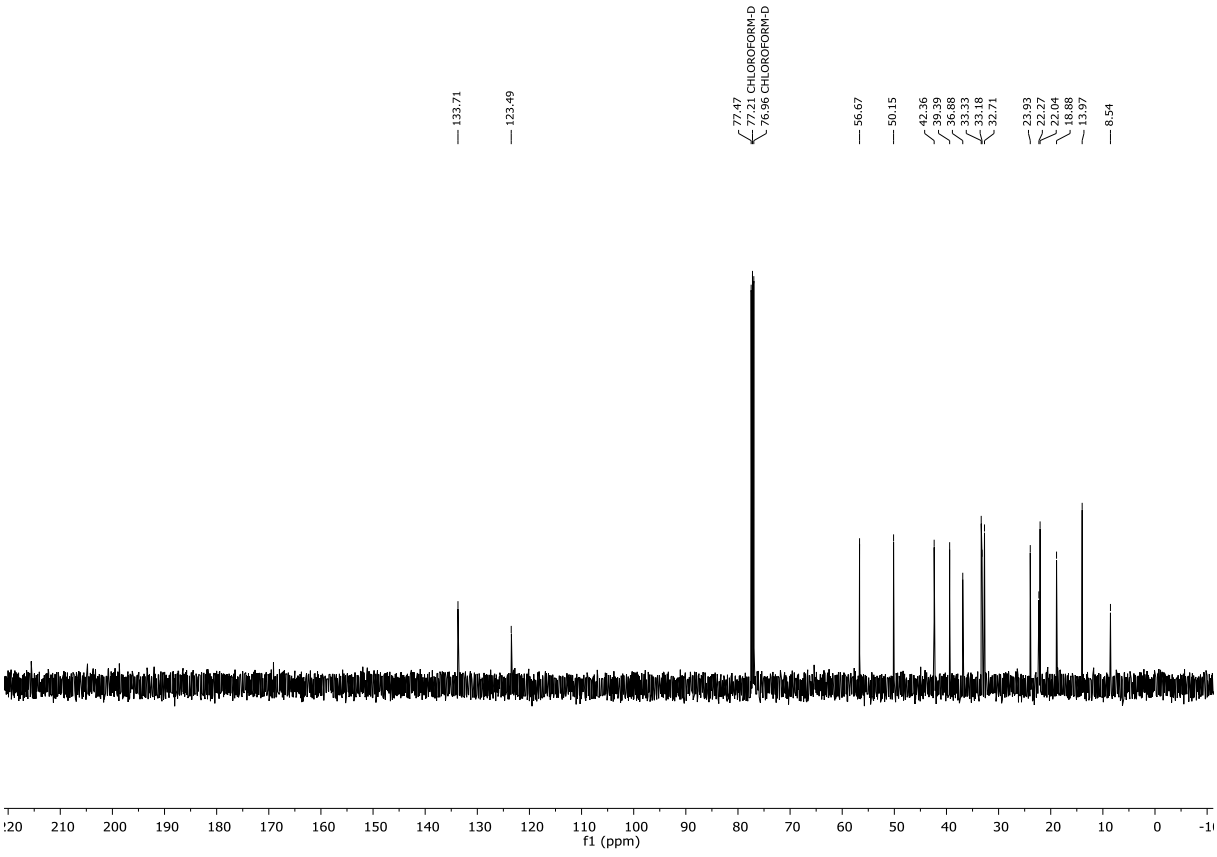
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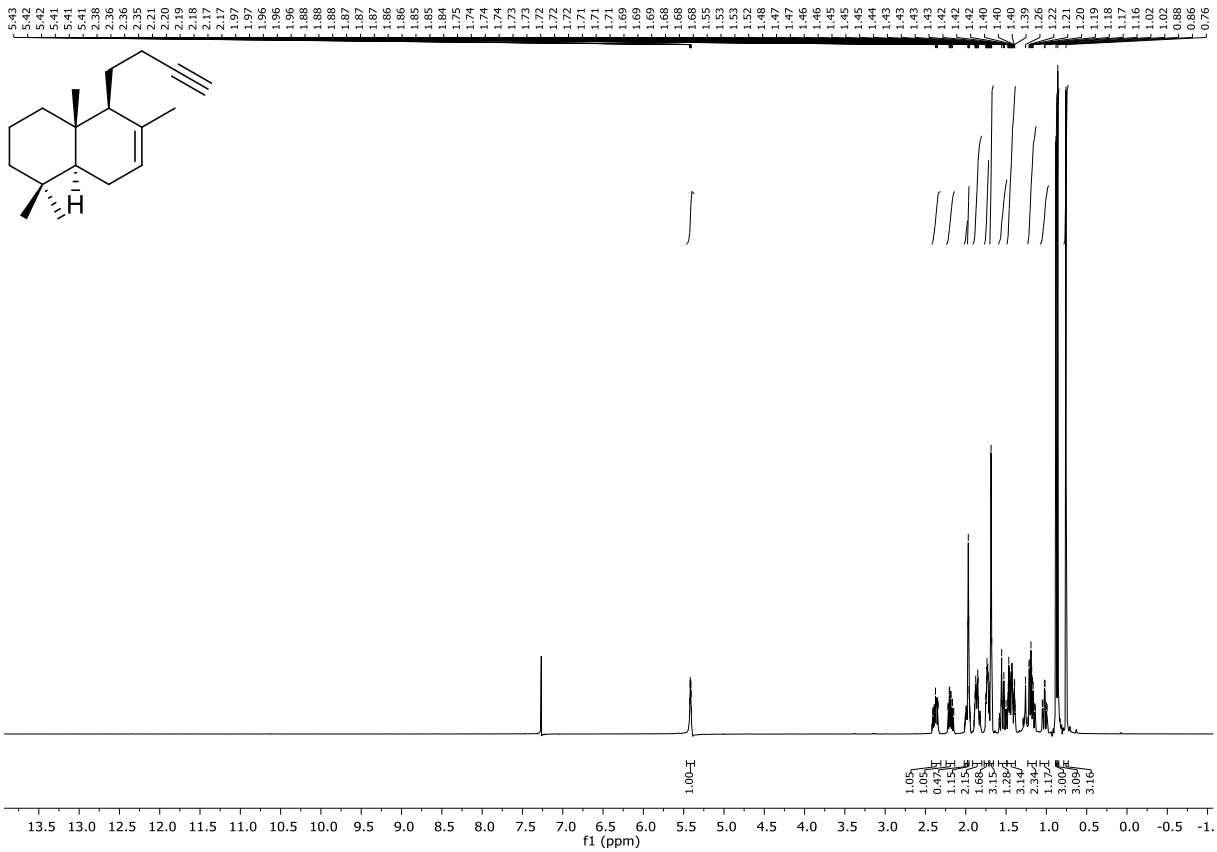
8.54
f1 (ppm)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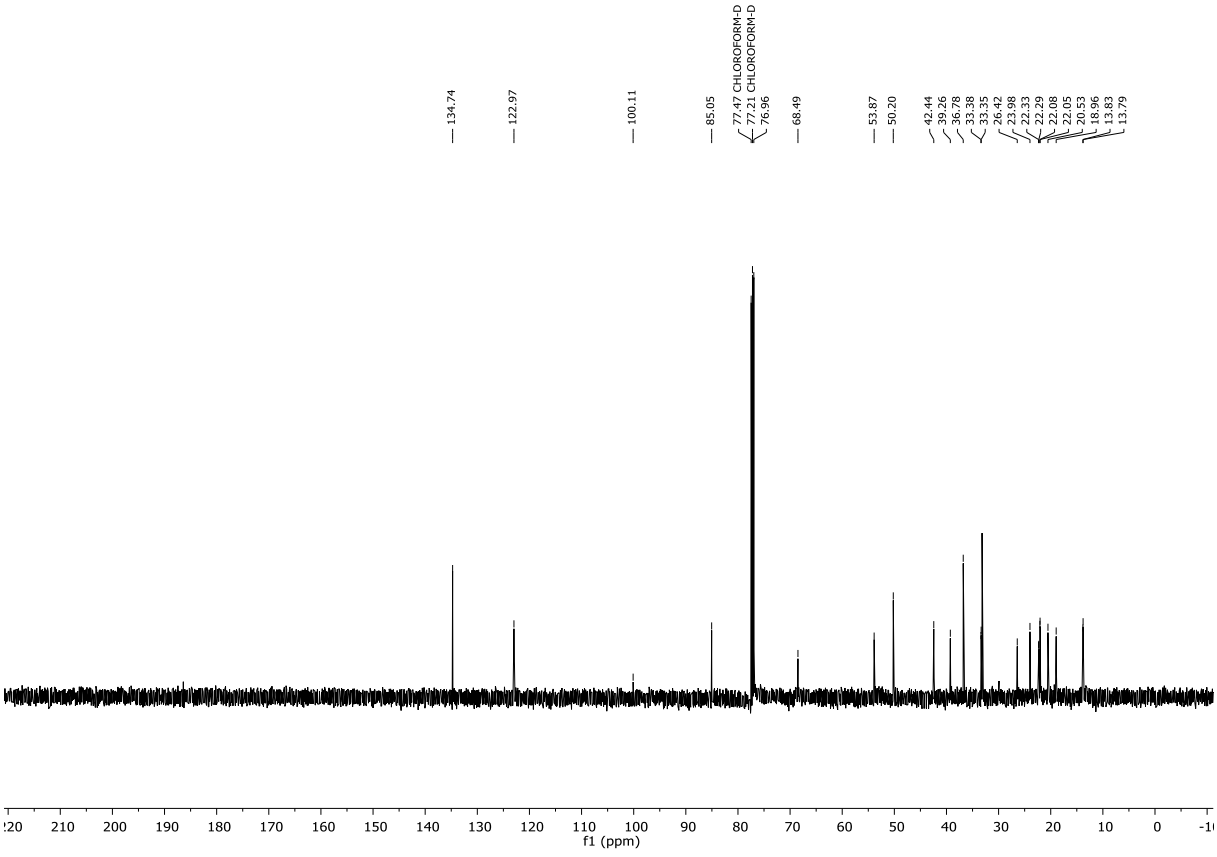
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36.78
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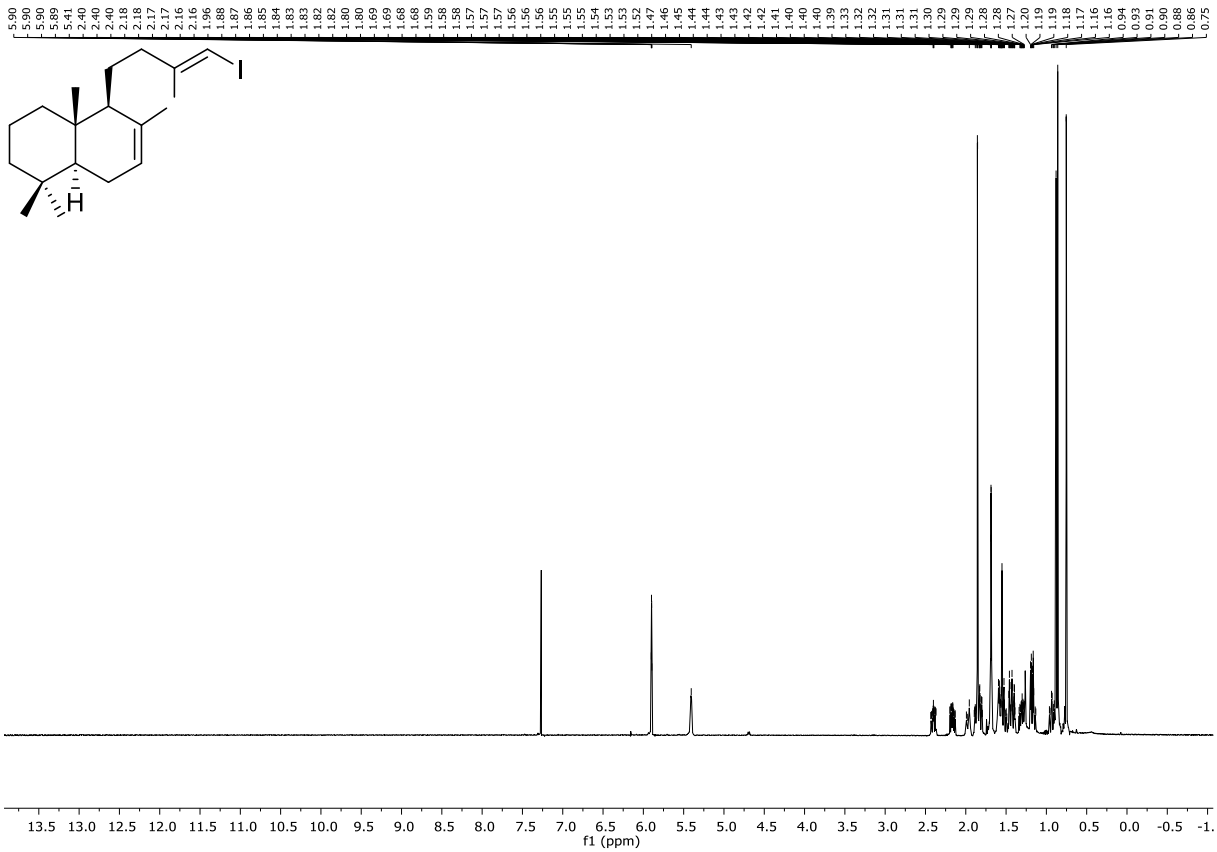
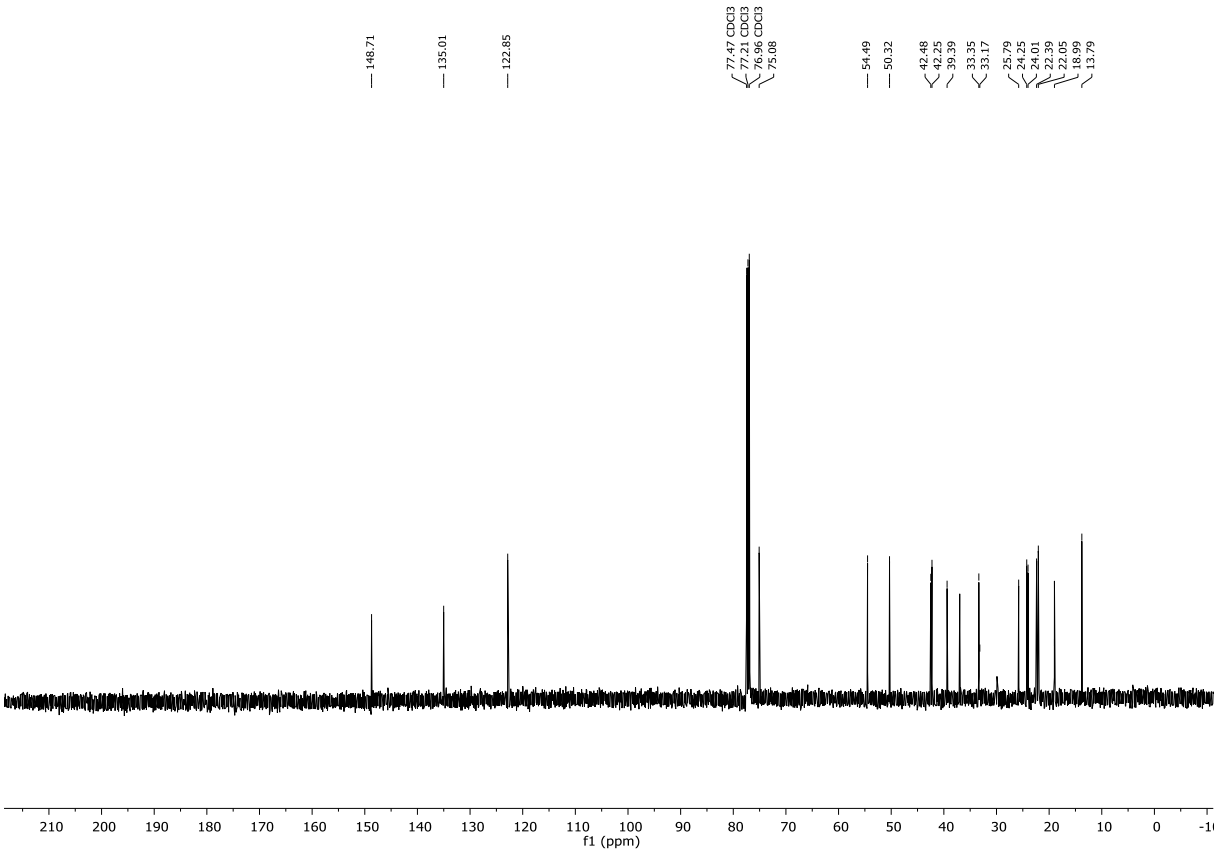
f1 (ppm)


5.90 5.90 5.90 5.89 5.41 2.40 2.40 2.40 2.18 2.18 2.17 2.17 2.16 1.96 1.88 1.87 1.86 1.85 1.84 1.83 1.82 1.82 1.80 1.80 1.69 1.69 1.68 1.68 1.59 1.58 1.58 1.57 1.57 1.57 1.56 1.56 1.56 1.55 1.55 1.55 1.54 1.53 1.53 1.52 1.47 1.46 1.45 1.44 1.44 1.43 1.43 1.42 1.42 1.41 1.40 1.40 1.40 1.39 1.33 1.32 1.32 1.31 1.31 1.31 1.30 1.29 1.29 1.29 1.28 1.28 1.27 1.20 1.19 1.19 1.18 1.17 1.16 1.16 0.94 0.93 0.91 0.90 0.88 0.86 0.75
I
H
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.
f1 (ppm)


148.71
135.01
122.85
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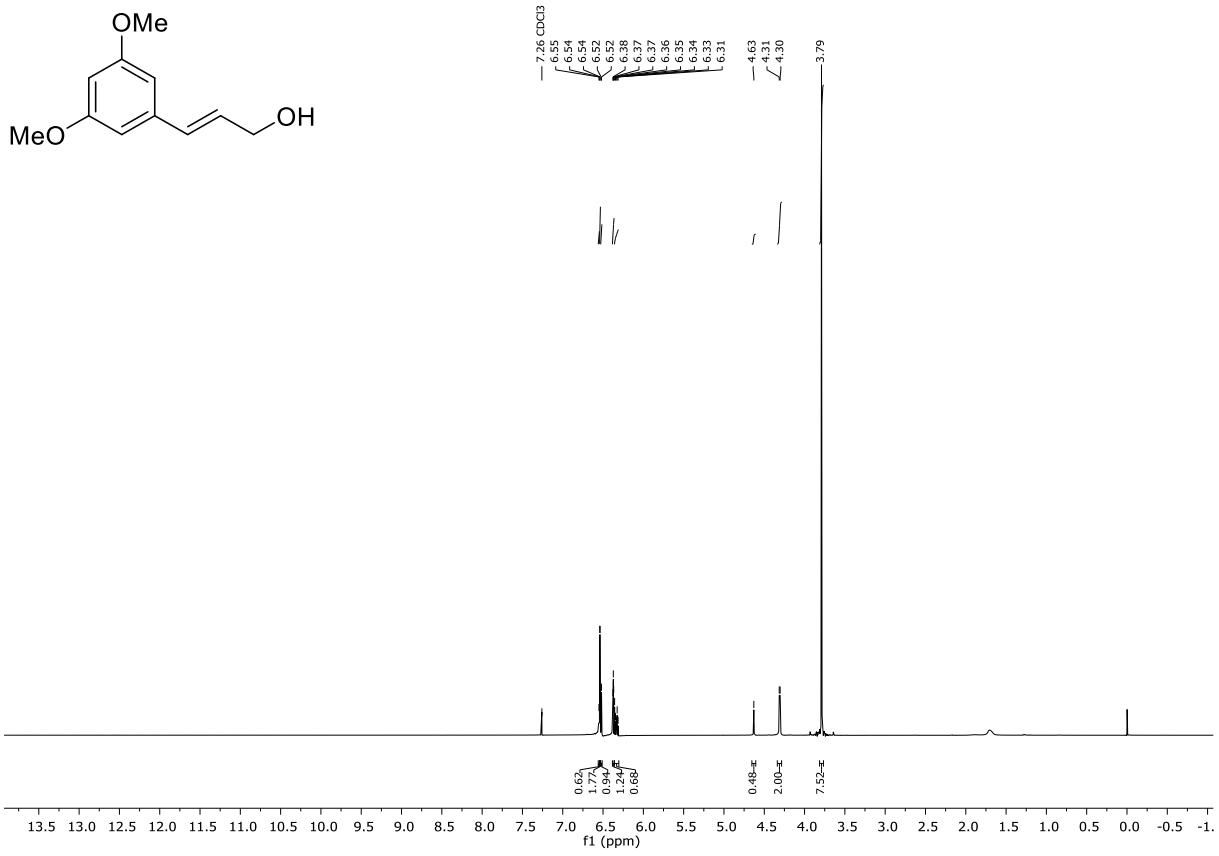
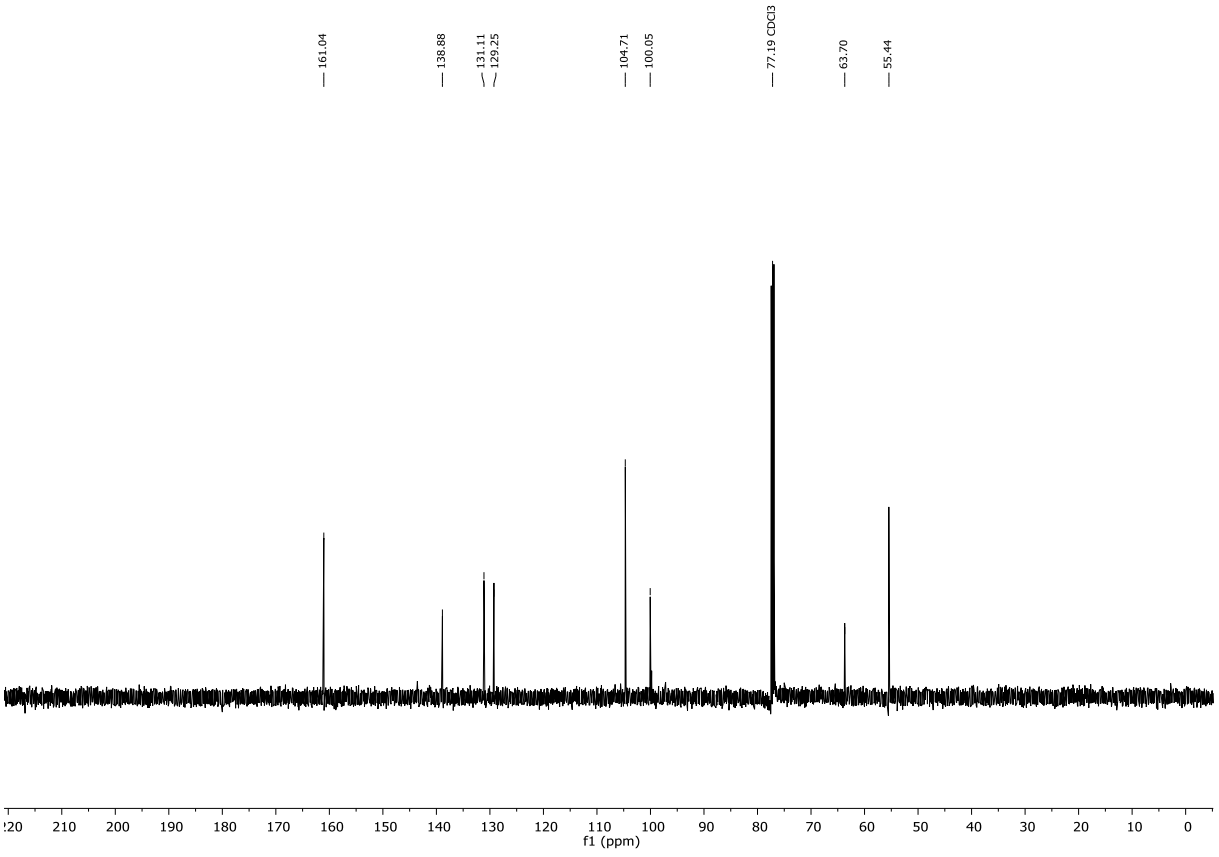
77.21 CDCl3
76.96 CDCl3
75.08
54.49
50.32
42.48
42.25
39.39
33.35
33.17
25.79
24.25
24.01
22.39
22.05
18.99
13.79
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


OMe
MeO
OH
7.26 CDCl3
6.55
6.54
6.54
6.52
6.52
6.38
6.37
6.37
6.36
6.35
6.34
6.33
6.31
4.63
4.31
4.30
3.79
0.62
1.77
0.94
1.24
0.68
0.48
2.00
7.52
f1 (ppm)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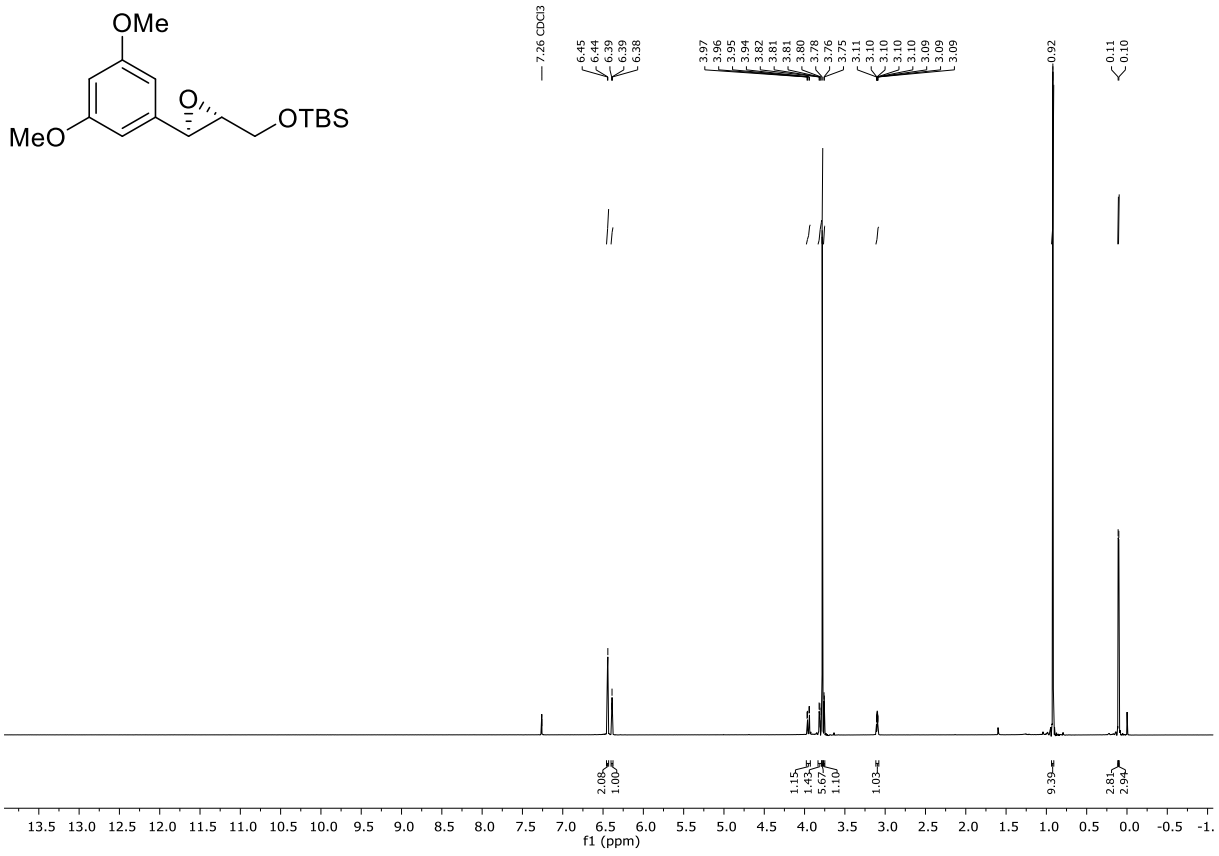
138.88
131.11
129.25
104.71
100.05
77.19 CDCl3
63.70
55.44
f1 (ppm)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MeO
O
OTBS
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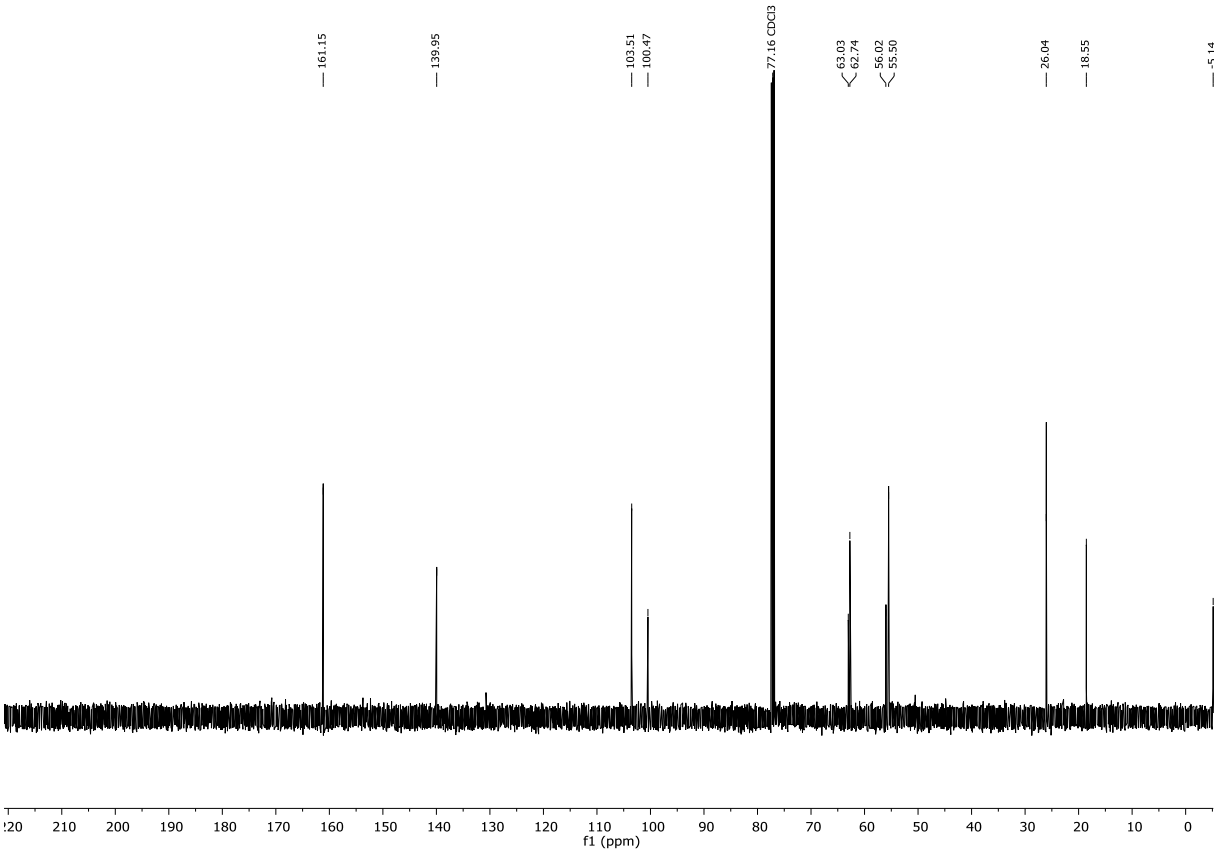
6.45
6.44
6.39
6.39
6.38
3.97
3.96
3.95
3.94
3.82
3.81
3.81
3.80
3.78
3.76
3.75
3.11
3.10
3.10
3.10
3.10
3.09
3.09
3.09
0.92
0.11
0.10
2.08
1.00
1.15
1.43
5.67
1.10
1.03
9.39
2.81
2.94
f1 (ppm)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26.04
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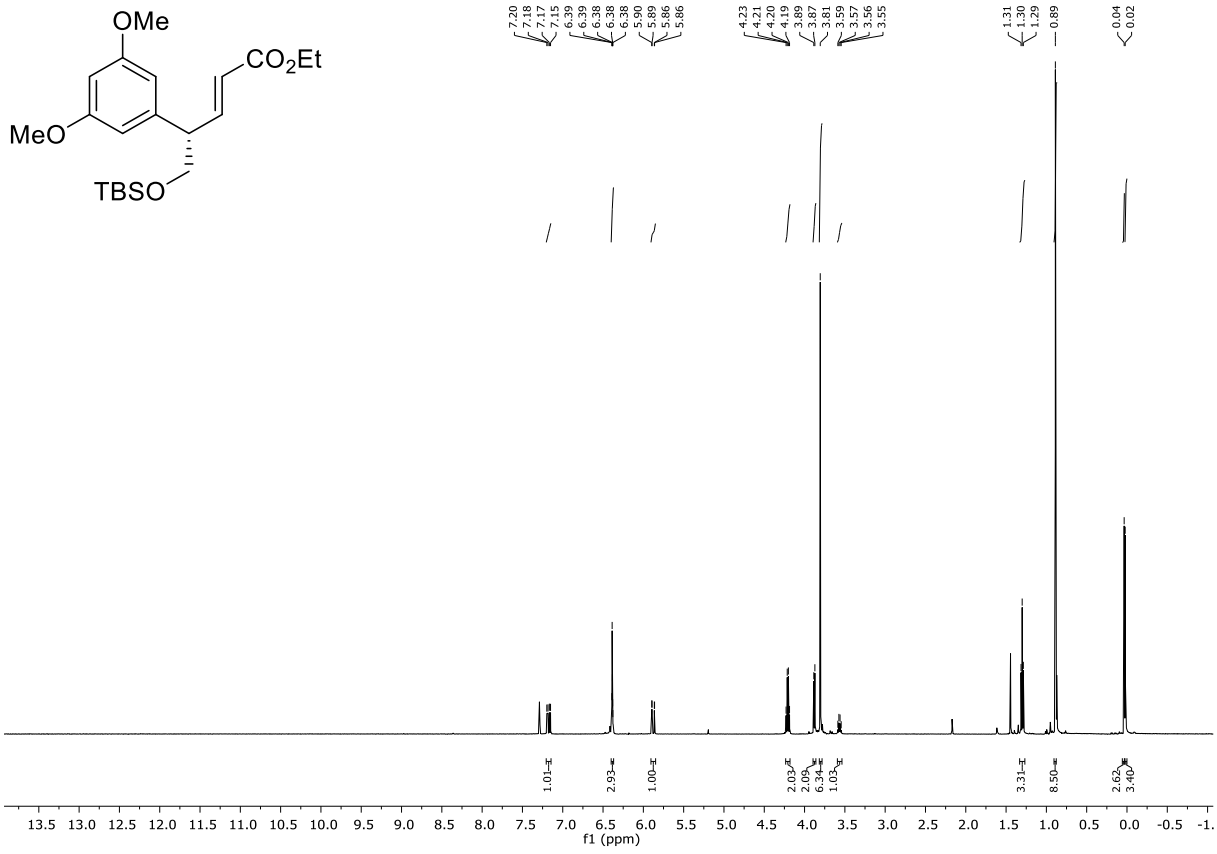
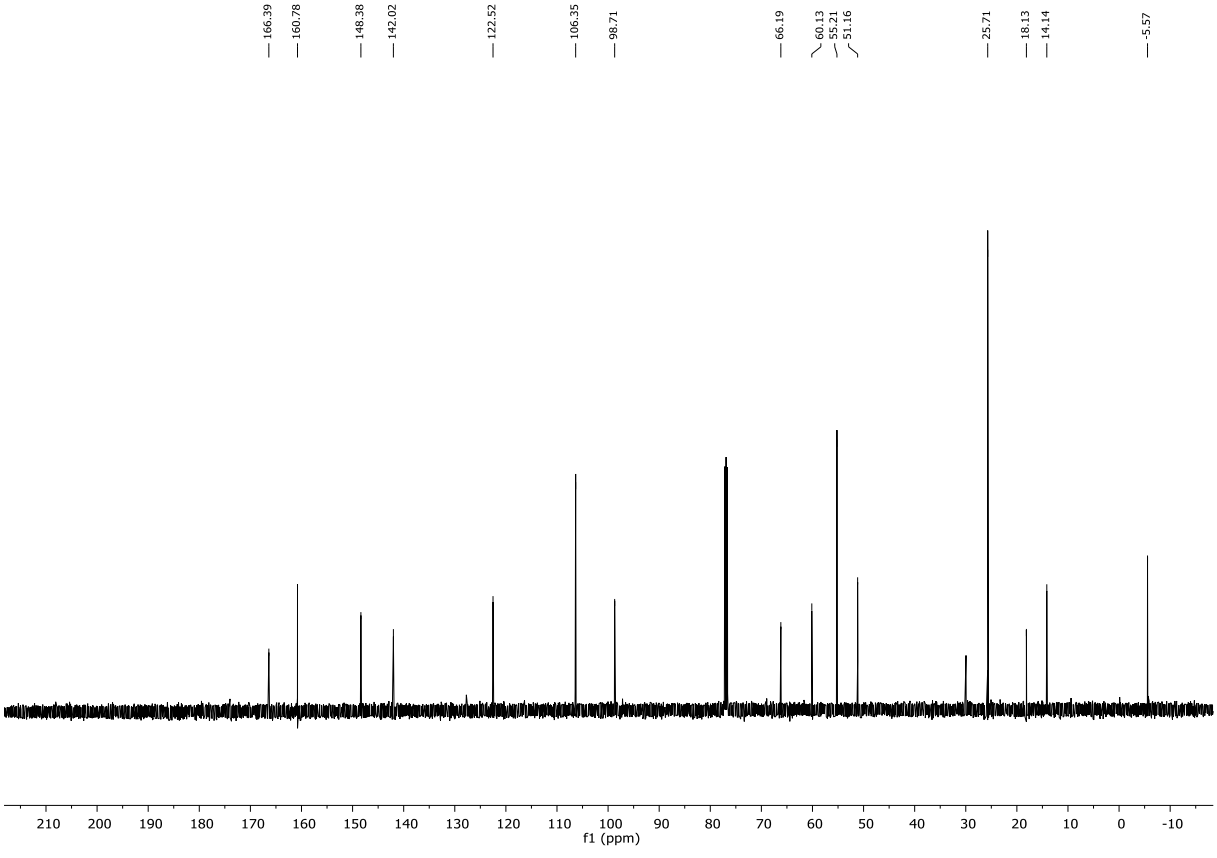
-5.14
f1 (ppm)


OMe
CO2Et
MeO
TBSO
7.20
7.18
7.17
7.15
6.39
6.38
6.38
6.38
5.90
5.89
5.86
5.86
4.23
4.21
4.20
4.19
3.89
3.87
3.81
3.59
3.57
3.56
3.55
1.31
1.30
1.29
0.89
0.04
0.02
1.01
2.93
1.00
2.03
2.09
6.34
1.03
3.31
8.50
2.62
3.40
f1 (ppm)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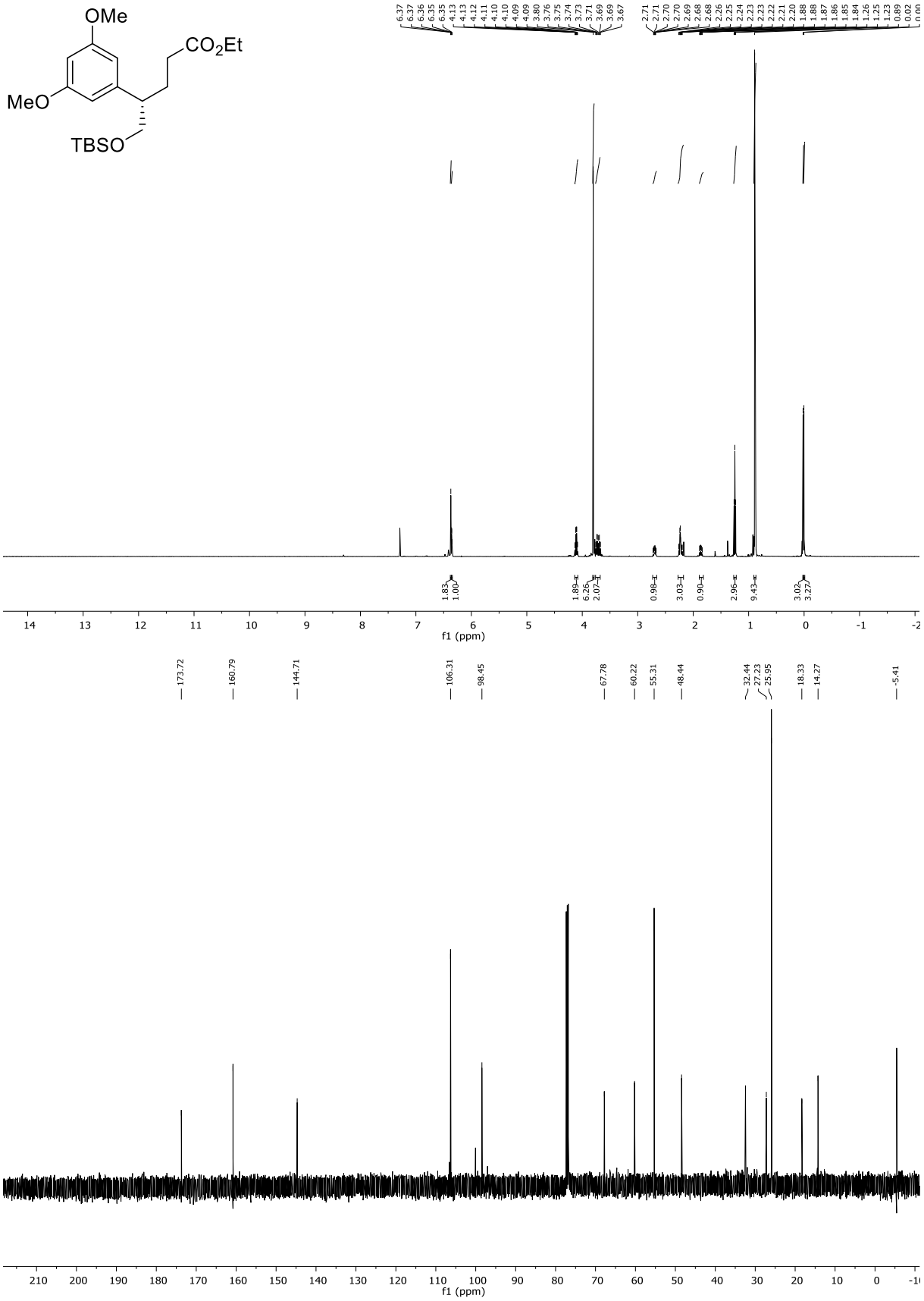
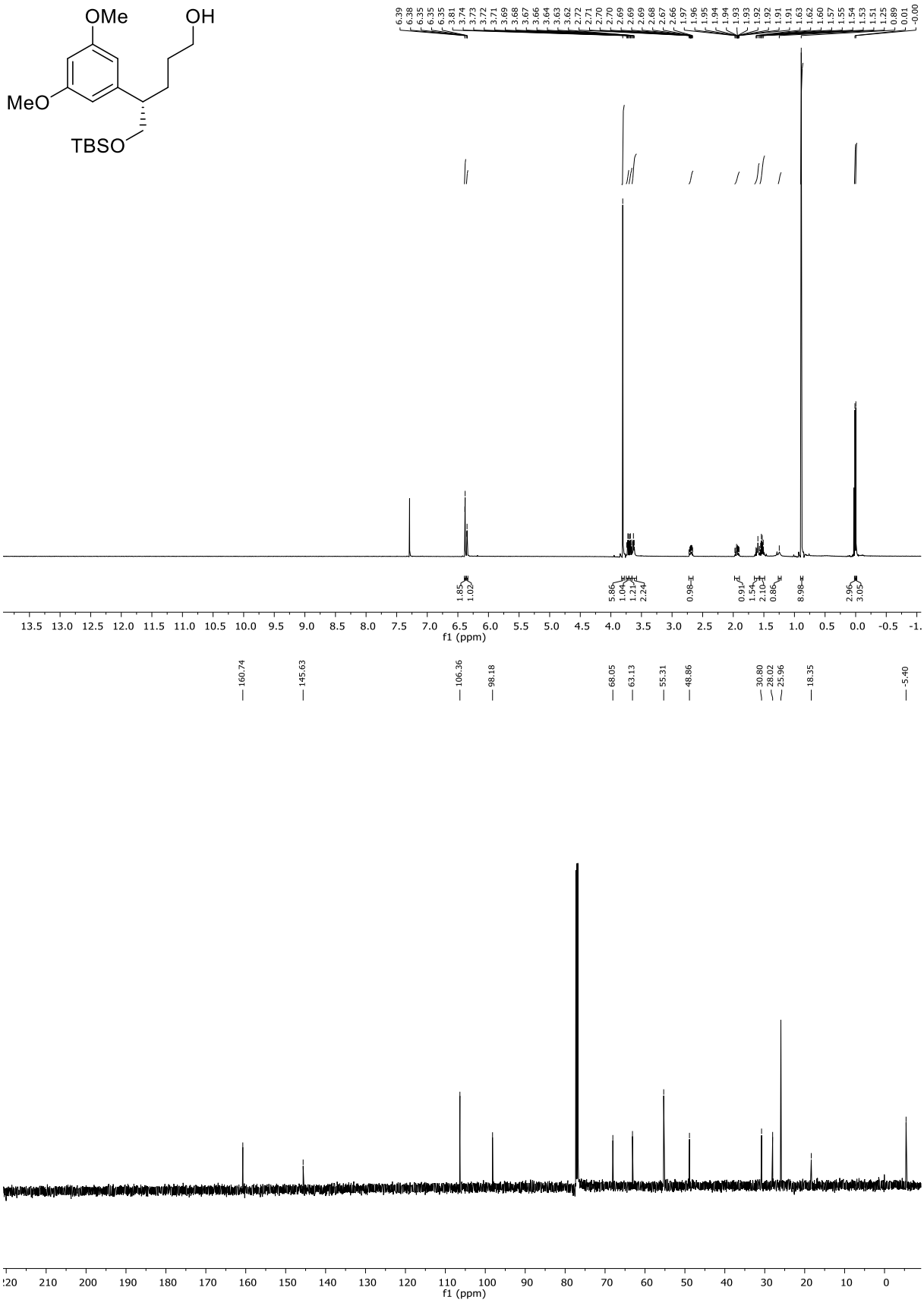
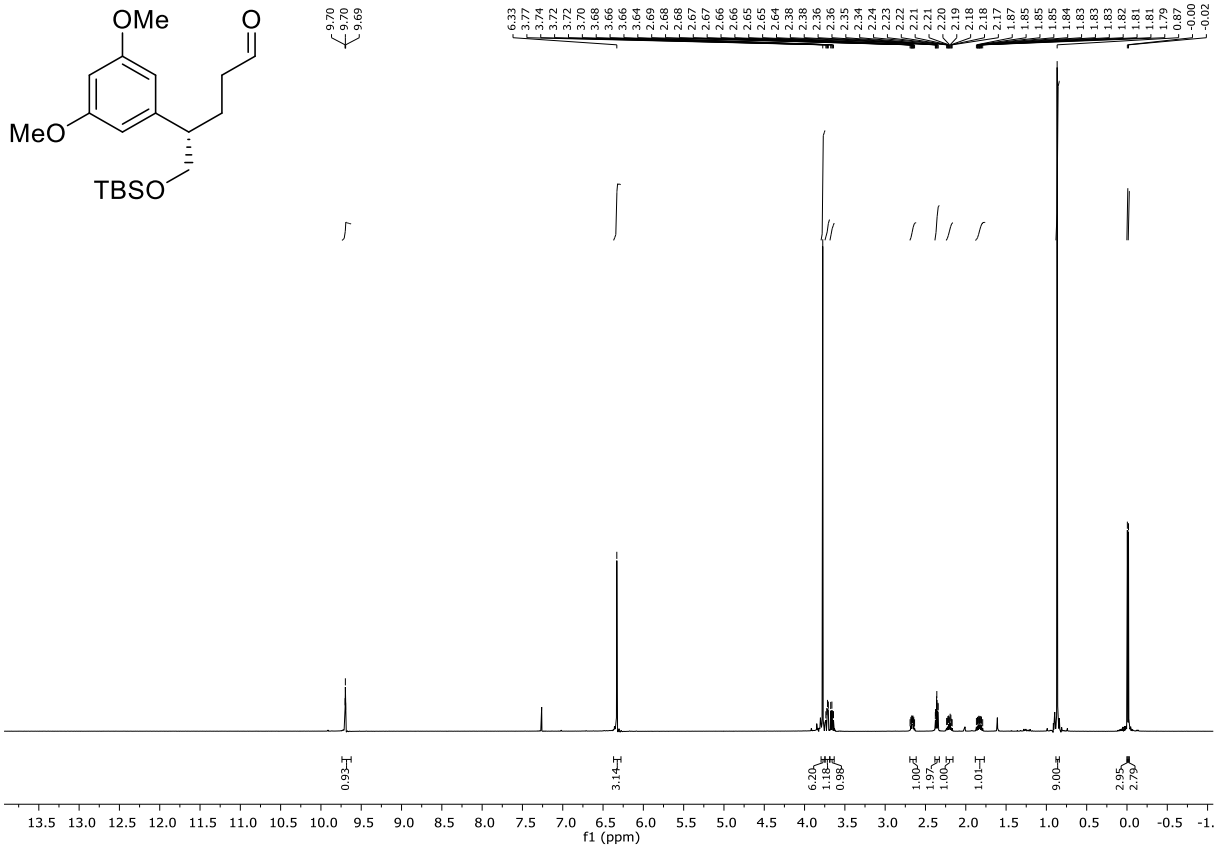
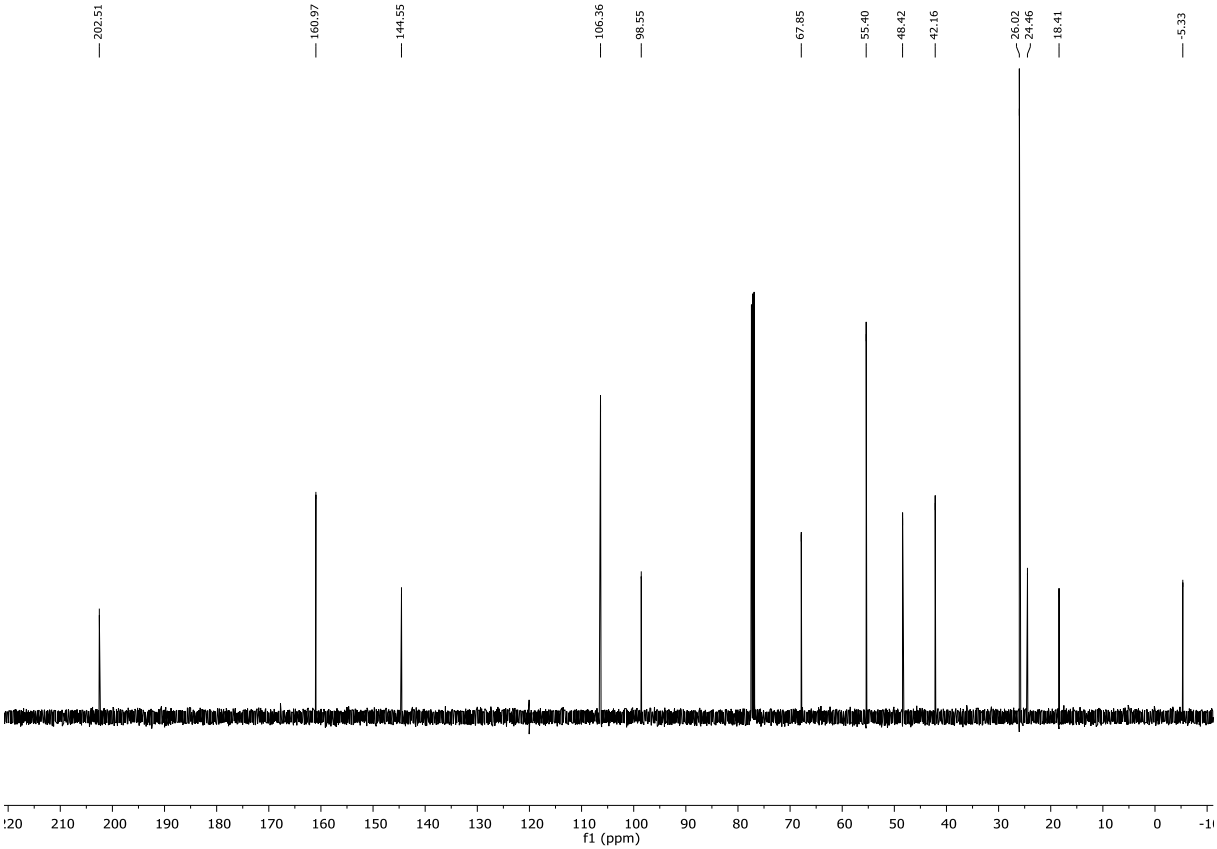
148.38
142.02
122.52
106.35
98.71
66.19
60.13
55.21
51.16
25.71
18.13
14.14
-5.57
f1 (ppm)


OMe
CO2Et
MeO
TBSO
f1 (ppm)
f1 (ppm)


OMe
OH
MeO
TBSO
f1 (ppm)
f1 (ppm)


OMe
O
MeO
TBSO
f1 (ppm)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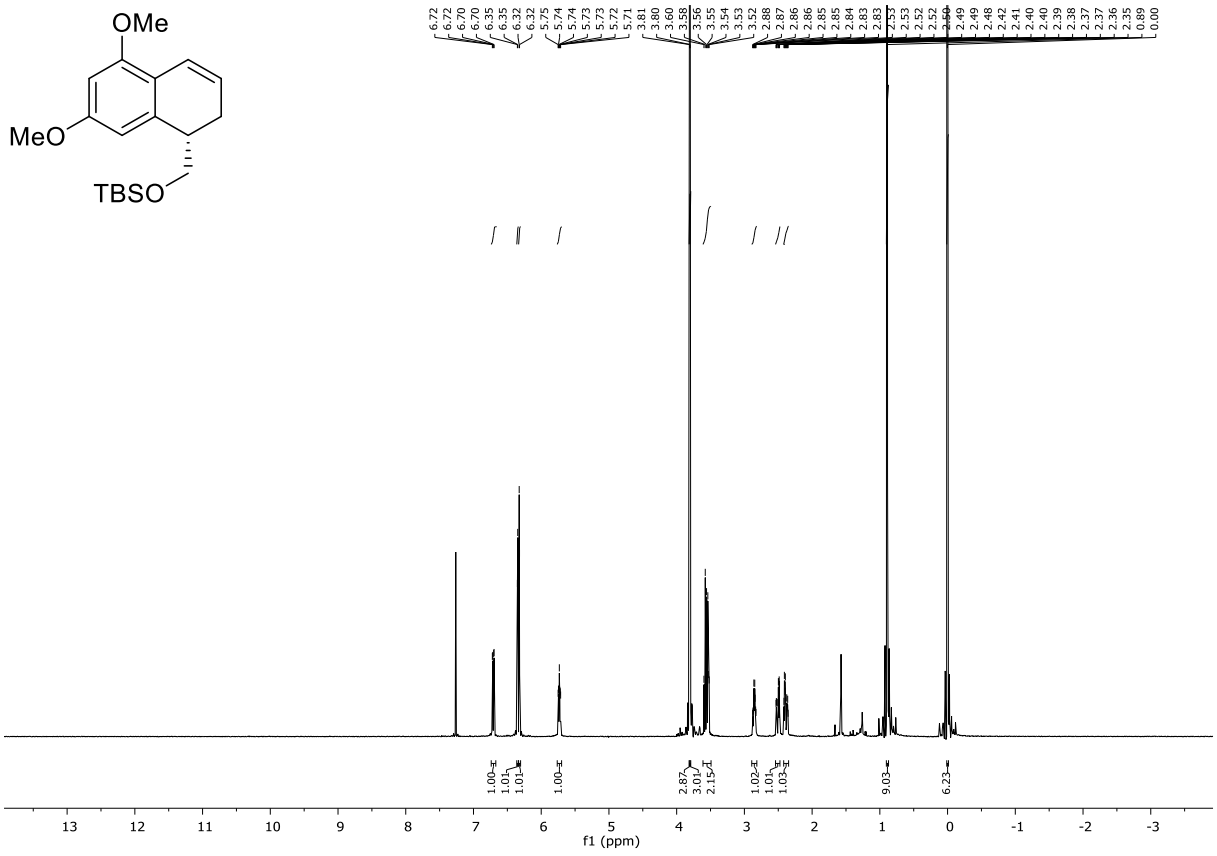
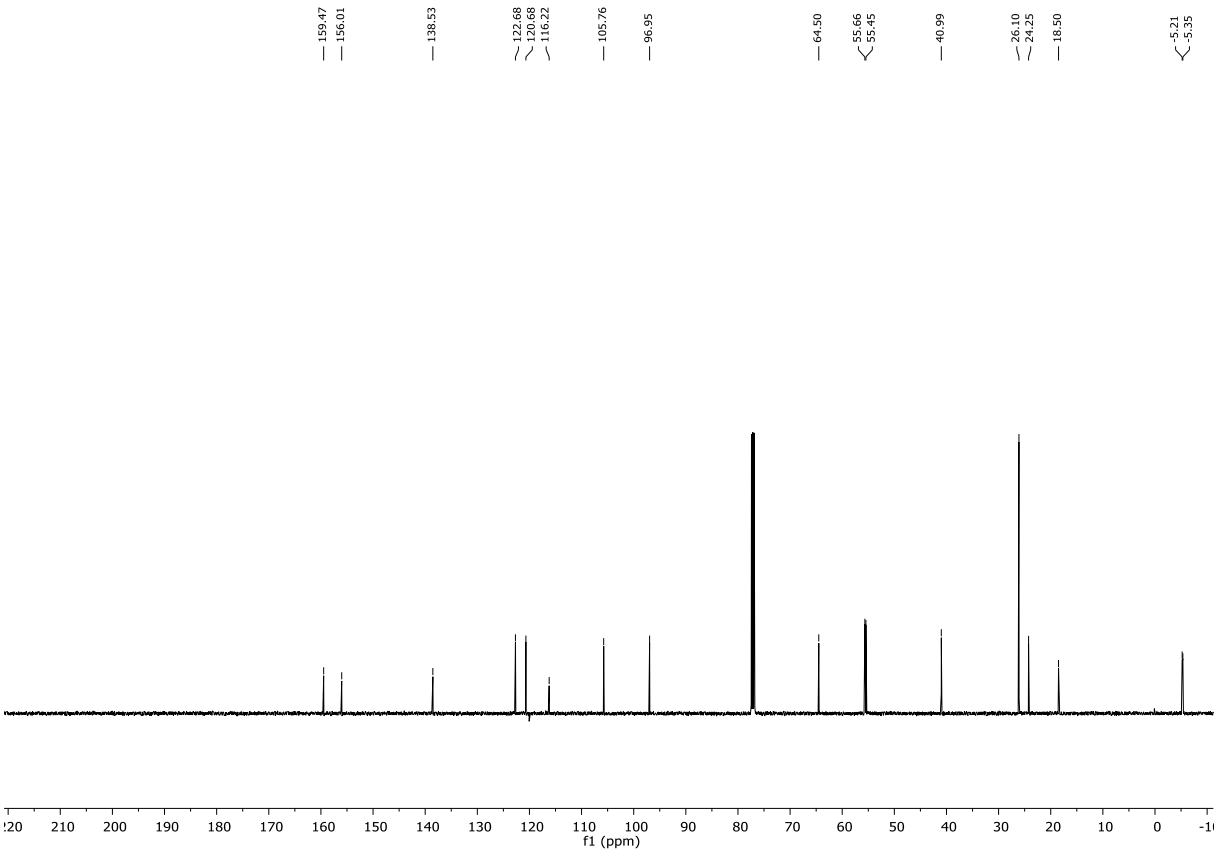
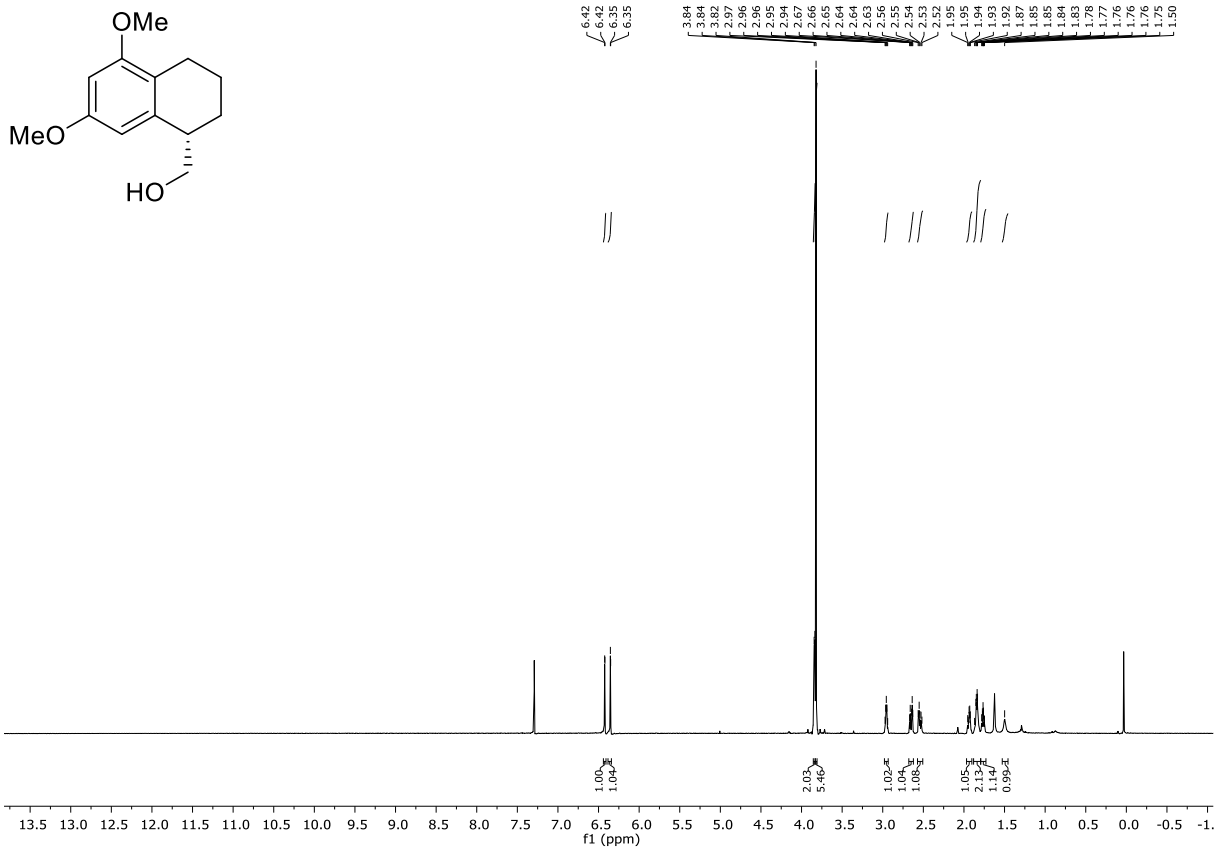
98.55
67.85
55.40
48.42
42.16
26.02
24.46
18.41
-5.33
f1 (ppm)


OMe
MeO
TBSO
f1 (ppm)


f1 (ppm)


OMe
MeO
HO
6.42
6.42
6.35
6.35
3.84
3.84
3.82
2.97
2.96
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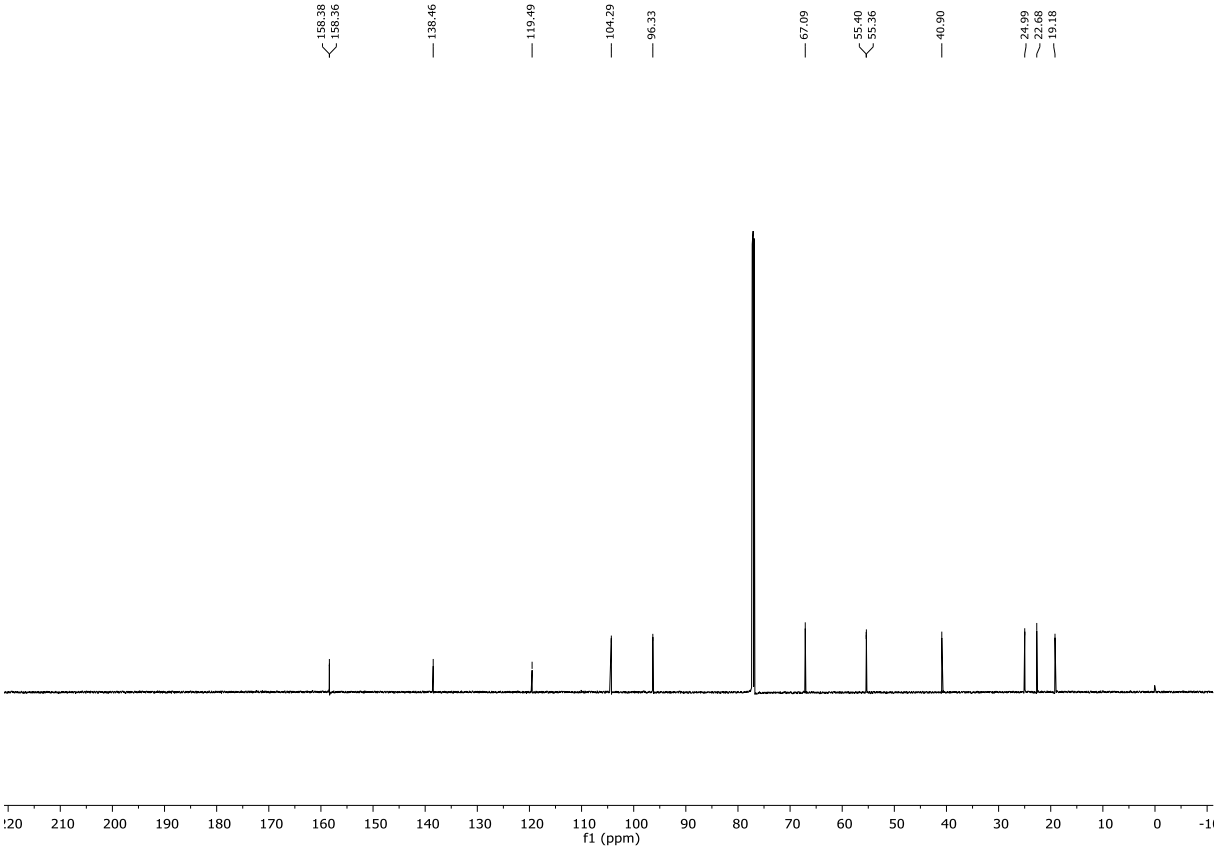
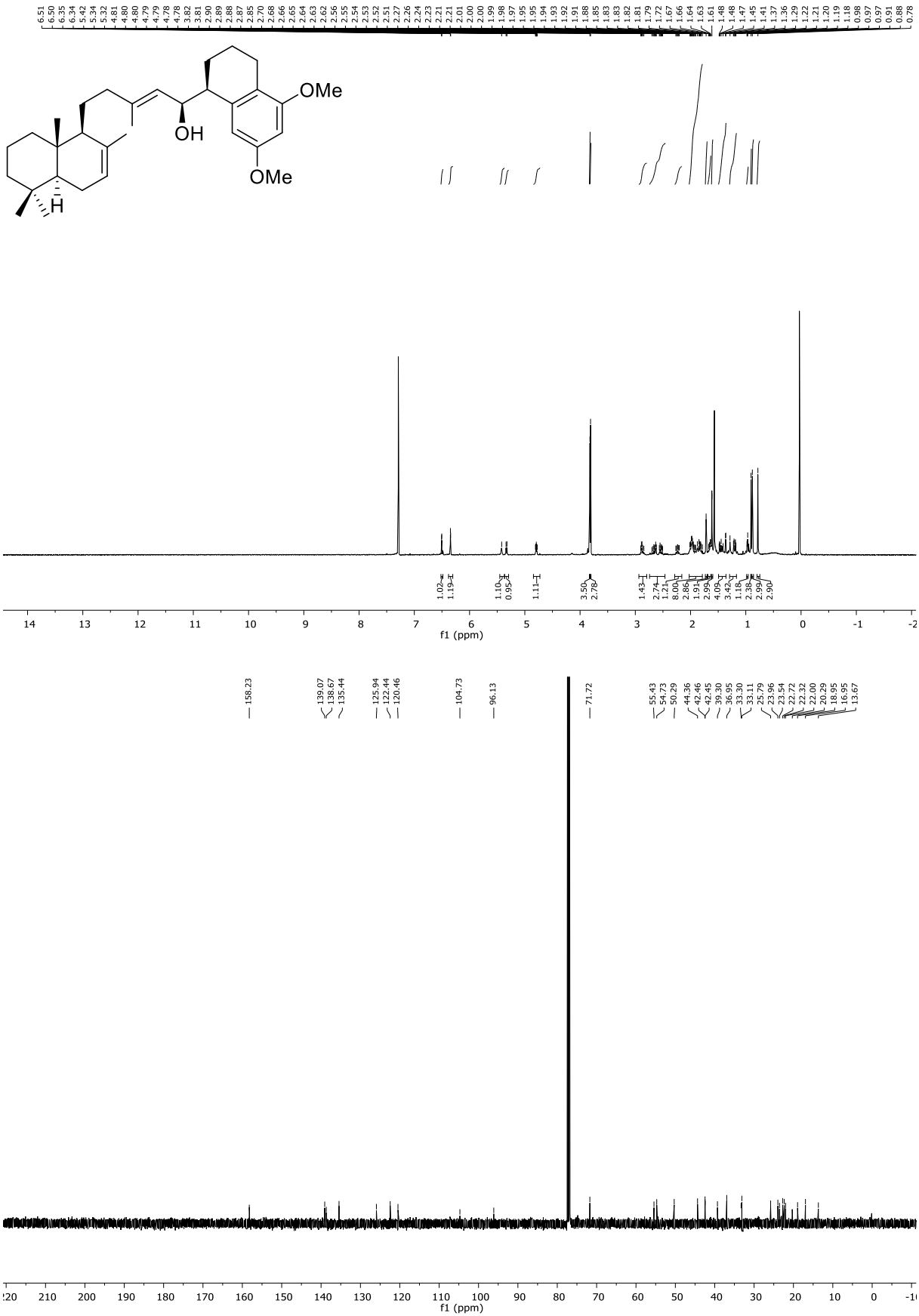
2.95
2.94
2.67
2.66
2.65
2.64
2.64
2.63
2.56
2.55
2.54
2.53
2.52
1.95
1.95
1.94
1.93
1.92
1.87
1.85
1.85
1.84
1.83
1.78
1.77
1.76
1.76
1.76
1.75
1.50
1.00
1.04
2.03
5.46
1.02
1.04
1.08
1.05
2.13
1.14
0.99
f1 (ppm)


158.38
158.36
138.46
119.49
104.29
96.33
67.09
55.40
55.36
40.90
24.99
22.68
19.18
f1 (ppm)


OMe
OH
OMe
H
f1 (ppm)
f1 (ppm)

6.1.3 Mechanistic Studies on the Organocatalytic α-Chlorination of Aldehydes: The Role and Nature of Off-Cycle Intermediates

The supporting information was slightly changed in comparison to the published version (no page numbers and Wiley template). The pages and the page width were adjusted to the format of this thesis. The information was left as it is in the original version.

6.2 Publications and scientific contribution

Publications

1) **M. Menger**, D. Lentz, M. Christmann, Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)–C(sp3) Cross-Electrophile Coupling, *J. Org. Chem.* **2018**, *83*, 6793–6797.

2) **M. Menger**, M. Christmann, Formal Synthesis of Actinoranone Using a Racemization-Free One-Pot Semipinacol Rearrangement/Wittig Reaction, *manuscript in preparation*.

3) S. Ponath, **M. Menger**, L. Grothues, M. Weber, D. Lentz, C. Strohmann, and M. Christmann, Mechanistic Studies on the Organocatalytic α-Chlorination of Aldehydes: The Role and Nature of Off-Cycle Intermediates, *Angew. Chem. Int. Ed.* **2018**, *57*, 11683–11687.

Conference contributions

M. Menger, D. Lentz, M. Christmann, Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)–C(sp3) Cross-Electrophile Coupling, 20th Frühjahrssymposium, Konstanz, Germany, 03/2018

M. Menger, D. Lentz, M. Christmann, Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)–C(sp3) Cross-Electrophile Coupling, 19th Tetrahedron Symposium, Riva del Garda, Italy, 06/2018

6.3 Curriculum vitae

Der Lebenslauf ist aus Gründen des Datenschutzes nicht enthalten.